Encyclopedia of Canine Clinical Nutrition

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The book is the result of a collaboration with international authors who are specialized in different areas of veterinary medicine. Our warmest thanks to all those who have been involved in producing this Encyclopedia.

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'Let food be thy medicine'

Hippocrates (460-377 BC)

Since its establishment in 1968 by the veterinarian Jean Cathary, true to its values of 'Knowledge and Respect, Royal Canin has shared a common goal with the veterinary community: **improving the health and the longevity of dogs and cats worldwide**.

The Royal Canin Center for Research and Development has developed innovative nutritional programs dedicated exclusively to veterinarians, based on a two-pronged preventive and curative approach.

With this expanded approach to health, Royal Canin has built the foundations of a solid partnership with veterinarians. The aim is to contribute to the development of their activities rather than trying to eclipse them in favor of other players in the nutrition market.

In the pursuit of this shared goal – improving the health of dogs and cats – the number one priority is to enhance the status of the veterinarian profession by:

1. sharing scientific knowledge acquired through practical experience
2. bringing innovation firmly anchored in scientific fact and characterized by measured clinical efficacy
3. creating specific and unique tools and services

Essentially, strengthening the veterinarian's advisory role in nutrition through the quality and exclusivity of products and giving a new meaning to the prescription of food through a variety of services offered to veterinarians.

The field of nutrition prescribed by the veterinarian to support the treatment – known as clinical nutrition – or to help prevent disease is the common ground on which the veterinarian profession and Royal Canin meet every day.

Our ambition with this encyclopedia was to draw together the latest advancements in Canine Clinical Nutrition in a single publication, from the perspective of clinicians and nutritionists – something that has never before been done.

This new publication is another in the long list of communication tools produced by Royal Canin for veterinarians around the globe. A list that includes the encyclopedias of dogs and of cats, Focus magazine and the special editions of Focus, as well as the Scientific Meetings.

More than ever, this Encyclopedia of Canine Clinical Nutrition, produced in association with eminent experts from the world of veterinary medicine, has been driven by the desire to share the knowledge that Royal Canin has acquired since its establishment.

Nutrition always has an impact on the clinical expression of some pathologies and to achieve its clinical and educational objectives this Encyclopedia offers a panorama that is both broad and deep, brought to life in full-color illustrations.

Produced under the supervision of the Royal Canin Center for Research and Development, this Encyclopedia of Canine Clinical Nutrition was conceived in the spirit of collaboration with our scientific partners.

I would like to express my sincere thanks to all those whose high-quality and precise work has enabled the production of this Encyclopedia.

Alain Guillemin
Chief Executive Officer

Health and nutrition; more closely related than ever before

Clinical nutrition for companion animals is a fast developing discipline, as demonstrated by the many scientific articles published in this field in the last 50 + years. Indeed, in 2004 alone, there were 2648 articles published stressing the relationship between health, nutrition and the prevention of disease representing a 100% increase in available scientific information in just over a decade.

So why add a 500-page encyclopedia to the body of scientific literature already available? "Science for science's sake" is not one of Royal Canin's concerns. Our ultimate goal is to improve the health and well-being of dogs and cats by ensuring their diet is carefully tailored to their individual needs. This encyclopedia is therefore chiefly aimed at practitioners. We aspired to create a reference book which helps veterinary practitioners easily find answers to all of their questions (and those of their clients) concerning the role of nutrition in achieving both optimal health and in treating specific nutrition-responsive disease.

Compared to existing books, this Encyclopedia has three additional features.

1/ It provides updated knowledge about nutrition
Each chapter summarizes the updated knowledge about nutritional therapies and reviews the most commonly asked questions, e.g.

- What is the role of dietary hypersensitivity in the development of intestinal bowel disease?
- Is it necessary to restrict fat intake in exocrine pancreatic deficiency?
- Is renal function affected by a high protein diet?
- What is the influence of urinary pH on the formation of calcium oxalate uroliths?
- What is the optimum sodium level for a dog with asymptomatic cardiac disease?

2/ Clinical experts and nutritionists have worked together to ensure that nutrition is included as part of a holistic clinical approach.
All chapters in this text have been written by world-recognized experts in their respective field. We would like to take this opportunity to warmly thank the authors for having responded so marvellously to our editorial request. Together, we have produced one book covering all the available knowledge in the field of canine nutrition which we hope is easy to consult, pleasant to read and colourfully illustrated.

3/ "Royal Canin Nutritional Information" offers additional information
Each chapter includes appendices provided by veterinarians and nutritional experts of Royal Canin. These sections summarise the key points of nutritional management as well as offering additional information about select nutrients.

Royal Canin aims to make a real difference in the communication of scientific knowledge. In addition to this book, Royal Canin produces multiple nutrition guides, The Waltham Focus journal and Special Edition Focus magazines to inform and help veterinary practitioners in their day-to-day work.

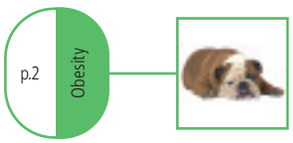
We sincerely hope that you enjoy this Royal Canin Encyclopedia and that nutrition is an integral part of your daily practice in veterinary medicine.

Pascale Pibot, Denise Elliott,
and Vincent Biourge

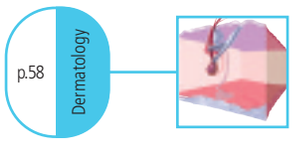
Contents

XI — Foreword

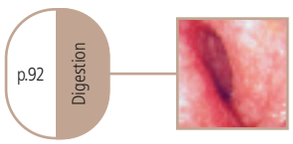
XIII — Introduction



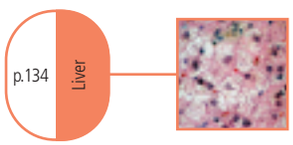
Chapter 1
Obesity: epidemiology, pathophysiology and management of the obese dog



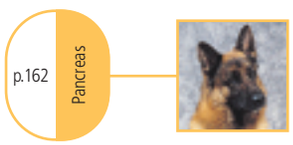
Chapter 2
Nutritional dermatoses and the contribution of dietetics in dermatology



Chapter 3
The most common digestive diseases: the role of nutrition

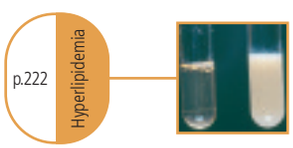


Chapter 4
Nutrition of dogs with liver disease

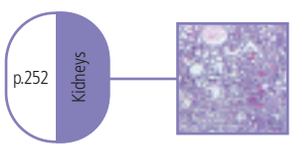


Chapter 5
The role of nutrition in the pathogenesis and the management of exocrine pancreatic disorders

Chapter 6
Diabetes mellitus: nutritional strategies



Chapter 7
Canine hyperlipidemia: causes and nutritional management



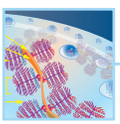
Chapter 8
Chronic renal disease: the importance of nutrition

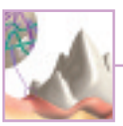
Chapter 9
Nutritional management of canine urolithiasis

Urolithiasis p.284

Chapter 10
Cardiovascular diseases: nutritional modulation

Heart p.316

Chapter 11
Main nutritional imbalances ~~implied~~ in osteoarticular diseases

Skeleton p.348

Chapter 12
Canine nutrition and oral health

Oral Health p.388

Chapter 13
Nutritional status of dogs with cancer: dietetic evaluation and recommendations

Cancer/Cachexia p.408

Chapter 14
Critical care nutrition of dogs

Critical care p.426

Chapter 15
The social role of food and behavioral pathologies in the dog

Behavior p.452

Chapter 16
Integration of nutrition into clinical practice

Clinical practice p.462

Index
p.478

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Obesity: epidemiology, pathophysiology and management of the obese dog

1 - Canine obesity 5
2 - Treatments for obese animals 27
3 - Clinical food 39
4 - Post-diet monitoring 44
5 - Prevention of obesity 45

Owners' questions . . . . . 46`
Questions veterinarians should ask themselves 47
References 48
Examples of home-prepared diets for the treatment of obesity 54
Royal Canin Nutritional Information 56

Obesity: epidemiology, pathophysiology and management of the obese dog

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Canine obesity is a condition that leads to serious alterations in various bodily functions and limits the longevity of the animal. It is the most common nutrition-related canine disease in industrial countries, but its treatment is effective. The prevention of obesity demands nutritional discipline throughout the life of the animal and specifically at certain key times when the risk of becoming overweight is increased. The treatment of canine obesity is complicated by various problems, including a lack of awareness among owners, who often fail to recognize or minimize their animal's obesity. Without the total cooperation of owners, it will be impossible to obtain weight loss in the dog. The veterinarian will therefore first have to convince the owner before implementing weight loss protocols and obese animal care.

While various stages or degrees of weight gain can be distinguished in dogs, in this summary we use the term "obesity" to qualify any pathological weight gain. We strive to define obesity, to explain its pathogenesis and related problems, its evaluation, the various types of diet and the practical treatment of this disease.

1 - Canine obesity

► Definition

Obesity is a "pathological condition characterized by excessive fat deposition leading to modifications to various bodily functions." The World Health Organization *(WHO, 1997)* goes even further, defining human obesity as "excessive fat leading to harmful consequences for health." Although this definition appears fairly brutal, it can certainly be extrapolated to companion animals. At a quantitative level, obesity is described as being 15% overweight as compared to optimal weight. This somewhat reduced approach is no longer used as such; it has been replaced by body mass indices, which determine an optimal weight range for men and women of a given size. No such tool exists for dogs. A "mathematical" definition of obesity is of little use *(Markwell & Butterwick, 1994)* as it requires knowledge of the healthy weight, which, even for purebreed dogs is not always easy to determine. The ideal situation is to know the weight of the adult dog before it became obese. This body weight is used as a benchmark in both the initial and follow-up evaluations of the animal. In some cases, the optimal body weight is unknown as the animal has always been overweight, even during the growth phase.

© Alex German

Body condition scores are practical, specific tools that have been developed for veterinarians (see below). A dog is obese when its body condition score is more than 3 on a 5-grade scale.

► Epidemiology of obesity

> Frequency

TABLE 1 - FREQUENCY OF OBESITY IN THE CANINE POPULATION

References	Country	Sampling size (number of dogs)	Estimation
Krook et al, 1960	Sweden	10993	9%
Mason, 1970	UK	1000	28%
Edney, 1974	UK	1134	34%
Meyer et al, 1978	Germany	266	30%
Edney & Smith, 1986	UK	8268	24%
Armstrong & Lund, 1996	USA	23000	25%
Lund et al, 1999	USA	30517	28%
Royal Canin, survey (2000)	France UK Spain Germany	400 veterinarian respondents	20-22%
Jerico & Scheffer, 2002	Brazil	648	17%
Robertson, 2003	Australia	860	25%

In the most recent studies, the frequency of obesity in dogs presented at consultation varies from 24% to 44% depending on the author **(Table 1)**, the epidemiological study location and the predefined criteria *(Mason, 1970; Meyer et al, 1978; Edney & Smith, 1986; Armstrong & Lund, 1996; Robertson, 2003)*.

These data do not always reflect the local situation. Some studies continue to serve as a reference despite being over 30 years old, while others have been conducted in a limited number of veterinary clinics and do not necessarily reflect differences between countries. Nevertheless, all studies conducted in veterinary consulting rooms in industrialized countries and large cities show a prevalence of obese dogs of at least 20%. A telephone survey conducted among 400 veterinarians in four European countries (France, Germany, Spain and the United Kingdom) in May 2000 showed that these veterinarians estimate the proportion of obese dogs (where obese is associated with the necessity of implementing a low calorie diet) to be 20% *(Royal Canin, 2000)*.

In conclusion, the epidemiological data does not prove that the frequency of obesity has been increasing for 10 years, but obesity is still a major medical problem in the canine population.

> Risk factors (Table 2)

TABLE 2 - OBESITY RISK FACTORS

- Predisposed breeds
- Genetic factors
- Age
- Sex
- Neutering
- Contraceptive treatments
- Obesity caused by endocrine disease
- Obesity caused by medications
- Sedentary and lack of exercise
- Food not adapted to the energy requirement of the individual
- Social aspect of the food
- The individual dog

• *Breed*

Breed is an obesity risk factor in the canine species but the predisposed breeds vary depending on the author and the study. For example, in the United Kingdom the Labrador Retriever, the Cairn Terrier, the Collie, the Basset Hound, the Cavalier King Charles Spaniel, the Cocker Spaniel, the longhaired Dachshund and the Beagle were predisposed and often cited in the 1980s *(Edney & Smith, 1986)*.

These breeds were very popular in the United Kingdom when the study was conducted. The breeds that suffer may vary depending on the country and certain other factors. Krook et al *(1960)* report that the breeds predisposed to obesity in Sweden were the Rottweiler, the Saint Bernard, the Collie, the Newfoundland, the Scottish terrier and the Chow Chow. Conversely, some breeds – sighthounds and sheepdogs – appear to be more resistant. In a study conducted by Meyer et al *(1978)* in Germany, German Shepherds, Poodles and Boxers were frequently obese. It is therefore neces-

FIGURE 1 - COMPARISON OF THE DISTRIBUTION OF LEAN AND FAT MASS IN SEVERAL LARGE-BREED DOGS

(Royal Canin, 2003-2004)

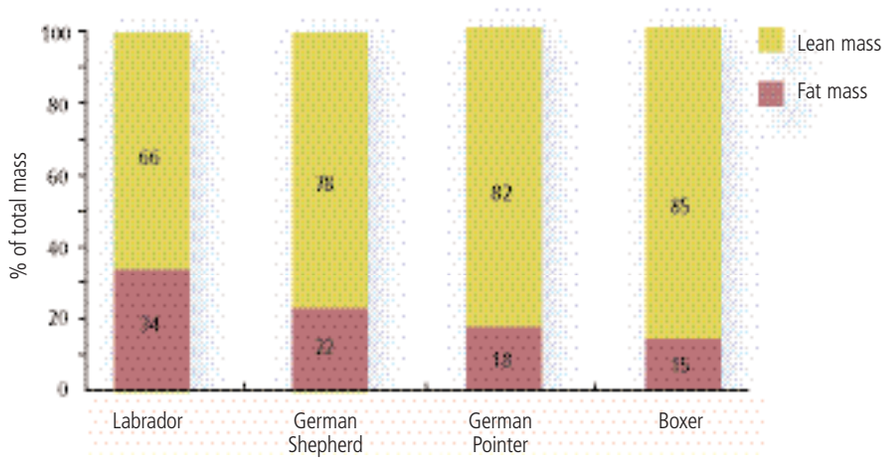

TABLE 3 - CANINE BREEDS PREDISPOSED TO OBESITY
(From Edney & Smith, 1986)

Small	Medium	Large	Giant
Cairn Terrier Dachshund Cavalier King Charles Scottish Terrier	Beagle Cocker Spaniel Basset Hound	Labrador Retriever Collie Golden Retriever Rottweiler	Bernese Mountain Dog Newfoundland Saint Bernard

Conversely, the German Shepherd, the Greyhound, the Yorkshire Terrier, and the Doberman are among the breeds least predisposed to obesity.

The Bernese Mountain Dog is one of the giant breeds predisposed to developing obesity.

sary to qualify this idea of breed predisposition, even though practitioners do state that they encounter more obese Labrador Retrievers than obese sighthounds. Obesity also appears to be a problem in other breeds **(Table 3)**. The type of selection may influence the physical condition (and the weight) of dogs, for example, by substituting beauty or size criteria for working aptitude. Breed predispositions are partly related to genetic factors, more specifically in the fat mass/lean mass ratio that determines the maintenance energy requirement **(Figure 1)**.

Not all breeds are the same when it comes to nutritional risk during growth. The energy excess predisposes small-breed dogs to obesity, whereas the major risk among large breeds is osteoarticular complaints *(Grandjean & Paragon, 1996)*. The association of articular problems and obesity is frequent at the end of the growth phase of large breeds.

The Collie is one of the medium breeds most at risk from obesity.
The Labrador Retriever is one of the large breeds most at risk from obesity.

- ***Genetic factors***

The purpose of a complex system of genetically determined factors is to maintain balance between dietary intake and energy expenditure. These regulatory mechanisms are particularly well adapted to helping wild species survive in times of famine. Nevertheless, when food is abundant, these factors do not appear to maintain a balance between intake and expenditure in domesticated animals in a confined environment, which has led to an increase in the obese population. Whatever the case may be, some individuals become obese while others living in the same conditions maintain their ideal weight. So it is not easy to distinguish between environmental factors in a wide sense and genetic predisposition *(Johnson, 2000)*.

Genetic factors leading to obesity in dogs are still poorly understood. It is however, undeniable that these factors play a role since obesity is particularly common in selected breeds of dogs and in certain lines. The polygenic nature of obesity is undisputed *(Schalling et al, 1999)*.

The Cairn Terrier and the King Charles Spaniel are among the small dogs predisposed to developing obesity.

- ***Age***

The frequency of obesity increases with the age of the dog *(Robertson, 2003)* and the age of the owner *(Edney & Smith, 1986)*. It is found in only 6% of puppies age 9-12 months, but in 40% of adult individuals *(Glickman et al, 1995)*. The avera-


© Dovicat

An overweight puppy is predisposed to obesity in adulthood.

ge age of diagnosis varies from 5 to 8 years. Less than 20% of dogs age 4 years and younger are obese, although that rises to over 50% in the 7-8-year category and to almost 70% for the 9-years-and-older category *(Meyer et al, 1978)* **(Table 4)**. In very old dogs there is a contradiction between the figures cited by Mason *(1970)* and more recent data that shows that the frequency of obesity declines in old dogs age over 12 years *(Armstrong & Lund, 1996)*.

Obese bitches between 9 and 12 months are 1.5 times more likely to become obese adults than lean bitches during growth *(Glickman et al, 1995)*. By way of comparison, in humans, 80% of obese adolescents become obese adults and they are also fatter than those adults that become obese without having being overweight during growth *(Abraham & Nordseick, 1960)*. These data are confirmed by epidemiological studies *(Eriksson et al, 2003)*.

- ***Sex***

The various data presented in **Table 5** show that females are more predisposed to obesity than males. In certain studies, females represent more than 60% of obese dogs *(Krook et al, 1960; Jerico & Scheffer, 2002)*. Furthermore, Glickman et al *(1995)* have observed an obesity percentage of 40% in a study of 289 adult dogs.

TABLE 4 - EFFECT OF AGE ON THE FREQUENCY OF OBESITY: % OF OBESE DOGS IN THE VARIOUS AGE CLASSES

Study location	Age (in years)	1	2	3	4	5	6	7	8	9	10	11	12 +
UK	*Mason, 1970*	16.2				33.1			37.2				40.5
Germany	*Meyer et al, 1978*	6.1		19		29.9		52.6		66.7			
USA	*Armstrong & Lund, 1996*	19				41	43	44	45	46	42	43	<35

TABLE 5 - EFFECTS OF SEX AND NEUTERING ON THE FREQUENCY OF OBESITY (%)

References	Intact males	Neutered males	Males (total)	Intact females	Neutered females	Females (total)
Krook et al, 1960			38%			62%
Mason, 1970			23%			32%
Meyer et al, 1978			42%			58%
Adapted from Edney Smith, 1986 (1)	17%	38%		22%	45%	
Jerico & Scheffer, 2002 (2)	5%			63%		
Robertson, 2003 (3)			26%			25%

(1) The percentages in the sampling are:
- intact males: 46%; neutered males: 4%
- intact females: 29%; neutered females: 17%
- dogs whose sexual status is not identified: 4%
(2) The percentage of neutered males and females is 33%.
(3) Frequency of obesity in neutered animals (males and females together): 31.7% versus 14.8% in intact animals.

- ***Neutering***

Gonadectomy increases the frequency of obesity in males and especially female dogs *(Anderson, 1973; Edney, 1974; Karczewski et al, 1987; Miyake et al, 1988; Robertson, 2003)*. Edney and Smith *(1986)* have observed that neutered bitches were twice as likely to be obese compared with intact bitches. A more recent study shows that this is also true for male dogs. The frequency of obesity is 32% and 15% in neutered and unneutered animals, respectively, males and females together *(Robertson, 2003)*. The sexual hormones are not prime regulators of metabolism, but they nevertheless have a direct impact on body weight at the level of the central nervous system, or indirectly by modifying cellular metabolism. Moreover, estrogens exercise an inhibitor effect on feeding. Dietary consumption thus varies in the female's sexual cycle. It is minimal during estrus, increases during metestrus and is maximal during anestrus *(Houpt et al, 1979)*.


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Various studies show that females are more predisposed to obesity than males.

The influence of premature neutering on the incidence of obesity is not well known. An American epidemiological study reports that the frequency of obesity is lower in a population of dogs neutered before 5.5 months than in animals neutered between 5.5 and 12 months. The authors also report an overall incidence of obesity of 27% in the neutered population *(Spain et al, 2004)*.

ESTIMATION OF THE SCALE OF NEUTERING IN THE CANINE POPULATION IN THE UNITED STATES
(From Mahlow, 1999)

Canine population	Percent neutered
Total population	26.9%
Males	22.6%
Females	31.4%

There are great disparities between countries. In Japan and the United States, around 30% of dogs are neutered, males and females together. This percentage is much lower in Europe, but precise data are unavailable.

While it is difficult to clarify the link between neutering and obesity due to its multifactorial nature, several explanations may be considered. The first point to consider is the variation of food ingestion during the sexual cycle as stated above and the inhibitor effect of estrogens on food consumption. It is logical to suppose that this inhibitor effect is no longer exercised in neutered females. For a period of three months following neutering, four female Beagles consumed 20% more food than the unneutered control animals and their weight increased significantly *(Houpt et al, 1979)*. Another study addressed this problem by measuring not only the weight gain in the neutered females, but also the quantities of energy needed to maintain a body weight considered ideal for Beagle bitches. A 30% reduction in daily energy intake compared with intake before neutering has been shown to be necessary to maintain bitches at their ideal weight in the weeks following an ovario-hysterectomy *(Jeusette et al, 2004a)*. This level of energy restriction appears to be high, but one of the explanations advanced is that the Beagle is particularly predisposed to obesity. Neutering also leads to a reduction in spontaneous activity, especially among males. This last point is difficult to quantify in the breeding kennel.

The weight gain after neutering may accordingly be prevented with strict dietary measures and regular exercise. In a study on German Shepherds trained on an obstacle course and used as patrol dogs, no difference in body weight was apparent between neutered and unneutered bitches, although they all received the same quantity of food *(Le Roux, 1983)*. This fact demonstrates that the maintenance of regular exercise after neutering can prevent weight gain.

The scale of neutering in the canine population may explain the increase in the frequency of obesity since the first epidemiological studies were reported in 1960. Moreover, as the practice of neutering becomes more and more widespread, we must expect an increase in the frequency of obesity in the coming years, particularly in those countries that have yet to be affected by obesity.

• *Contraceptive treatments*

Contraceptive treatment with medroxyprogesterone acetate led to a significant weight gain in 17.4% of the bitches treated during a clinical trial. The authors reported bulimia and obesity in some animals *(Picavet & Le Bobinnec, 1994)*. The increase in weight following this contraceptive treatment is well documented in the bitch *(Harel et al, 1996)*.

• *Obesity and endocrine diseases*

Obesity may be associated with certain endocrine diseases, such as diabetes mellitus *(Krook et al, 1960; Mattheeuws et al, 1984a; Wolfscheimer, 1990; Ford et al, 1993; Hoenig, 2002)* and hypothyroidism *(Kaelin et al, 1986; Forbes & White, 1987; Roche et al, 1991; Ford et al, 1993; Panciera, 1994, 2001; Dixon et al, 1999)*. According to the authors, at least 40% of bitches suffering from these conditions are obese. Obesity may also be secondary to hyperadrenocorticism. In a clinical study, five dogs presented fat deposits typical of obesity and different from a pendulous abdomen *(Spearman & Little, 1978)*.

• *Obesity secondary to medication*

Some medications may lead to hyperphagia and weight gain, particularly antiepileptics and glucocorticoids.

• *Sedentary lifestyle and lack of exercise*

Lack of exercise is a primary factor in the development of obesity: the prevalence of obesity declines in proportion to the duration of daily exercise. It is not possible to establish whether obesity is responsible for restricting exercise or whether the lack of exercise constitutes one of the factors responsible for obesity *(Robertson, 2003)*. The duration of daily exercise is a more precise criteria than the type of habitat when evaluating energy expenditure.

Generally speaking, there are more obese animals among dogs living in an apartment than among dogs living outdoors (31% versus 23%) *(Robertson, 2003)*. Nevertheless, it would be a mistake to believe that access to an open play space systematically increases energy expenditure. Some animals that live in a confined environment walk for several hours a week, while others that have access to a garden are content with a few minutes a day.

German Shepherd
Regular physical exercise is an effective way of preventing obesity.

• *Type of food*

The following dietary habits have been clearly identified to contribute to obesity: dietary intake that does not take account of the energy requirements ("the dog eats everything it's given") and supplements in the form of treats or snacks not accounted for in the energy intake. Highly palatable food high in easily assimilated fats and carbohydrates also predispose a dog to obesity. An undeniable risk factor is *ad libitum* feeding leading to overconsumption of energy.


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Dachshund
Many small dogs spend the majority of their time in the home. In Asia, 65% of small dogs have a 100% indoor lifestyle: these dogs do not go outside and use a litter tray in the same way as a cat does.

Food can be highly palatable due to the presence of aromas or large quantities of fat. Foods with the highest fat content are also those with the highest energy concentration. Although it tolerates and utilizes fats as sources of energy, the dog is also able to immediately store them in the form of abdominal fats.

Altering the nutrient composition of a diet by an 8% increase in fat, without modifying the total energy intake resulted in a significant increase in the deposition of abdominal fat without modifying body weight in a group of bitches *(Kim et al, 2003)*. In humans the fat intake is the main determination in the development of obesity *(Garaulet et al, 2001)*. In dogs, highly digestible food – low in dietary fiber and with a very high energy concentration – may also be responsible for weight gain. Various treats, leftovers and nutritional supplements are additional risk factors *(Kienzle et al, 1998; Robertson, 2003)*.

There is disagreement about the influence of home-prepared diets on the development of canine obesity *(Lewis, 1978)*. The underlying idea is that the dogs that receive home-prepared rations will most often be compensated with treats and will receive larger quantities of food. This can only be defended in countries where dogs continue to be fed in the traditional way, with home-prepared rations or leftovers. In North America, 95% of animals are given commercial food and yet canine obesity is at least as widespread as in some European countries *(Lund et al, 1999)*.


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Female Auvergne Pointing Dog
Hypothyroidism is often associated with obesity.

An epidemiological study has not shown the particular influence of a type of food (wet versus dry) on the frequency of obesity *(Roberson, 2003)*.

Contrary to some preconceived ideas, dividing the daily diet into several meals does not lead to an increase in the frequency of obesity. In epidemiological studies obese dogs are generally fed once a day *(Kienzle et al, 1998; Robertson, 2003)*. It is clearly important not to confuse the division of the appropriate daily ration with the multiplication of the additional treats.

• *Social aspect of the food*

The place of food in the relationship between the human and the dog plays a major role in the development of obesity.

Among the sociological factors, a study conducted in Germany *(Kienzle et al, 1998)* reported that the relationship between the human and the obese dog is characterized by excessive anthropomorphical behavior. For example, owners of obese animals talk to their dog more, allow their dog to lie on their bed, are not concerned about zoonoses and consider exercise, work and the protector function of their dog to be of minor importance. So it is unsurprising that obese animals are given meals or treats more often than animals of normal body weight. This study confirms that the owners are often obese (54% versus 28% of owners of dogs of normal weight), as stated above *(Mason, 1970; Kronfeld, 1988)* and fairly inactive. The owners of obese animals translate every appeal by the animal as being an appeal for food. These owners clearly have little concern for balancing the diet.


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Saint Bernard puppies
Ad libitum feeding must be advised against as most dogs are unable to regulate their food consumption. It is better to feed puppies of a given litter separately during the weaning stage.

Some of these aspects are very familiar to practitioners *(Kienzle et al, 1998)*.
The data presented above may appear to be fairly discouraging at first glance and they do not clearly differentiate the simple correlation (between the weight of the owner and the weight of the dog) and the causes of obesity. They are however, very useful for developing methods of preventing and treating canine obesity. They help focus attention on environmental factors in the wider sense, at first glance external to the animal itself but of primary importance to the health of the animal.

The owners of obese dogs may also interpret bulimia as a sign of good health *(Kronfeld, 1988)* and excess weight as a sign of beauty in some breeds. Some owners also make the mistake of using foods as a palliative treatment to prevent unmonitored animals from becoming bored or destroying things. Lastly, for a dog living in a family environment, receiving food from children (as a reward or in a game) can become a bad habit. Multiple pet households may pose problems with respect to individual food consumption. Nevertheless, contrary to a predetermined idea, the frequency of obesity is greater in households with only one dog *(Kienzle et al, 1998; Robertson, 2003)*.

In conclusion, it appears that the energy requirements of dogs are often incorrectly estimated and accordingly, in many situations energy intake can be excessive. It is up to the clinician to determine whether the obesity is primary or secondary so as to establish the subsequent treatment.

Individual rationing is necessary in a group of several dogs,even if they are of the same breed.

► Pathology associated with obesity

Until the end of the 1980s there was little clinical data on the conditions associated with obesity in dogs. Some epidemiological studies conducted on humans have been extrapolated to the dog. However, the simple extrapolation of human data on diabetes mellitus, hypertension, etc. to dogs is not satisfactory. It is necessary to study clinical data on obese dogs. A survey is given in **Table 6**.

TABLE 6 - PATHOLOGY ASSOCIATED WITH CANINE OBESITY

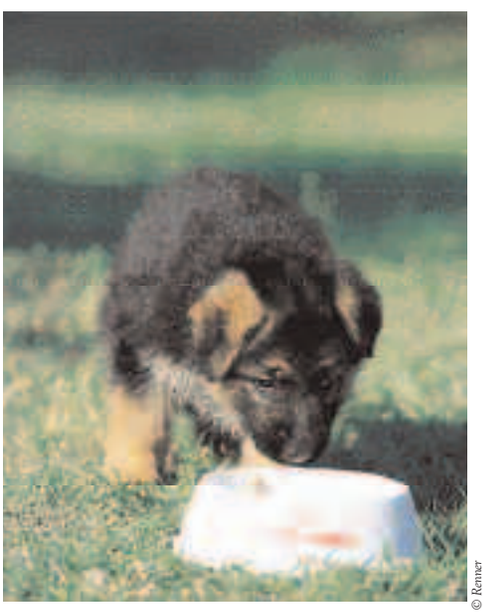
Proven factors	Disputed factors
Reduction in longevity	
Osteoarticular diseases	
Intolerance to effort	Incontinence and urinary calculi
Cardiorespiratory problems	Reproductive problems
Diabetes mellitus	
Reduced immunity	
Hyperlipidemia and dyslipidemia	
Dystocia	
Mammary tumors	
Malassezia dermatitis	
Difficulties in using exploratory techniques	Other tumors
Surgical inconveniences	Other dermatoses
Modifications in the thyroid function	

> Reduction in longevity

It has been clearly shown that obesity leads to a reduction in the longevity of dogs. Kealy et al *(2002)* followed a group of 48 Labradors, half of which received limited quantities of food throughout their life. From the start a group of dogs were fed *ad libitum* with a growth food and a second group received 75% of the energy intake of the first group. The body weight of all the animals in the *ad libitum* group as well as the group that received a lower energy intake, increased until age 3 years and 4 months, reaching the average values 35 kg and 27 kg respectively. At this point two dietary modifications were introduced: a food with a lower energy concentration was given to all dogs and the intake of the *ad libitum* group was restricted (provision of a set quantity of food), while the second group continued to receive 25% less energy.

The modification of the experimental protocol induced a reduction in the body weight of all dogs, which was subsequently stabilized. At 5 years of age, the average difference between the two groups of dogs was 10 kg. At 8 years of age, the body index was 6.8/9 for the dogs eating the most food and 4.5/9 for the control group dogs (1: cachexia; 9 : massively obesity).

At age 12 years the average energy intake of the control group dogs and the dogs receiving 75% of intake were 1745 kcal and 1352 kcal (around 127 kcal/kg and 115 kcal/kg of body weight (BW) $^{0.75}$) respectively. The dogs of the second group weighed on average 26% less than those of the control group. The dietary restriction helped prolong longevity to 13 years rather than 11.2 years in the control group. The energy restriction helped slow down the development of chronic diseases and more specifically arthrosis. Furthermore, different metabolic parameters (insulin, glucose, blood lipids) were also favorably influenced in the dogs receiving 25% less energy. The above study is extremely important in terms of its contribution to science: it confirms an undeniable relationship between energy intake and longevity in dogs. It constitutes an argument against *ad libitum* feeding and provides valuable data showing the consequences of obesity for the development of osteoarticular diseases.

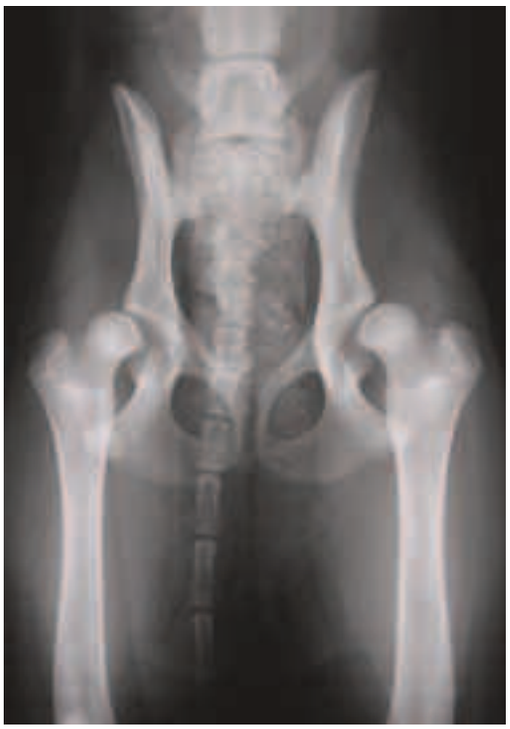


© Renner

The food consumption of large-breed puppies must be monitored from a very early age.

The positive effect of energy restriction on life expectancy has also been observed in humans. Individuals presenting with an average body mass index live longer than overweight individuals *(Manson et al, 1987)*.

> Osteoarticular conditions



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Hip dysplasia
Major dysplasic lesions at left with subluxation and arthrosis. Obesity is a cause or an aggravator of hip dysplasia. Energy restriction helps slow down the appearance and development of the different forms of osteoarthritis.

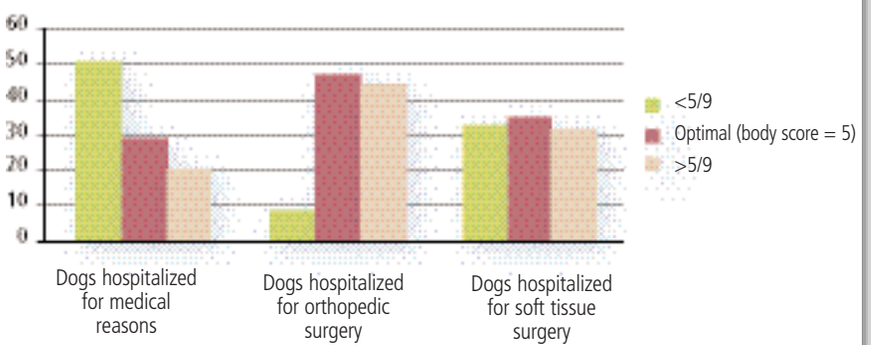
Obesity predisposes dogs of all ages to osteoarticular pathology **(Figure 2 and Chapter 11)**. Obesity associated with over-consumption of food in large-breed puppies during the growth phase leads to the development of various orthopedic complaints or exaccerbated hip dysplasia *(Kealy et al, 1992)*. The symptoms of osteoarticular disease associated with obesity are generally observed after 6 months of age. In many cases, the lesions are irreversible.

In the above study of Kealy et al, the radiological signs of osteoarthritis of the coxo-femoral joint have been studied in Labradors from 4 months of age. They gradually became more common in the Labradors fed *ad libitum* compared with the dogs whose energy consumption was limited (52% versus 13% at 5 years of age). In the Labradors 8 years and over, the most common chronic disease was articular arthrosis affecting several joints (shoulder, elbow, hip, knee), with 90% of the Labradors afflicted *(Kealy et al, 1997, 2000, 2002)*. The study reported that the arthrosis was more severe in the group initially fed *ad libitum*.

Other orthopedic conditions are common in obese dogs *(Janicki & Sendecka, 1991)*. Torn cruciate ligaments and fractures of the humeral condyle were the subject of a wide epidemiological study on 854 Cocker Spaniels. The dogs afflicted with one of two orthopedic complaints presented a body weight greater than that of the healthy population. Interestingly, the reverse was true of those dogs with disc disease *(Brown et al, 1996)*.

The dogs suffering from osteoarticular diseases are caught in a vicious circle: the animal tends to reduce its activity, which leads to overfeeding and overweight if the energy intake is not adjusted. Furthermore, the observation of an articular condition (a torn cruciate ligament, for example) is certainly a major indication of the need to reduce the dog's weight, but it may also frustrate this process by making exercise impossible.

FIGURE 2 - RELATIONSHIP BETWEEN ORTHOPEDIC PATHOLOGY AND OBESITY: SPREAD OF HOSPITALIZED DOGS BASED ON THEIR BODY SCORE: SCALE FROM 1 (CACHEXIA) TO 9 (PROVEN OBESITY)
(Lhoest et al, 2004)



The class of overweight dogs (score higher than 5 out of 9) is overrepresented in the group of dogs presented due to orthopedic problems.

> Intolerance to effort and cardiorespiratory complaints

The principal symptoms associated with obesity are intolerance to effort *(De Rick & De Schepper, 1980)* and respiratory problems *(Ettinger, 1983)*. There is also a link between the frequency of tracheal collapse and obesity, although the correlation with other factors, such as breed, is greater *(O'Brien et al, 1966; White & Williams, 1994)*.

A field study has shown that when weight loss is achieved, the owner inevitably observes a change in the dog's behavior, whereby the dog is more alert and playful (unpublished Royal Canin data 2001, obtained on 13 dogs suffering from obesity for over a year and followed for at least 10 months).

The weight increase in the dog is accompanied by an increase in heart rhythm, ventricle volume, blood pressure and plasma volume *(Rocchini et al, 1987; Mizelle et al, 1994; Massabuau et al, 1997)*. The correlation between obesity and hypertension is however, controversial. There was a link between age and the increase in arterial blood pressure in dogs, but not between obesity and hypertension *(Bodey & Michell, 1996)*. Dogs have however been used in experiments to study the pathogenesis of hypertension induced by the increase in body weight and the associated insulin resistance *(Verwaerde et al, 1997; Truett et al, 1998)*.

The frequency of cardiovascular diseases increases with obesity. Some clinical studies report diseases including thrombosis of the portal vein *(Van Winkle & Bruce, 1993)*, hypoxia of the myocardium *(Baba & Arakana, 1984)* and valvular endocarditis *(Valtonen & Oksanen, 1972; Edney & Smith, 1986)*.

English Bulldog
Obese dogs are more prone to heatstroke when the ambient temperature rises compared with dogs that are not obese.

© Lanceau

The cardiovascular effects described above are also significant for nephrologists *(Alonso-Galicia et al, 1995; Joles, 1998)*. Can hypertension lead to modifications in renal function over time? A clinical study has shown that in dogs overfed for six months with a diet rich in animal fat, weight gain (58% heavier than the control group dogs) was accompanied by an increase in the weight of the kidneys (31% heavier), an increase in arterial pressure, glomerular filtration rate, renal blood flow and various renal histological lesions. The authors concluded that the lesions and the anomalies observed could be more severe in the case of prolonged obesity *(Henegar et al, 2001)*. This study also suggested that the negative effects may be due not only to the influence of dietary fats but also to the composition of the fat.

> Diabetes mellitus

Diabetic dogs may present with hyperphagia leading to weight gain at an early stage. The correlations between obesity and glucose metabolism are complex, but it is clear that obesity leads to profound changes in the metabolism of glucose and the secretion of insulin *(Mattheeuws et al, 1984a, b)*. It has been shown that the secretion of insulin, insulinemia and glucose intolerance increase proportionally to the degree of obesity. These changes are caused by a state of insulin resistance, one of the elements of which is chronic inflammation *(Festa et al, 2001)*. The model of the dog overfed with a diet rich in fats has also been widely used to study the syndrome of insulin resistance. Indeed, when the dog's obesity is induced by feeding *ad libitum* with a diet rich in fats, insulin resistance will gradually develop in relation to an increase in adiposity *(Rocchini et al, 1987; Bailhache et al, 2003a; Kim et al, 2003)* and an increase in the production of adipocyte cytokines *(Gayet et al, 2002, 2003b, 2004a, b; Jeusette et al, 2004b)*.

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It has not been clearly established that obesity is a risk factor in the development of diabetes mellitus in dogs. Nevertheless, the current increase in the incidence of diabetes mellitus in dogs could lead to that supposition (Hoenig, 2002).

> Reduction in immunity

Obese animals or animals fed a diet with a high fat content are less resistant to infection than animals fed a balanced diet *(Newberne, 1966, 1973; Williams & Newberne, 1971; Fiser et al, 1972)*.

> Hyperlipidemia and dyslipidemia

According to *Joshua (1970)*, fatty infiltration of the liver can be observed in obese dogs. An epidemiological study also shows that obesity increases the risk of acute hemorrhagic pancreatitis *(Hess et al, 1999)*. Some results show profound disruptions to lipid metabolism. Obese dogs present with increased lipid plasma concentrations – cholesterol, triglycerides and phospholipids – without exceeding the reference values for these parameters *(Chikamune et al 1995; Bailhache et al, 2003b; Diez et al, 2004)*. An increase in the contents of non-esterified fatty acids and lipoprotein modifications (increase in triglycerides in the VLDL and HDL, reduction in HDL cholesterol and increase in VLDL cholesterol) *(Bailhache et al, 2003a, b)* have also been observed. The consequences of these well-known modifications in humans must however, still be evaluated in dogs.

> Incontinence and urinary calculi

The hypothesis that there is a correlation between obesity and some forms of urinary incontinence, primarily in neutered bitches, has been suggested, but remains controversial *(Gregory, 1994)*. Some bitches become incontinent after becoming obese and weight loss helps solve the problem. In some cases, incontinence will be observed again in bitches that have regained weight after losing it. One hypothesis that has been advanced is that the presence of retroperitoneal fat can exercise mechanical effects on the bitch's urinary system *(Holt, 1987)*. The fact that neutered females are twice as likely to be obese compared with intact females must also be taken into account. This could explain the correlation between urinary incontinence and neutering. The debate is far from over.

Overweight dogs will also be more likely to develop urinary calcium oxalate calculi *(Lekcharoensuk et al, 2000)*.

> Reproduction problems

The correlation between obesity and reproductive problems is not clear, although it is accepted that excess fat may lead to dystocia *(Edney & Smith, 1986; Sonnenschein et al, 1991; Glickman et al, 1995)*.

> Cancers

The correlation between obesity and some cancers (breast, uterus, colon and prostate) is well established in humans *(National Institute of Health, 1998)*. Conversely, the lack of clinical data means such a link cannot be made in dogs with respect to anything but mammary tumors.

The first data were published in 1991. According to Sonnenschein et al, obesity or the consumption of a diet high in fat one year prior to the diagnosis does not increase the risk of mammary cancer in adult bitches, neutered or intact. These results have been contradicted by Perez Alenza et al *(1998, 2000)*.

On the other hand, the risk in neutered females was reduced in individuals that were slim between 9 and 12 months *(Sonnenschein et al, 1991)* and increased in females at the age of one year *(Perez Alenza, 1998, 2000)*. On the whole, the authors conclude that the condition of obesity in juvenile animals certainly plays a role in the predisposition to mammary tumors in adulthood.

A retrospective study has not confirmed these results *(Philibert et al, 2003)*. First of all, it was not possible to analyze the effect of early onset obesity on the development of mammary tumors. Neither did the authors report any correlation between obesity and the development of tumors, or

between obesity and the period of survival (10 months for obese bitches versus 14 months for others).

> Dermatological disease

The many reviews that deal with canine obesity often mention that skin problems are more common in obese dogs than in healthy dogs. Paradoxically, to our knowledge there have been few studies to demonstrate this fact. In a clinical study on 29 dogs suffering from dermatitis due to Malassezia pachydermatis, obesity was identified as a significant risk factor for the development of this dermatitis *(Pak-Son et al, 1999)*.

According to *Edney & Smith (1986)*, the correlation between skin problems and obesity is not clear.

> Exploratory techniques

It is more difficult to use some exploratory techniques on obese dogs than on healthy dogs: auscultation, palpation or radiography are complicated by the excess subcutaneous or abdominal fat *(Joshua, 1970)*.

> Surgical inconvenience

The risks associated with anesthesia are greater in obese dogs, but vary depending on the type of anesthetic used. The major risks are overdosing and lengthening of the period of recovery due to the storage of lipid soluble anesthetics in body fat. The other risks are associated with concurrent diseases that are common in obese patients, including circulatory, respiratory and hepatic problems *(Clutton, 1988)*. In a controlled study on the surgical times in bitches undergoing ovariectomy, the surgical time was significantly – on average 30% – longer among obese bitches (*Van Goethem et al, 2003)*.

In obese humans the surgical risk is increased due to various anomalies such as disruptions of the respiratory system, (reduction in respiratory capacity, hypoventilation), circulatory system (hypertension and cardiomegaly) or other functions (difficulties inserting tubes or maintaining water balance). Post-surgical complications are also more common in obese patients *(Fisher et al, 1975)*.

German Shepherd bitch and puppies
In humans, it has been shown that obesity reduces fertility (Pasquali et al, 2003). This may also be the case in dogs.

REVERSIBILITY OF PROBLEMS

- Intolerance to effort, inactivity, orthopedic and respiratory problems reported by owners are generally attenuated or may even disappear completely after weight loss *(Gentry, 1993; Diez et al, 2002, 2004)*.
- The same is true for some heart rhythm problems *(Baba & Arakana, 1984)*.
- Urinary incontinence may also be reduced or disappear completely after a diet *(Holt, 1987)*.
- Recent studies have shown the reversibility of the main metabolic complaints, particularly insulin resistance and disruptions to lipid metabolism *(Gayet et al, 2003a, 2004a, b; Jeusette et al, 2004b)*.

> Modifications in thyroid function

Thyroid function has been explored in obese dogs in comparison to a group of healthy dogs and in the course of a weight loss protocol. The concentrations of some thyroid hormones were higher in obese dogs, and they decline during the weight loss protocol. The authors concluded that obesity and the restriction of energy alter thyroid function but that these modifications should not alter the interpretation of clinical trials *(Daminet et al, 2003)*.

► Pathophysiology of obesity

In simple terms, obesity is the consequence of energy imbalance where intake exceeds expenditure for a variable period of time, which leads to a positive balance. There are a huge number of factors that can cause this situation and the interaction between these factors rather than the action of any one of them is felt to be responsible for obesity.

> Energy balance

• *The principles of energy balance*

The fundamental principal of energy balance is:
Modifications of reserves = energy intake – energy expenditure
A positive energy balance is the consequence of energy intake exceeding expenditure, and conversely, the balance is negative when expenditure exceeds intake. In normal conditions the energy balance oscillates meal after meal, day after day, week after week, without changing body weight and energy reserves in the long term. Many physiological mechanisms play a role in adapting intake to expenditure and expenditure to intake so as to maintain a stable body weight in the long term. If the energy balance is positive, expenditure increases (pointless cycles, uncoupling proteins, etc) and conversely, when the balance is negative, the body tends to reduce its expenditure (which contributes to the resistance to weight loss).

• *Energy intake*

The total energy intake provides all the food ingested, digested and metabolized by the body. **Table 7** shows the energy intake via different nutrients that provide energy. The coefficients used are derived from Atwater's and involve some risk of error, since they take account of only average digestibility. Fat provide more energy per unit of weight than digestible carbohydrate or protein. In carnivores, dietary fiber is not very digestible and energy contribution is negligible. It should

TABLE 7 - ENERGY INTAKE OF THE VARIOUS CATEGORIES OF NUTRIENTS
(Martin, 2001)

	1 g of carbohydrate	1 g of protein	1 g of fat
Gross energy	4.2 kcal	5.4 kcal	9.4 kcal
Digestible energy	3.7 kcal (88%)	4.8 kcal (89%)	8.5 kcal (90%)
Metabolizable energy	3.5 kcal (83%)	3.5 kcal (65%)	8.5 kcal (90%)
Real energy value (net energy)	3.2 kcal (76%)	2.2 kcal (41%)	8.2 kcal (87%)

Efficiencies expressed in % are calculated on the basis of gross energy.

however be noted that an energy value of 1-2 kcal/g is attributed to digestible fiber in humans. In dogs, some soluble fiber is completely digested *(Diez et al, 1998)* and acetate can contribute to 8% energy metabolism in the dog *(Pouteau et al, 1998)*.

The most commonly used equation to calculate the theoretical maintenance energy requirement is:

132 kcal per kg of metabolic weight (MW)*

* Where MW = (body weight) $^{0.73}$

This exponent is often rounded up to 0.75 to facilitate calculations, but the original value is 0.73.

• *Energy expenditure*

The second element in the equation is energy expenditure, which is split into three parts:
- Basal metabolic rate (BMR)
- Postprandial thermogenesis (production of heat subsequent to the meal)
- Physical activity

In sedentary human adults, basal metabolic rate, postprandial thermogenesis and physical activity represent 60%, 10% and 30% of energy expenditure respectively *(WHO, 1997)*. The contribution of each of these factors varies significantly however, depending on the regularity and intensity of the physical activity, which is the key variable in expenditure. Basal metabolic rate appears, on the other hand, to be a stable individual factor, that has a major impact on the amount of muscle mass of the organism (90-95% of energy expenditure of basal metabolism versus 5-10% for fat mass).

In dogs, the basal metabolic rate also represents 55-70% of the total expenditure *(NRC, 2006)*, but differences have been observed between breeds. By way of example, the Labrador has a lower basal metabolism rate than the Great Dane or the Spaniel. The basal metabolism rate declines with age in dogs *(Speakman et al, 2003)*. It is recommended to reduce the energy intake by 10-15% from age 7, while adjusting the diet depending on the physical condition of the individual. On the other hand, a low calorie diet is not always justified for all old dogs.

The necessary balance between intake and expenditure is the crux of the problem in dogs in general and in obese dogs in particular. The difficulties of estimating energy expenditure (requirements) are multiple.

First of all, the great diversity of the canine species: body weight varies between the extremes of 1 kg and over 100 kg. It is also easy to understand the difficulty of estimating the energy requirement of all the dogs with a simple equation. The average equation is 132 kcal/kg BW $^{0.75}$ *(NRC, 1974)*. An initial approach proposed was to group breeds on the basis of their weight and size: small, medium, large and giant.

Dogs of comparable weight and size in the same category may present very different energy requirements. The differences may be due to the thickness of the skin, the body composition (lean mass/fat mass ratio) or to the type of selection used (originally a working dog, then selected on beauty criteria and having the function of a companion animal). The body composition is extremely important: the dogs that present a great muscle mass expend more energy and are less susceptible to obesity than fat dogs.

Besides breed, individual factors, both genetic and otherwise, also generate great diversity in energy requirements. In dogs of the same breed of comparable weight, the males are generally a little less fat than the females and so their expenditure is greater (on the order of 10%) however, this is a controversial point *(Kienzle & Rainbird, 1991)*.

As observed above, neutering will reduce expenditure (to the order of 20-30%) **(Figure 3).** Aging of the animal is an example of a physiological condition that may reduce energy expenditure by reducing the basal metabolic rate. Moreover, body composition changes during aging. The fat mass tends to increase at the expense of the muscle mass.

Breed can have a strong influence on energy requirement, even between two dogs of similar weight in similar environmental conditions. When it comes to theoretical rationing (NRC 1974), it is wise to reduce the Newfoundland's ration by around 10%. The ration of a Great Dane on the other hand must often be increased by 40% to maintain the dog's weight.

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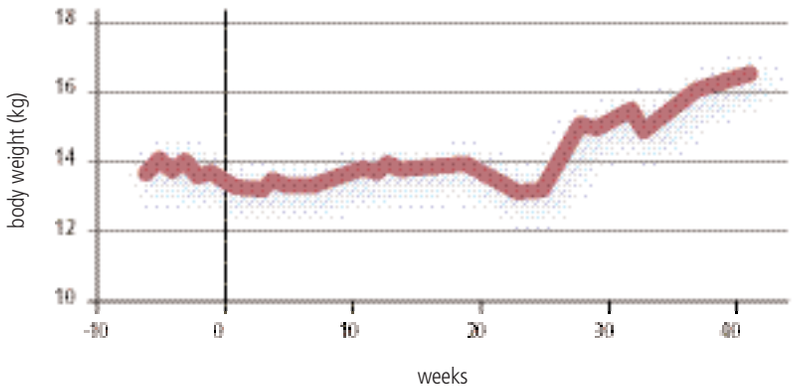
Energy expenditure associated with physical activity has not been quantified in dogs. From a practical perspective, it is not possible to say how many kilocalories correspond to an hour's walking, hunting or racing.

FIGURE 3 - DEVELOPMENT OF AVERAGE WEIGHT OF BEAGLE BITCHES AFTER NEUTERING
(Jeusette et al, 2004a)



Four neutered Beagle bitches age 2 years received a standard maintenance food. A 30% reduction in energy intake was necessary to maintain their body weight constant for 26 weeks. After 26 weeks on a controlled diet the food was given ad libitum, leading to an overconsumption of energy and a weight increase of 22% above their initial weight (16.7 kg versus 13.7 kg). (There was no control group)

In a neutral thermal environment, the energy expenditure associated with the thermoregulation of dogs living indoors is low. The seasonal effect is accordingly negligible. On the other hand, to maintain thermoregulation the energy expenditure of dogs kept in an outdoor kennel increases when the ambient temperature falls. In the literature however, the quantification of supplementary energy expenditure is controversial. In the German Shepherd for example, a variation of 1°C is accompanied by a variation in the energy requirement of the order of 1% *(Manner, 1991)*. Other data show an increase from 2.3 up to 3.8% per degree below the thermal neutrality zone *(NRC, 2006)*.

To conclude, the estimation of the energy requirement is not easy in dogs. While there is a large quantity of data, the data is fragmented and it is difficult to generalize. In practical terms, monitoring weight and knowing what the dog needs to consume to maintain a constant weight are the most important pieces of energy-requirement-based information for any given individual.

> The physiological regulation of body weight

In their original habitat, wild canids are generally active and in an environment with abundant food it is extremely rare for adult animals to be obese. The biological mechanisms regulating body weight are present throughout the animal kingdom and appear to be fairly efficient in combating underconsumption.

In domesticated animals, the environmental pressure makes the mechanisms likely to manage overconsumption more useful. The hormonal regulators of appetite, food consumption and energy expenditure are becoming more and more well-known, particularly leptin, ghrelin and adiponectin.

Leptin is a cytokine produced and secreted by the fat cells. It acts as an energy balance modulator signal, both centrally (on the hypothalamus) and peripherally (liver, pancreas, etc). Leptin accordingly appears to play a key role in the regulation of food consumption. At the time of its discovery leptin was presented as a miracle treatment for obesity as leptin injections in obese and healthy mice induced significant body weight loss without any apparent side effects. Nevertheless, it has been shown that obese humans and dogs *(Ishioka et al, 2002; Gayet et al, 2003a; Jeusette et al, 2003, 2004b)* do not suffer from leptin deficiency. On the contrary, in these two species, leptin is produced in proportion to the quantity of fat cells such that the rates of plasma leptin are higher in obese individuals than in healthy individuals. Leptin increases energy expenditure in healthy individuals but in obese individuals the situation is less clear due to a resistance phenomenon.

On the other hand, it appears that insulin and many other mediators also play a role in regulating leptin *(Lonnqvist et al, 1999)*. Clinical studies conducted on humans tend to show that the blood concentration of leptin is dependent on the secretion of insulin, the composition of the food and exercise *(Koutsari et al, 2003)*. From a practical perspective, the main point to remember with respect to obesity is that leptin reduces the appetite. Leptinemia increases in dogs during periods of weight gain *(Gayet et al, 2003a, 2004b; Jeusette et al, 2004b)*.

- **Leptin** is a protein that increases energy expenditure in healthy individuals.
- **Ghrelin** is an orexigenic hormone principally secreted by the stomach and the duodenum.
- **Adiponectin** acts in synergy with leptin. It is secreted by adipose tissue.

Ghrelin (GH releasing hormone) has been identified by Kojima et al *(1999)*. It stimulates the secretion of growth hormone (GH) and increases food ingestion in humans and rodents. We have observed that the plasma concentration of ghrelin is lower in obese dogs than it is in healthy animals *(Jeusette et al, 2003, 2004b)*.

Adiponectin is a cytokine secreted exclusively by the adipose tissue. It affects carbohydrate homeostasis, sensitivity to insulin and probably energy homeostasis. It will act in synergy with leptin *(Yamauchi et al, 2001)*. Its expression is reduced in obese and diabetic mice *(Hu et al, 1996)*. It is also reduced by half in obese dogs compared with healthy dogs *(Gayet et al, 2004b)*.

Additional regulatory factors include TNF-α (tumor necrosis factor). This cytokine was originally identified as a pro-inflammatory molecule that participates in anorexia and cancer cachexia. It has been found in particularly high quantities in the adipose tissue of obese animals and patients. The expression and the concentrations of TNF-α are positively correlated to the degree of obesity and the resistance to insulin *(Hotamisligil et al, 1995)* as shown in dogs *(Gayet et al, 2004a)*.

Besides the mechanisms mentioned above, the activity of uncoupling proteins (UCP) deserves emphasis. These proteins belong to a family of transporters in the internal membrane of the mitochondria, which uncouple the respiration of ATP synthesis by dispersing the mitochondrial proton gradient. The activity of these proteins varies according to thermoregulation and postprandial thermogenesis. The expression of UCP-1 is greatly reduced in the adipose tissue of obese, insulin-resistant dogs *(Leray et al, 2003)*.

To conclude, it appears that many factors involved in the development of obesity in humans and rodents have also been identified in dogs, whether they are factors limiting appetite or factors increasing expenditure.

From a certain phase of obesity the food consumption may decline without the dog losing weight, because the basal metabolic rate is relatively low.

> The dynamics of weight gain

Despite these regulator mechanisms, a positive energy balance can induce weight gain if it continues for a long enough period of time. There is controversy as to the period of imbalance (energy intake greater than expenditure). In humans the perceived hypothesis is that obesity is established slowly, following a prolonged imbalance (several years) that does not have to be sizeable. Clinicians distinguish three phases:

- **A pre-obesity static phase** during which the individual's energy intake is increased but its weight remains the same

- **A dynamic phase**, during which the individual gains weight, primarily increasing its fat mass but also its non-fat mass, if only by a low increase in the blood volume

- **A static phase** during which the balance between intake and expenditure is re-established due to the reduction in food consumption. In this phase, the weight is extremely high, but the basal metabolic rate is relatively low. In this new state of balance obesity is usually considered to be morbid *(WHO, 1997)*.

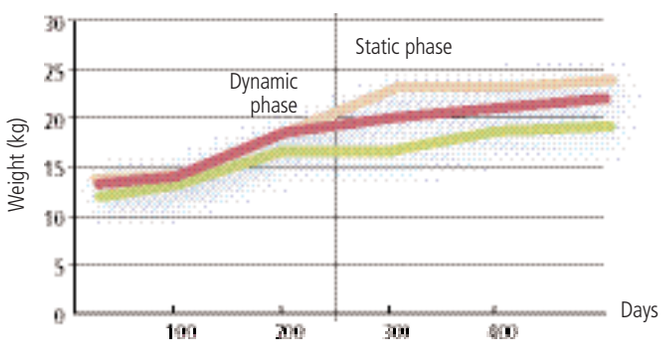
These data can almost be extrapolated to companion dogs, after a few adjustments. With respect to the period of imbalance, the data must be adapted to the life expectancy of the dog and practical observations must be taken into account. Weight gain can occur rapidly, in a few weeks or months. Rapid weight gain may occur in the weeks following the neutering of bitches. *Ad libitum* feeding during growth may induce major weight gain in puppies aged 8 months.

The pre-obesity phase has not been described in dogs. The dynamic and static phases on the other hand have been well documented **(Figure 4)**. The dynamic phase may be linear or segmented. Weight is stabilized during the static phase; appetite may be normal or diminished. This explains why it is common to see obese dogs in the clinic that "do not eat a lot." What is clear is that the energy intake was greater than the dog's needs at a given moment in its life – sometimes several years earlier. But once these animals have been stabilized, their energy requirements are low and physical activity is often very limited, the more so at this stage.

> Quality of dietary intake

Various studies conducted on humans and laboratory animals show that dietary factors, particularly energy intake and fat content, are directly correlated to obesity.

FIGURE 4 - WEIGHT DEVELOPMENT OF THREE BEAGLE DOGS FED WITH A DIET RICH IN FATS



Weight gain is very large during the first 200 days: the dogs gain 40-70% of their initial weight (dynamic phase). Then the weight gain becomes moderate (2-6% increase between 200 and 400 days).

- ***Energy intake and macro-nutrients***

For dogs, the calculation of the energy provided by a food is based on its chemical composition. Fats are the nutrients that contain the most energy. The over-consumption of fatty food is accordingly an essential factor in the genesis of obesity. Fat is added to food to both increase palatability and the energy density of the diet.

In terms of metabolizable energy, the protein and carbohydrate intake is equal. When the net energy intake is calculated however, the utilization of proteins for energy is lower **(Table 7)** *(Rubner, 1902)*. This is one of the reasons, other than the specific effect of some amino acids (lysine, phenylalanine, leucine), for proteins having more of a satisfying effect than carbohydrates. The carnivorous nature of dogs may explain to some degree the resistance of wild canids to obesity.

Digestible carbohydrates clearly provide the same quantity of energy, but they induce different metabolic effects, particularly on the secretion of insulin. This point is addressed in more detail below.

From a theoretical perspective, it can be accepted that the mathematical adaptation of energy intake to energy expenditure suffices to prevent canine obesity. But this will be disregarded in some cases, because it is based on 'metabolizable energy.' The simple modification of the food's chemical composition – without modifying the total energy intake – can lead to changes to the body composition and the basal metabolic rate. This point has been proven in dogs and is well established in human nutrition *(Bouché et al, 2002)*.

► Diagnosis and evaluation of obesity

One of the major tasks facing the clinician is to evaluate how obese the animal is as in many cases the optimal body weight is unknown. In human medicine, it is easy to calculate an optimal weight range based on size, using the BMI (body mass index), which is the ratio of height to weight. In human medicine, doctors have a BMI reference table they can consult. These tables are not available for domesticated carnivores. Various attempts at morphometric measurement have proved inconclusive due to the great diversity of canines breeds. Other less standardized tools have accordingly been proposed for veterinary medicine.

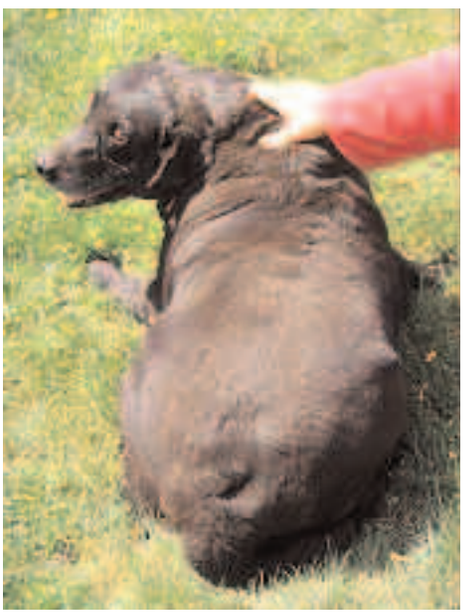
> Body weight

The simplest method is the body weight reference. It is easy to weigh a dog, but weight alone is not enough to evaluate obesity. Without an indication of the dog's ideal weight this data is of little use. While it is easy to use breed standards as a reference for purebred dogs, this method is not completely satisfactory, because the animal's body weight can vary quite significantly depending on its stature **(Table 8)**.

When visiting the veterinarian it is important that the dog is weighed and its medical file is updated accordingly. The ideal weight must be identified or estimated to ascertain an obese animal's diet. This is the most important factor in formulating a diet that will enable the dog to lose weight.

> Morphometric measures

The combination of data on stature and on body weight introduces the concept of morphometric techniques to evaluate body composition. Morphometry measures the outer form, evaluates certain body regions and how their dimensions change and shows their relationship to modifications in body composition. The morphometric techniques used on dogs are body condition scoring and techniques that combine diverse body parameter measurements (length and circumference of various parts of the body).



A massive deposit of adipose tissue on the spinal column and the base of the tail are among the criteria used to identify obesity.

TABLE 8A - REFERENCE WEIGHT VARIATION ACCORDING TO SEX IN SEVERAL SMALL BREEDS

Small breeds	Average weight of the male (kg)	Average weight of the female (kg)
Chihuahua	2.0 ± 0.6	1.5 ± 0.4
Yorkshire	2.6 ± 0.5	2.3 ± 0.5
Miniature Spitz	3.6 ± 0.8	2.5 ± 0.6
Italian Greyhound	4.1 ± 0.5	4.6 ± 0.1
Shi Tzu	5.8 ± 1.3	5.0 ± 0.8
Miniature Poodle	5.8 ± 1.4	5.0 ± 0.8
West Highland White Terrier	7.5 ± 1.2	6.9 ± 0.6
Cairn Terrier	8.1 ± 0.2	7.4 ± 1.2
Cavalier King Charles	8.7 ± 1.5	7.0 ± 1.1
Standard Dachshund	9.2 ± 1.2	7.5 ± 1.8

Measurements conducted on 184 males and 221 females of small breeds.

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King Charles Spaniel puppies

TABLE 8B - REFERENCE WEIGHT VARIATION ACCORDING TO SEX IN SEVERAL MEDIUM BREEDS

Medium breeds	Average weight of the male (kg)	Average weight of the female (kg)
Pyrenean Shepherd Dog	12.8 ± 2.8	13.4 ± 3.8
French Bulldog	13.0 ± 1.6	11.3 ± 1.9
English Cocker Spaniel	13.0 ± 2.3	11.8 ± 1.0
Whippet	13.9 ± 1.1	11.7 ± 0.7
Brittany Spaniel	17.9 ± 2.2	15.5 ± 1.5
Staffordshire Bull Terrier	24.0 ± 1.1	21.0 ± 1.4
English Bulldog	26.0 ± 4.3	22.4 ± 3.6
Collie	23.9 ± 0.5	19.8 ± 2.0
Siberian Husky	24.0 ± 0.9	18.5 ± 1.0
Shar Pei	24.9 ± 1.7	18.4 ± 0.6

Measurements conducted on 98 males and 99 females of medium breeds.

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English Bulldog puppies

TABLE 8C - REFERENCE WEIGHT VARIATION ACCORDING TO SEX IN SEVERAL LARGE BREEDS

Large breeds	Average weight of the male (kg)	Average weight of the female (kg)
Irish Setter	26.1 ± 1.9	25.5 ± 4.5
Belgian Sheepdog	27.1 ± 4.5	23.2 ± 2.0
German Pointer	28.5 ± 0.9	24.6 ± 2.3
French Spaniel	29.4 ± 2.1	26.3 ± 3.6
Weimaraner	33.6 ± 3.7	30.5 ± 4.3
Golden Retriever	33.7 ± 3.4	30.4 ± 3.6
Boxer	33.9 ± 3.5	28.8 ± 2.4
Labrador	35.5 ± 4.5	30.7 ± 3.4
German Shepherd	35.9 ± 3.6	28.4 ± 2.7
Doberman	39.0 ± 5.5	28.50 ± 5.0

Measurements conducted on 530 males and 488 females of large breeds.

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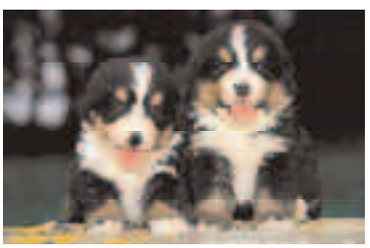
Labrador puppies

TABLE 8D - REFERENCE WEIGHT VARIATION ACCORDING TO SEX IN SEVERAL GIANT BREEDS

Giant breeds	Average weight of the male (kg)	Average weight of the female (kg)
Rottweiler	46.8 ± 4.8	39.7 ± 4.9
Bernese Mountain Dog	59.9 ± 6.9	43.3 ± 6.5
Leonberger	57.0 ± 6.4	49.9 ± 6.8
French Mastiff	58.6 ± 7.3	46.8 ± 7.5
Bullmastiff	58.8 ± 7.5	47.7 ± 6.4
Irish Wolfhound	63.1 ± 1.4	54.3 ± 4.9
Newfoundland	63.5 ± 6.2	51.1 ± 8.6
Great Dane	70.5 ± 8.2	56.6 ± 7.1
St Bernard	81.5 ± 7.2	61.0 ± 8.9
Mastiff	87.0 ± 10.5	71.6 ± 9.2

Measurements conducted on 580 males and 628 females of giant breeds.



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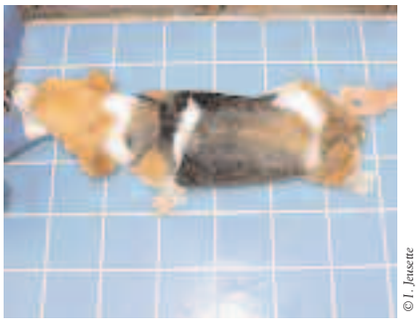
Bernese Mountain Dog puppies

The body index is a semi-quantitative subjective evaluation method combining the evaluation of visible characteristics and palpation of certain regions of the body. This evaluation is conducted in accordance with simple criteria: the size and location of major adipose deposits, the visible and invisible skeletal structure, and the silhouette of the animal.

Several types of index have been proposed:
- 3 grades: 1 = slim, 2 = optimal, 3 = excessive
- 5 grades: 1 = gaunt, 2 = slim, 3 = optimal, 4 = overweight, 5 = obese *(Edney & Smith, 1986)* **(Table 9)**
- and even 9 grades: 1-4 = emaciated to slim; 5 = optimal; 6-9 increasingly overweight *(Laflamme, 1993; Laflamme et al, 1994a)*.

The animals presenting an average index corresponding to an optimal weight have a fat mass of around 13%. When a 9-grade body index is used, every grade in the index represents a 9%-increase in fat mass *(Mawby et al, 2000)*. As a consequence, an animal presenting a body index of 9, which corresponds to the qualification 'morbid obesity,' has a fatty mass of over 40%. The advantage of these index systems is that they can be easily applied by the clinician and that they do not apply exclusively to the diagnosis of obesity but also to its active prevention. It is easy to weigh the animal during a routine consultation and find the value in the index.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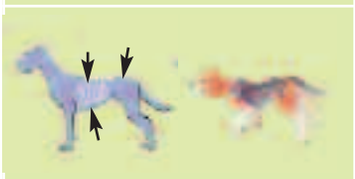
The transition from a 5-grade scale to a 9-grade scale is easily accomplished by applying intermediate graduations in the 5-grade scale. Here, the body index of this Beagle bitch can be 4.5/5 or 8/9.

TABLE 9 - BODY CONDITION SCORING

	Grade	Dog
	**1. Cachexia** more than 20% below optimal weight	- Clearly visible ribs, vertebral column, pelvic bone (short hair) - Clear loss of muscle mass - No palpable fat around thoracic cage
	**2. Thinness** 10-20% below optimal weight	- Visible ribs, top of vertebrae, pelvic bone - Clear abdominal belt (waist) - No palpable fat around thoracic cage
	**3. Ideal Weight**	- Ribs, vertebral column not visible, but clearly palpable - Clear abdominal belt (waist) - Thin layer of palpable adipose tissue around thoracic cage
	**4. Excess Weight** 10-20% above optimal weight	- Ribs, vertebral column palpable with difficulty - No abdominal belt (waist) - Clear adipose deposit around vertebral column and base of the tail
	**5. Morbid obesity** from 40% above optimal weight	- Massive adipose deposit around thorax, vertebral column and base of the tail - Clear abdominal distension

Each half-grade above grade 3 represents an increase in weight of 10%. So a dog graded 4.5 presents 30% overweight.

The measures of the various circumferences – thoracic and pelvic for example – and their use in the equation systems do not enable any appreciation of the fat mass due to morphological differences between individuals. They are however a good way of monitoring the weight loss in a given dog. The various body measures do require experience from the practitioner, as well as the cooperation of the animal *(Burkholder, 2000)*.

> Ultrasound measurements

Ultrasound has been used to measure the thickness of the subcutaneous fat layer in dogs *(Anderson & Corbin, 1982; Morooka et al, 2001)*. Combining this technology with others may be a good way to localize the main fat deposits and understand the mechanisms that drive the development of obesity *(Morooka et al, 2001)*. Furthermore, this technology is relatively simple and non-invasive; it is useful in the clinic provided good equipment is available. Its field of application is narrow however – it can only be used to evaluate subcutaneous fat. Several body regions have been tested, including the middle of the lumbar region and the L6 and L7 lumber or S1 sacral apophyses. The problem is reproductibility: it is necessary to shave the hair, standardize the animal's position and the pressure of the sound probe, and use objective benchmarks. The use of ultrasound in two dimensions helps improve the technique and obtain more precise figures *(Morooka et al, 2001)*.

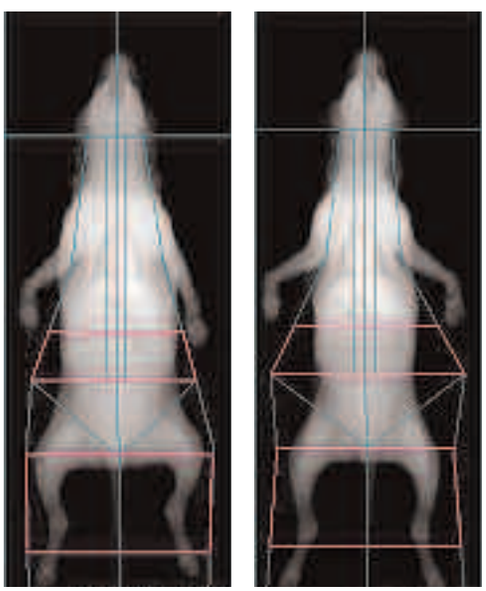
> DEXA

The use of DEXA (Dual Energy X-ray Absorptiometry) *(Munday et al, 1994)* is a way of differentiating between the nature and the quantity of each tissue in the parts of the organism subjected to examination and to monitor the development of the dog's body composition during the period of weight loss. This examination requires that the animal is anesthetized for the procedure. The results relate to the bone mineral mass, adipose tissue and lean mass of the organism **(Figure 5)**.

> Heavy isotopes

Body water is primarily stored in lean tissue; as a consequence, it is an indirect measure of lean mass. The quantity of total body water can be estimated by establishing the dilution of deuterium oxide (D_2O) or of water enriched with O^{18}. The fat mass and its percentage can be calculated on the basis of the difference. Deuterium and O^{18} are two excellent non-radioactive and non-toxic tracers at low doses. This method requires a blood sample before the subcutaneous injection of the tracer and a second blood sample four or five hours post injection. It can be used in practice to estimate the percentage of fat tissue in obese dogs, provided there is access to mass spectrometry. This non-invasive method has been validated in dogs *(Pouteau et al. 1998; Son et al, 1998)*.

FIGURE 5 - IMAGES (OBTAINED BY DEXA) OF A NEUTERED MALE LABRADOR AGE 4.5 YEARS, BEFORE (T0) AND 5 MONTHS AFTER (T+5) THE INTRODUCTION OF A LOW CALORIE DIET



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	T0	T+5
Weight (kg)	45.90 kg	37.10 kg
Total fat mass	20.45 (45.4%)	12.72 (35.1%)
Total lean mass	23.14 (54.6%)	22.18 (64.9%)
Total weight loss = 8.8 kg (19.2% of initial weight)		

The weight loss is spread between 87% fat mass (7.7 kg in all) and 13% lean mass (1.12 kg in all). Final fat mass is still high (35%), but compatible with the breed of the dog.

> Bioelectric impedance

In humans, the measurement of bioelectric impedance is a fast and simple non-invasive method for studying the body composition that is both portable and reproducible. The method has been tested on cats and dogs *(Elliott et al, 2002a, 2002b)*.

These three methods – which have only recently been used on carnivores – produce well correlated results *(Son et al, 1998)*. They are certainly more applicable to research settings than to clinical situations, but nevertheless, they do open interesting perspectives for comparing the efficacy of different low energy foods available in the marketplace *(Diez et al, 2002)*.

2 - Treatments for obese animals

► Pharmacological treatments

A large pharmacological arsenal has been developed to treat human obesity. It should be noted that some of these pharmaceuticals have been developed for dogs. Some studies have been conducted with these agents to reduce the body weight of obese dogs *(Bomson & Parker, 1975)*. These trials have not been successful.

Dehydroepiandrosterone (DHEA) administered at a large dose (60 mg/kg of body weight /day) reduces the deposition of fatty tissue and has been used as an agent to facilitate weight loss, in combination with a low-energy diet in obese dogs *(MacEwen & Kurzman, 1991; Kurzman et al, 1998)*. DHEA also exhibits hypolipemic and hypoglycemic properties. Its mechanism of action has yet to be fully clarified. Due to the many uncertainties as to the various effects of this hormonal precursor, its utilization in dogs can not be recommended at this time.

Injections of human recombinant leptin have also been used in dogs. The administration of leptin to healthy or obese dogs induced a significant loss of weight proportional to the duration and the dose used. Weight loss is nevertheless greater in healthy dogs. The dogs start to gain weight a week after the end of the treatment, gradually returning to their initial weight. The weight loss is essentially due to a reduction in body fat mass. In a study comparing the effects of leptin administration in obese males and females, a similar loss of weight was observed in the two groups at doses of 0.5 mg/kg BW/d and 5.0 mg/kg BW/d *(Lebel et al, 1999)*. This type of specific trial does not argue in favor of the use of leptin in obese dogs, especially due to the lack of long-term data and the presence of the rebound effect after the end of the treatment.

Whatever place pharmacological treatment will have in the future, it should not be forgotten that in a global approach (behavioral and dietary) of obese dogs, medication should never be used as it does not change the owner's behavior.

► Surgical treatments

In human medicine various surgical interventions help limit food consumption. These techniques are not used on animals at this time.

► Approach of the owner

The psychological approach of the owner is essential. The objective is to motivate the owner by explaining the causes and the damage caused by obesity as well as the advantages of having a healthy animal. Clear explanations, regular checkups and the establishment of a weight curve are steps that will contribute to successful treatment *(Lewis et al, 1987; Norris & Beaver, 1993)*. No diet is possible without the cooperation of the owner.

Clinical trials conducted on obese dogs provide various findings. The first is that in a weight loss program initiated by the owner, over 50% of those owners did not return for checkup visits. It must therefore be concluded that over 50% of dog owners abandon the diet in the month following the first visit *(Remillard, 2000)*. In another study, 75% of dogs registered stopped losing weight *(Gentry, 1993)*. These details will be addressed from a more practical perspective under Clinical Food.

► Nutritional treatment

Two techniques can be used to reduce the dog's weight. Fasting is applicable and effective provided the animal does not present with a concomitant pathology like hepatic insufficiency or diabetes mellitus. It is necessary to hospitalize the animal and to give it daily mineral and vitamin supplements. Many authors have shown that the dog can easily bear complete nutritional privation *(De Bruijne & Lubberink, 1977; Brady & Armstrong, 1977)*, but according to Abel et al *(1979)* prolonged fasting past 36 days can lead to heart lesions. Furthermore, this method is not to be recommended for ethical reasons and because it does not bind the owner to long-term dietary modifications.

The restriction of energy intake is accordingly the only truly valid option. The dietary balance must be established with the owner. In the absence of precise information on the quantities of food ingested, it should be possible to estimate the total daily energy typically consumed by the animal. A very strict protocol must then be established with the owner's full cooperation.

> Level of energy restriction

The choice of the ration's energy level depends on several criteria, including the degree of weight excess, the animal's sex and the projected duration of the diet. The first step consists of defining the ideal weight; the second is setting the energy restriction level. The diet is generally calculated to provide 40% – a very severe restriction – *(Markwell et al, 1990)* to 60% *(Edney, 1974)* or 75% *(Dzanis, 2000)* of the energy needed to maintain the optimal weight. **Table 10** provides an

TABLE 10 - OVERVIEW OF SELECTED WEIGHT LOSS TRIALS CONDUCTED ON OBESE DOGS: DEGREE OF ENERGY RESTRICTION AND WEIGHT LOSS

	N	BCS	% overweight	Duration Weeks	Energy allocation % of MER for IBW	Weight loss % of IW/week	References
Experimental trials	39 (various breeds)		20	16	100[a] 75 60 50	1.14 1.56 2.18 2.63	*Laflamme & Kuhlman, 1995*
	12 (crossbred dogs: 12-22 kg)	-	-	7	60[b] 60	2.3 1.9	*Borne et al, 1996*
	8 (Beagles)	4.3/5	56 45	23.5 18.3	66[c] 62	1.57 1.31	*Diez et al, 2002*
	12 (Beagles)	7.2/9	56 45	27.5 23.5	75[c] 87	1.30 1.31	*Jeusette et al, 2004*
Clinical trials	20 (various breeds)		50 (24-77)	40	60 50-75[c]	insufficient	*Gentry, 1993*
	9 (various breeds)		27	18.3	50-75[c]	1.91	*Diez et al, 2002*

N: number of animals
BCS: Body Condition Score
MER: Maintenance Energy Requirements
IBW: Ideal Body weight
IW: Initial Weight

a: calculated using the formula 144 + 62.2 x IBW
b: calculated using the formula 1500 kcal/m²/day
c: calculated using the NRC 1974 formula (132 kcal/kg $BW^{0.75}$)

overview of the various clinical and experimental trials. Theoretically, the higher the energy restriction, the shorter the restriction period needed.

The practitioner may be tempted to opt for very severe energy restriction to limit the duration of the diet. This is not recommended. Too severe a restriction may lead to a significant feeling of hunger in the animal, generating an augmentation of activity after meals *(Crowell-Davis et al, 1995b)* and consequently the dissatisfaction of the owner and a lack of cooperation with respect to following a strict diet. The diet runs the risk of being abandoned after a few weeks or even a few days. Additionally, the loss of muscle mass can also be exaggerated by a sudden loss of weight, as has been shown in humans *(Pasanisi et al, 2001)*. In experimental conditions, the rebound effect (weight gain after the end of the diet) is so much more intense and fast when the energy restriction is severe *(Laflamme & Kuhlman, 1995)*. The explanation advanced for the severity of the rebound effect is that the dogs present a reduction of metabolic activity associated with an increase in energy efficiency during the diet. The more severe the energy restriction, the less the physical activity is of the dog *(Crowell-Davis et al, 1995a)*. This reduction in activity constitutes a second risk factor for muscle mass loss.

Lastly, the long-term modification of the owner's behavior is more desirable than a rapid change. As a consequence, a very severe energy restriction is not recommended for all animals, but should be reserved for the most severe cases of obesity, when the weight gain is more than 40% and there is a medical indication for rapid loss, such as serious respiratory, cardiac or orthopedic problems. The same applies if the animal has to undergo anesthesia in the short or medium term.

Various experimental and clinical trials show that a reasonable objective is to maintain a loss of 1-2% of the initial (obese) weight per week, or 4-8% per month. There is a wide consensus on this degree of weight loss. **Table 11** proposes various degrees of energy restriction based on several parameters: body weight excess, sex and desired weight loss period.

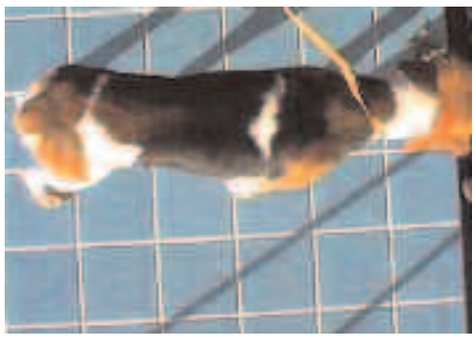
TABLE 11 - RECOMMENDATIONS OF VARIOUS ENERGY INTAKE LEVELS AS PART OF A LOW-CALORIE DIET

Excess weight **Fat mass** **BCS**	20-30% 25-35% 7		30-40% 35-45% 8		> 40% > 45% 9	
Loss of 6% of the initial weight per month (approx. - 1.5% per week)						
Daily energy intake (kcal/ kg IBW$^{0.75}$)	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
	85	80	75	65	60	55
Probable duration of weight loss	15-18 weeks		18-20 weeks		20-22 weeks (minimum)	
Loss of 7.5% of the initial weight per month (approx. - 2.0% per week)						
Daily energy intake (kcal/ kg IBW$^{0.75}$)	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
	80	75	65	60	55	50
Probable duration of weight loss	9-11 weeks		11-13 weeks		15-17 weeks	

BCS: Body Condition Score on a scale of 1 to 9
IBW: Ideal (Optimal) Body Weight
Initial Weight: weight of the obese dog

To initiate weight loss without imposing too severe a restriction immediately, the recommended initial energy allocation is:
- 65% (or 85 kcal/kg IBW$^{0.75}$) of the maintenance energy requirement for a male, falling to 55% (or 75 kcal/kg IBW$^{0.75}$) if the dog is neutered.
- 60 % (or 80 kcal/kg IBW$^{0.75}$) of the maintenance energy requirement for a female, falling to 50% (or 65 kcal/kg IBW$^{0.75}$) if the bitch is neutered.
These options can be subsequently revised depending on the period of weight loss.

> Differences between males and females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For weight loss of 1.5% per week, at least 3.5-4 months are needed to change a body score from 7/9 to 5/9 (or from 4/5 to 3/5).

A study conducted on Beagles showed that it was more difficult to induce and maintain the weight loss in obese females – neutered or unneutered – than in neutered males. The initial degree of obesity was comparable, as was the weekly loss of weight.

In the course of time, the adjustments to the quantities were more severe for the females compared with the male dogs. For female dogs, an energy intake limited to 54% of the calculated maintenance energy need based on the ideal weight did not lead to the attainment of the target weight. The 60% level used at this time appears to be inappropriate for females. The development of body composition was not affected by sex *(Diez et al, 2002)*. The maintenance food of obese dogs needs to be examined to understand this difference between the sexes. At comparable weight, obese bitches consume an average 15% less energy than males by unit of ideal metabolic weight and their lean mass is generally inferior. It is therefore illogical to apply the same weight-loss protocol to individuals of different sexes *(Jeusette et al, 2004c)*.

> Modification of the food

It is totally contraindicated to achieve energy restriction by simply reducing the quantity of the food typically consumed. This will lead to deficiencies in essential nutrients and will have little probability of success. An animal that is denied food may develop unpleasant behavior: nervousness, theft of food and sometimes even aggression *(Branam, 1988)*. These behaviors discourage the owner and the diet will be highly unlikely to succeed. Crowell-Davis et al *(1995a)* relate the effects of the restriction on the behavior of a group of dogs in the kennel: during the first few days of calorie restriction the animals showed a greater propensity to chew objects, heightened aggression among some subjects and an increase in the frequency of barking. The selection of a food specially adapted for weight loss is therefore imperative if deficiencies are to be avoided and the dog is to receive sufficient food, while simultaneously limiting energy intake.

> Low-calorie foods

There are various ways to reduce the concentration or energy density of commercial dog food. The simplest way of effectively reducing the energy concentration of a commercial food is to reduce the fat content and increase the dietary fiber content. These two major changes are indeed essential, but all nutrients (amino acids, fatty acids, minerals and vitamins) must be given due consideration in the formulation of a food, as described in more detail below.

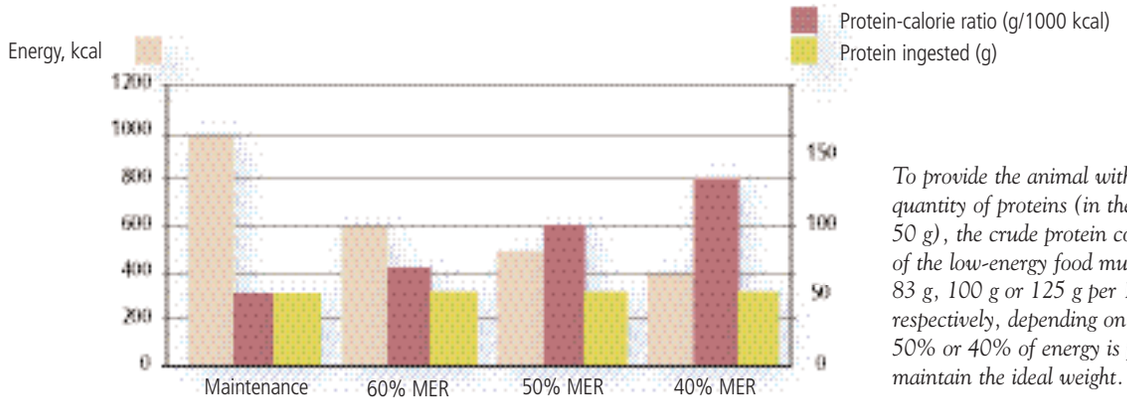
In addition, it should be noted that the production of extruded dry food containing large quantities of air will help increase the volume of the ration. This method mainly has a psychological impact on the owner and less on the dog, since the weight of the daily ration is reduced. The change in the size, texture and shape of the kibble may be a way to increase the ingestion time and satiating power. In the case of wet food, very high hydration (over 80% water) also helps maintain a relatively large volume. Nevertheless, the impact on satiation is dubious, as the water – or the liquid fraction of the food – is evacuated from the stomach in 20-30 minutes depending on the size of the particles. The addition of viscous dietary fiber that binds water does on the other hand slow down gastric emptying *(Russell & Bass, 1985)*.

- ***The essential nutrient content*** of low-calorie foods is extremely important. A more or less severe restriction imposed on an animal must never be accompanied by any deficiencies of proteins, essential amino acids, essential fatty acids, minerals, vitamins or trace elements.

• ***The protein concentration*** of low-calorie foods must be greater than those of maintenance foods to provide the essential amino acids. **Figure 6** illustrates the necessity of increasing the protein content in the food to avoid the energy restriction causing a protein deficiency.

The same reasoning is valid for all essential nutrients. High-protein diets have been used successfully for several years in humans and have demonstrated many benefits.

FIGURE 6 - ADAPTATION OF THE DIETS'S PROTEIN LEVEL BASED ON THE ENERGY RESTRICTION



Energy allocation based on the maintenance energy requirement (MER)

To provide the animal with the same daily quantity of proteins (in the example, 50 g), the crude protein concentrations of the low-energy food must be increased to 83 g, 100 g or 125 g per 1000 kilocalories respectively, depending on whether 60%, 50% or 40% of energy is provided to maintain the ideal weight.

- Positive effect on body composition by maintaining lean tissue mass. High-protein diets minimize muscle wasting and facilitate the loss of fat *(Durrant et al, 1980; Piatti et al, 1994)*.These effects have also been observed in dogs as part of a low-calorie diet. Three similar diets differing in protein concentration (20%, 30% and 39% of energy intake) were fed to 42 obese dogs. The diet with the highest protein content led to increased loss of fat mass and minimized the loss of lean tissue *(Hannah, 1999)*. These results have been confirmed in another trial comparing two low-energy diets. The high-protein diet contained 157 g of protein/1000 kcal or 47.5% of dry matter *(Diez et al, 2002)*.

- Lower yield in terms of net energy intake for proteins compared with carbohydrates. At the same weight, digestible carbohydrates and proteins provide comparable levels of metabolizable energy, but proteins provide lower net energy levels *(Rubner, 1902)*. This means that the use of proteins costs the organism energy. The energy expended is accordingly not stored in the form of fat, which is advantageous for obese individuals.

- Satietogenic power of proteins (Louis-Sylvestre, 2002): the increase in the prevalence of obesity has fueled interest in foods with a strong satiating power. The results of many studies conducted on humans have shown that the absorption following the consumption of high-protein foods was lower than after consumption of foods with a high carbohydrate or fat content. The amino acids from the digestion of proteins are absorbed slowly and the main path of their metabolism is gluconeogenesis. Therefore, proteins are sources of glucose that induce little insulin secretion and they slow down the appearance of hypoglycemia, which contributes to the feeling of hunger. The speed of digestion varies from one protein to the other and amino acids induce the secretion of insulin to varying degrees, so the satietogenic power may also differ from one protein to another. This certainly merits studies specific to the dog.

- **Beneficial effect on palatability.** This property is particularly significant when using low-calorie foods.
- **Improved conservation of weight loss after the diet.** This effect has been shown in humans *(Westerterp- Plantenga et al, 2004)*.

The quality of the protein is also important. It is necessary to increase the protein content of the ration when significant quantities of mixed dietary fiber (association of soluble and insoluble fiber) are added, due to the reduction in the digestibility of the dry matter (DM) (including the protein) caused by some fiber.

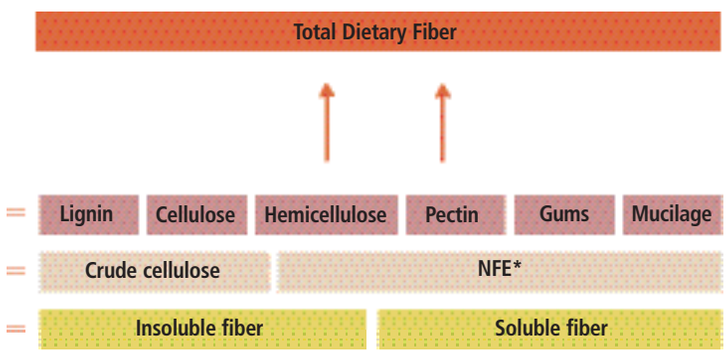
• ***The fat content*** of low-calorie foods is generally reduced to less than 25% of energy intake. Nevertheless, a minimal fat concentration is necessary to ensure the intake of essential fatty acids and the transport of fat soluble vitamins. The most recent recommendations are at least 5.5% of DM (for a food containing 4000 kcal/kg of DM, or 14 g/1000 kcal). Low-calorie commercial foods never contain less than 5% of fat. In addition, the choice of fat sources of different origins (vegetable oil, linseed oil or fish oil) ensures the intake of essential long-chain fatty acids.

• ***The use of dietary fiber*** has fueled a wide debate in both human and animal nutrition. The incorporation of fiber is not universal rather it is one of many approaches *(Diez & Nguyen, 2003)*. Fiber can be advantageous for the nutritional management of obesity in dogs.

Dietary fibers, in purified form or in high-fiber food like vegetables or whole-grain cereals, have a universally acknowledged satietogenic effect in humans, but they may lead to gastro-intestinal problems, such as flatulence and diarrhea.

- Fiber is generally a dilution element and allows a reduction in the energy density of a food. A standard dry maintenance food has an energy concentration of 3500- 4000 kcal per kg of DM, but several authors *(Lewis, 1978; Hand, 1988)* advocate a low energy concentration. It is however difficult to formulate a food with an energy concentration lower than 2800 kcal/kg of DM.
- Soluble fiber slows down gastric emptying and induces slower absorption of nutrients in dogs *(Russel & Bass, 1985)*.
- Insoluble fiber acts as a bulking agent, increasing the volume of the food and accelerating dietary transit *(Burrows et al, 1982; Fahey et al, 1990)*.
- Fiber leads to a feeling of satiation: a diet containing at least 20% total dietary fiber *(Total Dietary Fiber (TDF); Prosky et al, 1994)* reduces the voluntary energy intake in dogs *(Jewell et al, 2000)*.

FIGURE 7A - CRUDE CELLULOSE DOES NOT PREDICT NUTRITIONAL VALUE



The crude fiber must be declared in the analysis of a commercial food. However, it only represents a small part of the total fiber of the food. In dog food, it is vital to remember that the total dietary fiber concentration is the only important quantitative factor.
**NFE: nitrogen-free extract (carbohydrates)*

But fiber also presents some inconveniences, which vary according to the nature of the fiber and the rate of incorporation:

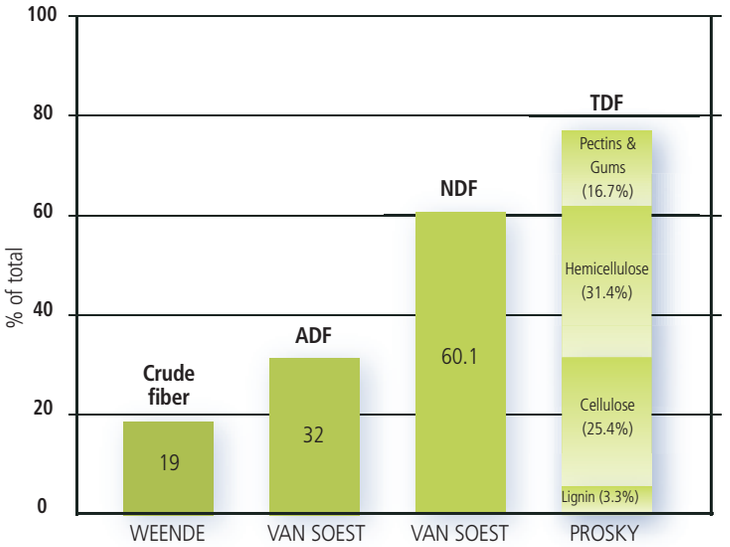
- Fiber increases the quantity of feces and the frequency of defecation (a general effect of dietary fiber)
- Fiber causes a reduction in the digestibility of certain nutrients like proteins and minerals, which demand their incorporation in greater quantities
- Fiber adversely affects palatability *(Meyer et al, 1978)*, which can be easily corrected by the addition of palatability factors
- Fiber may lead to gastro-intestinal problems, such as flatulence and diarrhea.

> Fiber and chemical analysis

From a legal perspective, the fiber content shown on pet food labels is crude cellulose (also known as crude fiber). This fiber content arises from an analytical method that does not fully reflect the actual fiber content of the food. A chemical analysis of the crude cellulose only measures part of the insoluble fiber, primarily the cellulose and some hemicelluloses **(Figures 7A & B)**. Yet other types of fiber are also used by the pet food industry including soluble fiber (psyllium, guar gum), and mixed fiber (mixtures of soluble and insoluble fibers).

The preferred method for measuring any dietary fiber (soluble and insoluble) is to measure the enzymes in the total dietary fiber. This is the only way to acquire significant nutritional information. The difference between crude fiber and total dietary fiber is much greater than in food containing more mixed fiber or soluble fiber content. **Table 12** for example shows that in the case of cereals, the ratio of the two values is 1 to 4. At the extreme, a food containing significant quantities of soluble (non-cellulose) fiber will have negligible crude cellulose content.

FIGURE 7B - PRESENTATION OF THE VARIOUS DIETARY FIBER DOSING METHODS IN RELATION TO THE CHEMICAL COMPOSITION: APPLICATION TO BEET PULP



ADF: acidic detergent fiber
NDF: neutral detergent fiber
TDF: total dietary fiber

In the case of beet pulp, the total dietary fiber is composed of 3.3% lignin, 25.4% cellulose, 31.4% hemicellulose and 16.7% gum pectins.

TABLE 12 - SOURCES OF FIBER USED IN LOW-CALORIE DIETS: CHEMICAL COMPOSITION

	Crude cellulose % DM	Total fiber % DM	Predominant type of fiber	
			Soluble	Insoluble
Sources of concentrated fiber				
Cellulose fiber	75	86		++++
Peanut shells	65	86		++++
Fructo-oligosaccharides	0	71	++++	
Pea fiber	55	78	++	++
Guar gum	1-2	80	+++	+
Beet pulp	19	59-77	+	+++
Psyllium *	21	58	+++	
Wheat bran	10-19	38-40	+	+
Cereals				
Wheat	2.5	10-12	+	+++
Corn	2.3	8-9		++++
Corn flour	0.5-1	2.6-4.5		++++
Barley	4	16	+	+++

** Psyllium is a source of soluble but non-fermentable fiber, in contrast to other sources of soluble fiber in the table.*

> Fiber and satiety

In obese humans undergoing low-calorie diets the ingestion of a daily supplement of insoluble fiber *(Ryttig et al, 1989; Astrup et al, 1990)*, soluble fiber *(Krotkiewski, 1984; Di Lorenzo et al, 1988)* or mixed fiber *(Burley et al, 1993)* induces better satiety or reduces the feeling of hunger.

It is much more difficult to evaluate the feeling of satiety in dogs than it is in humans. Various indirect methods are used to evaluate satiety, by measuring ingestion or the speed of gastric emptying. In the case of the latter, it is postulated that the distention of the stomach inhibits the physiological mechanisms leading to ingestion and as a consequence acts as a signal of satiety *(Jewell et al, 1996, 2000)*. However, the methodology for measuring gastric emptying in dogs has not been widely standardized. The repeated measurements in the hours following the meal necessitate manipulation of the animal that may slow down gastric emptying.

Butterwick et al *(1994)* reported that the addition of insoluble fiber in moderate concentrations did not have any affect on ingestion in dogs. A group of dogs presenting 15% overweight were given a food rich in various types of dietary fiber (from 6.6% TDF for the control group to 15.6% TDF of DM). The quantities of food were calculated to cover 40% of the energy requirements for maintaining optimal weight, which corresponds to severe energy restriction. Three hours after the main meal, a highly palatable second meal (wet food) was made available to the animals for 15 minutes; consumption was then measured. The trial was conducted twice in a 12-day period. The quantities consumed during the second meal were comparable for the different groups *(Butterwick et al, 1994)*. It is nevertheless difficult to draw any conclusion from these results as the control diet contained 6.7% TDF and the effect of the severe energy restriction had to dominate with respect to the dietary fiber. Lastly, it must be noted that most of the dogs are unable to control their consumption when they are given a highly palatable food.

> Fiber and its effect on weight and body composition

Energy restriction associated with the provision of a high-fiber, low-fat diet (23% and 9% DM respectively) leads to a greater reduction in body fat mass and blood cholesterol concentrations, in comparison to a high-fat, low-fiber diet *(Wolfsheimer et al, 1994a)*. The reduction in body weight and blood pressure are also greater in the case of the former, although the differences are not significant *(Borne et al, 1996)*. The two diets provide 35% of metabolizable energy in the form of protein, which is around 10% higher than a maintenance diet. The use of DEXA has made it possible to collect evidence of modifications in body composition following low-calorie diets, although the weight losses are statistically comparable. Nevertheless, conclusions should be carefully considered because the effects of the two parameters (fat content and fiber content) are confounding in this study. Furthermore, low-fat diets that are not supplemented with fiber produce the same effects in rats *(Boozer et al, 1993)*.

In humans, spontaneous loss of body weight *(Krotkiewski, 1984)* and body fat *(Raben et al, 1995)* has also been reported following the ingestion of soluble or insoluble fiber in obese and non-obese patients. Furthermore, the addition of a supplement of insoluble *(Solum et al, 1987; Ryttig et al, 1989)* or mixed fiber *(Godi et al, 1992)* produces a greater reduction in weight in obese patients subjected to moderate energy restriction (1200 kcal/day), compared with a control diet.

The results of the studies reported above suggest that dietary fiber plays a beneficial role in the weight loss of obese patients. The effects of fiber are summarized in **Tables 13A &B**.

> Carbohydrates

The content and quality of the digestible carbohydrates – primarily starch – of low-calorie diets has also been the subject of some studies. In human food, the concept of the glycemic index (GI) was developed by Jenkins et al *(1981)* as a means of predicting the glycemic response following

the ingestion of food containing established quantities of carbohydrates. The GI of a food is defined as the ratio (in %) of the glycemic response following the ingestion of a 50 g portion of digestible carbohydrates to the response after ingestion by the same individual of a 50 g portion of starch in the form of white bread.

Table 13a - Overview of the effects of dietary fiber

Effects studied
- Prevention of constipation, digestive hygiene - Dilution of the energy concentration and density of foods - Satietogenic effect - Control of glycemia and insulinemia - Control of blood lipids - Reduction in the odor of fecal matter
Disadvantages
- Reduction in the digestibility of dry matter - Increase in the quantity of fecal matter - Increase in the frequency of defecation

Table 13b - Effects of dietary fiber according to the level of incorporation in the food

	Insoluble fiber		Soluble and insoluble fiber		Soluble fiber	Fermentable fiber
Examples	Purified cellulose, peanut and soy shells, etc.		Beet pulp		Guar gum, pectins, psyllium, etc.	Inulin, MOS, FOS, etc.
Rate of inclusion	**< 5% dry matter (DM)**					
Prevention of constipation	+		+		+	+
Reduction of fecal odors	-		-		-	+
Health of the digestive tract	?		+		+	+
Rate of inclusion	**5-10% DM**	**> 10% DM**	**5-10% DM**	**> 10% DM**	**5-10% DM**	**5-10% DM**
Obesity - reduction of energy density - induction of satiety	+ ?	++ ?	+ ?	++ ?	+ ?	+ ?
Lipid dysmetabolism	-	-	-	+	+	+
Diabetes mellitus - control of glycemia	-	-/+	-	+	+	?
Chronic kidney failure - reduction of uremia	-	-	-	+	+	+
Health of the digestive tract - chronic intestinal bacteria proliferation - prevention of colon cancer	- ?	- ?	? ?	? ?	?	+ + (humans)
Various - stimulation of immunity						+

The GI is a concept utilized in the dietetic treatment of diabetic patients and in some diets (including the Montignac diet) that confirms the utility of sources of non-refined cereals or dietary fiber *(Wolever & Jenkins, 1986)*. The GI is controversial however, because individual responses can be variable and the development of glycemia after a complete meal is different from the changes induced by the absorption of a single type of carbohydrate *(Jenkins et al, 1988)*. Nevertheless, it would appear that the consumption of non-refined cereals plays a part in the prevention of human obesity, especially by acting on the hormonal regulators of obesity *(Koh-Banerjee & Rimm, 2003)*.

The application of this concept in diets for diabetic or obese dogs is fairly logical. The principle is to use sources of starch that stimulate the production of insulin only to a limited degree. This limits the storage of energy in the form of triglycerides in the adipocytes. The complete food that limits glucose production does not stimulate the production of insulin – a lipotrope hormone – as much. From a practical perspective, white rice is not recommended as a main cereal in low-calorie foods, whereas barley and corn constitute the best sources of energy *(Sunvold & Bouchard,1998)* **(Figure 8)**.

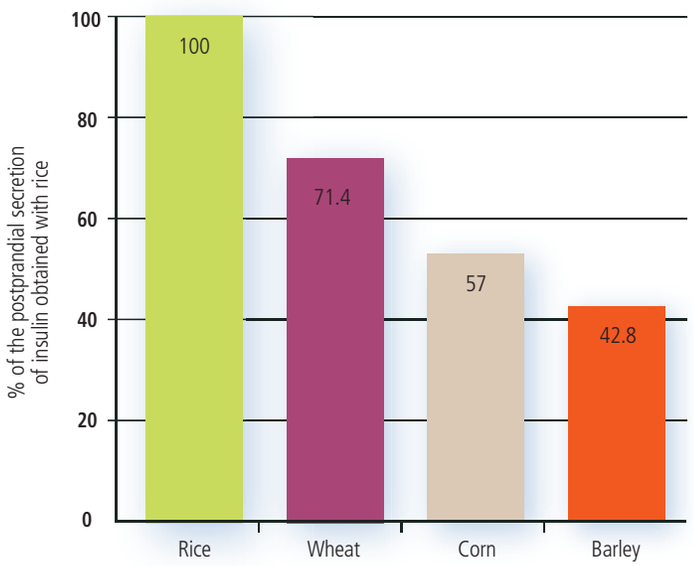
> Minerals, vitamins and trace elements

The mineral, vitamin and trace element concentrations of low-calorie foods must be higher than those in maintenance foods, similar to protein. Restricting energy intake and the quantities given must not lead to deficiencies of these essential nutrients.

> Special and nutraceutical ingredients

Several special ingredients (food additives or other nutritional supplements) are added to low-calorie foods to induce certain benefits. They are principally various sources of dietary fiber, antioxi-

FIGURE 8 - COMPARISON OF THE POSTPRANDIAL SECRETION OF INSULIN OBTAINED WITH VARIOUS SOURCES OF STARCH
(From Sunvold & Bouchard, 1998)



All the dogs in the study were fed with the same dry maintenance food containing the same quantity of starch (30%). Only the origin of the starch varied. The results are expressed as a percentage of the secretion of insulin (in mg/mL/min) measured in dogs fed with a food formulated on the basis of rice. Of the cereals used, barley induces the least post-prandial insulin secretion.

dants, L-carnitine, chromium and even chondroprotective agents. At this time, the addition of chromium to foods is not permitted in Europe. A non-exhaustive list of these products and the benefits identified are presented in **Table 14**.

L-carnitine is an amino acid synthesized de novo in the liver and the kidney from lysine and methionine and in the presence of ascorbate. L-carnitine is an agent that facilitates the transportation of long-chain fatty acids in the mitochondria where they are subjected to β-oxidation **(Figure 9)**. Adequate levels of L-carnitine are therefore needed in muscle to produce energy from fatty acids.

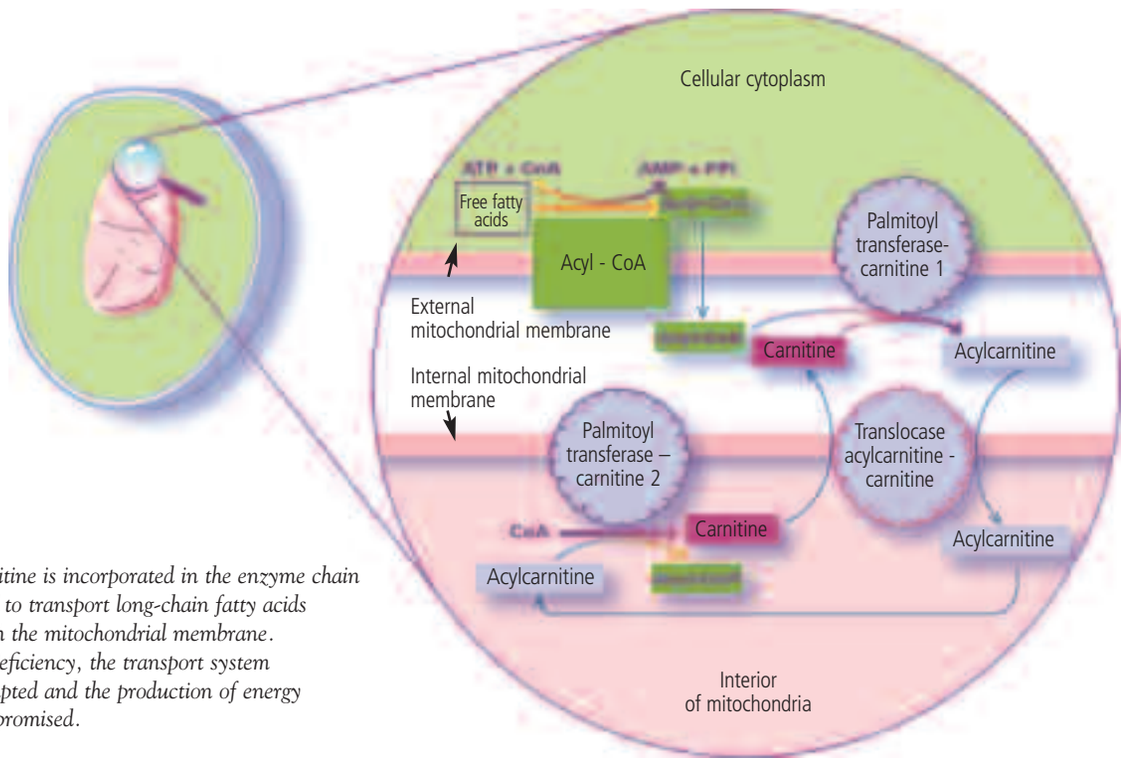
L-carnitine is not synthesized in muscle but provided by the blood following hepatic or renal synthesis or via the intestinal absorption of the L-carnitine present in food. The main dietary sources are red meat, fish and dairy products, whereas white meat is less rich in L-carnitine and vegetables do not contain any L-carnitine. L-carnitine is not considered to be an essential nutrient, because it is synthesized by the organism. L-carnitine deficiency is responsible for dilated cardiomyopathies in a small population of dogs. Several studies on monogastric animals have suggested that the provision in the diet of L-carnitine improves nitrogenous retention and modifies the body composition in favor of muscle mass. This effect has been shown in growing dogs *(Gross & Zicker, 2000)*.

TABLE 14 - PARTICULAR INGREDIENTS USED IN LOW-CALORIE COMMERCIAL DIETS AND THE EXPECTED BENEFITS

Ingredients	Expected benefits
L-Carnitine	- Stimulation of fatty acid oxidation
Chromium	- Control of glycemia
Fructo-oligosaccharides (FOS)	- Reduction of fecal odors - Optimization of intestinal flora - Normalization of blood lipids
CLA (conjugated linoleic acid)	- Anti-adipogenic action
Hydroxycitrate	- Prevention and reduction of visceral adiposity
Vitamin E, taurine, lutein	- Antioxidants
Vitamin A	- Normalization of the leptin blood concentration
Glucosamine, chondroitin	- Chondroprotective agents
Fish oil rich in EPA	- Sources of omega 3 fatty acids - Health of skin and coat

Because muscle mass requires more resting energy than fat mass, augmentation of muscle mass may prevent obesity. The incorporation of L-carnitine into low-calorie diets for obese dogs is recommended to modify body composition *(Allen, 1998; Sunvold et al, 1998; Caroll & Côté, 2001)*. The addition of L-carnitine to a low-calorie diet increases the weight loss in obese dogs and stimulates the maintenance of muscle mass *(Sunvold et al, 1998)*. In this trial, no significant differences were noted between the two supplemental levels (50 and 100 mg/kg of food).

FIGURE 9 - MODE OF ACTION OF L-CARNITINE



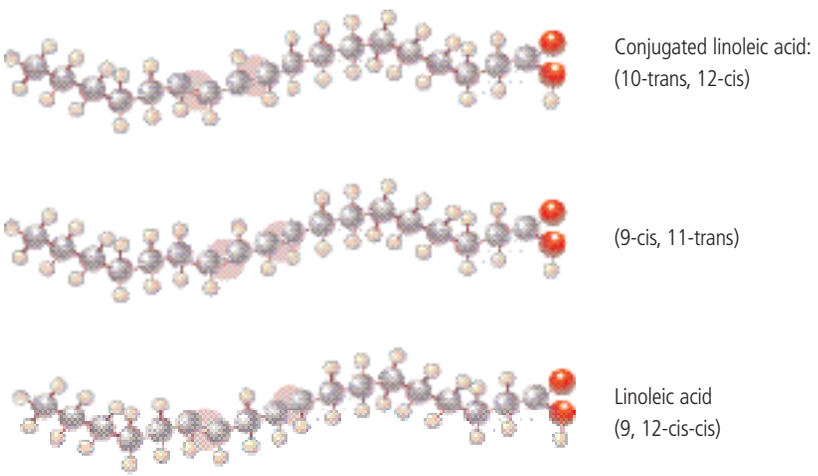
L-carnitine is incorporated in the enzyme chain needed to transport long-chain fatty acids through the mitochondrial membrane. With deficiency, the transport system is disrupted and the production of energy is compromised.

The incorporation of L-carnitine is recommended for obese dogs fed a low-calorie diet to prevent the rebound effect. In home-prepared rations the choice of ingredients naturally rich in L-carnitine is recommended.

Conjugated fatty acids derived from conjugated linoleic acid (CLA) have been widely studied in animals due to their various beneficial properties, with effects on neoplasias, atherosclerosis, obesity, the immune function and diabetes mellitus. CLAs are naturally found in ingredients that come from animals, such as dairy products, meats and fats. They are synthesized in the rumen by certain microorganisms and by some animal enzymes. The two isomers identified as being biologically active are 9-cis, 11-trans and 10-trans, 12-cis **(Figure 10)**. Some specific CLA isomers prevent the development of obesity in mice and pigs. Nevertheless, the properties of CLAs to modulate obesity in humans and monogastric animals remains a subject of controversy, as clinical trials have produced contradictory results *(Azain, 2003)*. It has however been shown that the 10-trans, 12-cis isomer prevents the accumulation of triglycerides in human pre-fat cell cultures. This antiadipogenic action is partly due to an effect on the regulation of the metabolism of glucose and fatty acids in the fat cells *(Brown & McIntosh, 2003)*.

In humans, the effect found is a reduction of fat mass. The work also supports the fact that the CLAs do not help reduce the body weight of obese patients but do increase the lean mass at the expense of the fat mass *(Kamphuis et al, 2003)*. The doses used in the clinical trials on humans were of the order of 1.4-6.8 g of CLA per day *(Blankson et al, 2000; Kamphuis et al, 2003)*.

FIGURE 10 - COMPARATIVE STRUCTURE OF CONJUGATED LINOLEIC ACID AND LINOLEIC ACID



The isomers (10-trans, 12-cis) and (9-cis, 11-trans) of linoleic acid are the main components of conjugated linoleic acid. Unlike linoleic acid, the double bonds are not separated by a methyl radical.

In dogs, the addition of CLA (0.6% DM) in a low-calorie high protein diet (55% DM) has helped limit the augmentation of the plasma nitrogen concentration typically observed when this type of diet is used *(Bierer & Bui, 2003)*. A second study shows a positive effect of CLAs on body composition and the ingestion of food in dogs fed *ad libitum*. Lastly, an in vitro fermentation trial shows that CLAs are produced in very low quantities by the intestinal bacteria in dogs. The authors therefore recommend the addition of CLA to low calorie diets *(Fukoda et al, 2002)*.

Garcinia Cambogia extract is used to limit lipogenesis in humans *(Cha et al, 2003; Hayamizu et al, 2003)*. The active ingredients are hydroxycitrates or AHA (alpha hydroxycitric acid), commonly known as "fruit acids." The expected benefits include inhibition of hepatic lipogenesis and a reduction of energy ingestion *(Westerterp- Plantenga & Kovacs, 2002)*. The mechanisms of action have not been clearly established.

Garcinia Cambodgia
The sole source of alpha hydroxycitric acid (AHA) in a concentrated form is found in certain plants, such as the fruit of Garcinia Cambogia, which comes from Southeast Asia.

> Low-calorie home-prepared diets

Obese dogs can be fed home-prepared diets. However, the conditions described above must be respected. Lean ingredients should be selected (lean meat), high-fiber sources of starch (complete cereals), vegetables, dietary fiber supplements in purified form (bran, soy fiber) and the diet must be carefully formulated to ensure it is complete and balanced. Compared with a maintenance diet the protein-calorie ratio will be higher as will the micronutrient concentration and the dietary fiber percentage. Nevertheless, this last point may pose problems if the animal sorts and leaves the vegetables needed to provide fiber. This can be avoided by using complete starchy food (bread, rice or pasta). The intake of crude fiber of the ration may then be raised to 4-5% DM. By using dietary fiber supplements it is possible to increase the concentration to 7-10% DM.

3 - Clinical food

A consultation with owners of obese dogs requires the veterinarian's time. It is important to respect the various steps described above and especially to convince the owner. Such a consultation is of no use if the owner does not want it or if those involved do not have the time. This problem needs at least 30 minutes of everyone's time.

► Approach of the owner

Most owners of obese dogs do not on their own accord schedule an appointment to explore solutions to the problem of obesity in their pet. On the contrary, they are generally unable to evaluate their animal's weight condition *(Singh et al, 2002)*. That means that it is up to the veterinarian to identify the problem, convince owners of its seriousness and motivate them to implement a dietary change. Owners also have to be warned that the diet will not be easy and will be spread over a long period.

Two types of approach are envisaged in terms of communication, positive messages that explain all the advantages of slimming for the dog's health (e.g. greater alertness, etc) and negative messages explaining all the adverse effects of obesity and associated diseases. It is advisable to adapt the approach to suit the owner of the animal. It is not always necessary to put forward a large number of arguments. Select the arguments that are most likely to appeal to the owner, such as longevity, quality of life and the owner's responsibility to keep the animal in a healthy condition. It is necessary to present precise arguments, directly linked to the problems presented by the animal and to focus on the improvement or eradication of the disease to motivate the owner. The owner will also feel that the problem is being taken seriously if the veterinarian or other clinic staff are available during the period of dietary therapy.

Motiving a change

(G. Muller)

Malarewicz wrote "every request for change is accompanied by a request not to change..." *(Malarewicz & Reynaud, 1996).*

With respect to our problem, this could be expressed as "I would like my dog to lose weight but I don't want to change its food" or "my dog is too fat but I love giving him treats and seeing him eat them with pleasure."

Every veterinarian knows that simply prescribing a diet will not be enough to obtain weight loss in the dog. The difficulty lies in motivating owners to keep to the diet and to help them remain strong when their dog begs for a treat.

Prochaska & DiClemente *(1984)* have created a model for motivating change, divided into various steps. This model is well suited to guiding your prescription **(Figure 11)**.

• Step one: Absence of awareness
In this pre-contemplation phase the veterinarian must state the facts of the case: "Your dog is overweight because…" or "Your dog has put on weight since the last visit." This step lasts until an owner is able to say that the dog is too fat..

• Step two: Contemplation
The owner has become aware of the problem and the veterinarian must invite her or him to contemplate change and the reasons for it. Owners have to be helped if they are not to revert to step one. They have to be shown that the situation is abnormal and that change is needed.

• Step three: Awareness of the problem and the necessity of change
The owner has to be shown how the change can be achieved. Clearly, as mentioned above, it is important to monitor that the situation does not go backwards. The benefit of the diet is always situated in the future, while the pleasure of the treat is immediate.

• Step four: Change
The owner must be given permanent support and must not be reproached if results are slow in coming. It is a difficult time and it is important to emphasize the importance of results.

► Rationing in practice

> Anamnesis and dietary history

The discussion must focus on several general points, not the least the dog's environment and specifically the way it is fed. While it is not always possible to calculate the energy ingested by the obese animal, a discussion with the owner will be a source of direct and indirect information and input for the formulation of solutions that avoid pitfalls. The following information may prove useful:
- Regular food: brand, type, energy value
- Daily quantity
- Feeding method: *ad libitum* versus limited quantity
- Identification of the person who feeds the dog and other people involved
- Distribution of treats, leftovers, etc.
- Number of animals in the home and the obese animal's potential access to food.

In the case of extremely obese animals it is essential to ensure that the quantities of energy given as part of a diet are lower than those typically consumed by the dog. In the extreme obesity phase energy expenditure can be very low.

> Clinical examination and determination of weight loss

The aim of the clinical examination, and where necessary various supplementary tests, is to check that the state of obesity is not secondary to an endocrine disease. The determination or estimation of ideal weight is necessary if an appropriate target is to be set for the owner and to determine the best energy allocation **(Table 11)**. The length of the diet can be calculated on the basis of this data. Bearing in mind this is a consultation by a general practitioner these parameters may appear to be fairly technical, but it must not be forgotten that the interviewee is the owner of the animal and clear, data-based messages ("Your dog must lose x kg in y months") are much more persuasive than a vague approach ("Your dog is too fat. We are going to put him on a diet").

© Diez

English Bulldog
A discussion with the owner will be enough to identify the dog's bad eating habits.

> Selection of food

Commercial foods for treating obesity in domesticated carnivores must have a low energy density. In fact, it is a legal requirement *(Diez et al, 1995)*, albeit a fairly vague one. The various types of low-calorie food are presented above. Whatever the type of product selected, it must be complete, balanced and palatable. A lack of palatability may actually cause the dog to refuse the food, which is not the desired goal. Traditional means can be used to increase the palatability of food, such as adding water or introducing a period of transition.

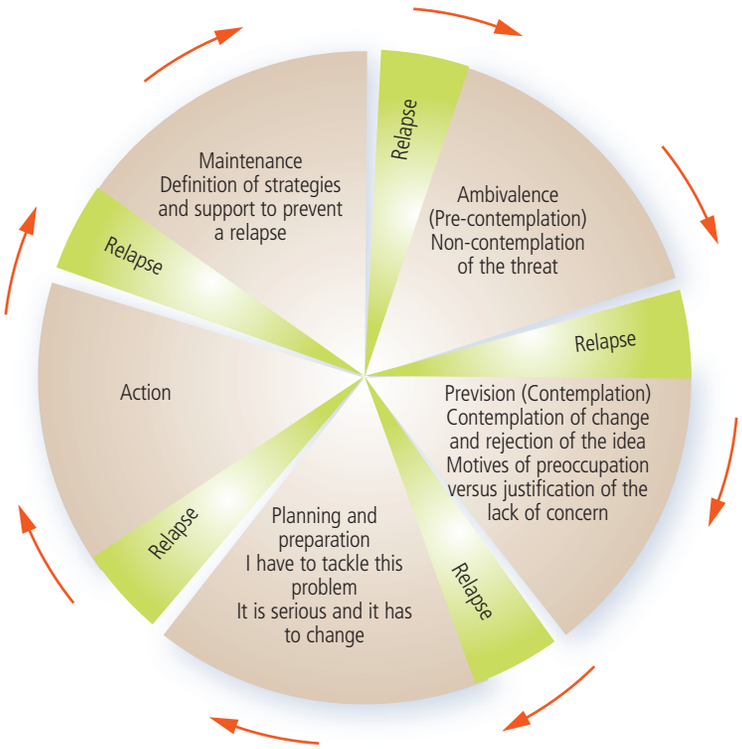
> Rationing and spreading

The selection of the level of restriction and the type of food depends to a large degree, on the initial situation. The aim is to obtain a sustainable modification in the food to obtain a sustainable reduction in body weight in the long term. In humans, the practice of highly restrictive diets that

permit rapid and easy weight loss is advised against. This method does not produce better results and fuels relapse and the rebound effect. The vicious circle of major restriction and compensatory hyperphagia provokes incessant weight fluctuations and in the long term aggravates the situation.

In the case of dogs the problems are not the same at all, because in principle the diet is controlled after weight loss has been achieved. That means that a severe restriction is not necessary if the dog is moderately obese and does not present clinical signs, and if weight loss is not considered necessary due to the appearance of a pre-diabetic state. A moderate restriction and a relatively slow loss of weight can certainly be contemplated in these cases. On the other hand, a much more radical approach will be necessary when the dog presents for example, severely obese and with a torn cruciate ligament, especially if the surgeon refuses to intervene before the dog has lost a significant amount of weight. Such a pathological history makes the owner highly vigilant with respect to the risk of relapse. In this case, his motivation is high enough to allow a severe restriction.

FIGURE 11 - THE DICLEMENTÉ AND PROCHASKA MODEL



The model explains why abstinence-based therapies fail most often. Owners do not advance directly from ignorance of a problem and absence of motivation to action and change. They first have to acknowledge the problem and contemplate solutions. Racing through these steps will end in denial and obstruction.

The veterinarian must identify which step an owner has reached in an interview. There is a specific response for each step. These responses are grouped in the table below.

1. Precontemplation	a) Demonstrating the anomaly/objectivizing the problem
2. Contemplation	b) Insisting on the importance of change versus ignoring the problems
3. Planning and preparation	c) Proposing a simple, realizable change
4. Action	d) Providing support without generating shame
5. Maintenance	e) Providing general information on the options without exercising pressure
6. Relapse	f) Presenting the least damaging solutions

The principles of rationing and the way the consultation of the obese dog is conducted as shown in **Tables 15 and 16** are inspired by the recommendations of several authors *(Andersen & Lewis, 1980; Lewis et al, 1987; Parkin, 1993; Laflamme & Kuhlman, 1993b; Laflamme et al, 1994b; Wolfsheimer, 1994b; Diez et al, 2002)*. The daily energy allocation is calculated on the basis of the initial obesity: 50-85 kcal /kg $BW^{0.75}$ is ideal and varies depending on the sex and the desired speed of weight loss **(Table 11)**. Such rationing leads to a weight reduction. If the weight of the animal does not fall, the intake will have to be reduced again after verifying that the owner is not giving the dog extra food or treats *(Markwell et al, 1990)*. The aim is to induce a weekly loss of 1-2% of the initial weight. Spreading the daily ration over three or four (and at least two) meals will increase postprandial thermogenesis *(Leblanc & Diamond, 1985)*.

TABLE 15 - EXAMPLE OF HOW TO DETERMINE THE QUANTITIES OF LOW-CALORIE FOOD TO BE GIVEN

Step 1	Determining the optimal weight and the excess weight	Neutered bitch of undetermined breed, body weight: 19 kg Estimated ideal weight: 15 kg Excess weight: (19/15) = 27%
Step 2	Selecting the daily energy allocation **(Table 11)**	Excess weight less than 30%: - 80 kcal/kg ideal $BW^{0.75}$, for a loss of 6% of initial weight per month - 75 kcal/kg ideal $BW^{0.75}$, for a loss of 7.5% of initial weight per month
Step 3	Calculating the daily energy allocation	Energy allocation = $80 \times 15^{0.75}$ = 610 kcal for a loss of 6% of initial weight per month
Step 4	Determining the daily quantity of food (energy concentration: 3275 kcal /kg)	Daily quantity: 610/3275 = 0.185 kg, spread over two or three meals
Step 5	Estimating the length of the diet based on a loss of 6% per month	Initial weight: 19 kg, quantity to be lost: 4 kg Length of the diet: 4 /(19 x 0.06) = 3.5 months

TABLE 16 - OVERVIEW OF THE OBESE DOG CONSULTATION

Step 1	Discussion with the owner, collection of information, identification of risk factors
Step 2	Clinical examination: body weight, body condition score, evaluation of ideal weight Supplementary tests if necessary
Step 3	Convince the owner to introduce a low-calorie diet and regular exercise, if the dog's state of health allows
Step 4	Selection of a low-calorie food and determination of daily quantities **(Tables 11 and 15)**
Step 5	Precise written document detailing quantities, mode of rationing and supplementary recommendations (no treats, exercise, etc.) Reference weight curve
Step 6	Planning checkups - weekly weighing - monthly checkup visits at surgery or clinic

© Lanceau

Yorkshire terrier
The increase in activity must be gradual. A brisk walk of 30 minutes 15 minutes twice daily is recommended every day.

> Behavioral support

Dietary habits must be changed to produce weight loss in the dog and then stabilize the weight. Giving leftovers and treats may lead the dog to beg *(Norris & Beaver, 1993)*. The dog should be fed only in its bowl and should be kept at a distance when the humans in the household are eating, especially if they are used to giving the dog food at these times. Bad habits can be replaced with new rituals.

> Monitoring the dog during the diet

• *Scheduling checkups*

It is reasonable to ask the owner of an obese animal to bring the dog for a checkup every month to evaluate the speed of weight loss, conduct a clinical examination and adjust the energy quantities and so the food given if necessary. The dog must be weighed once a week, however, at the same time and with the same scales, if at all possible.

• *Establishing a weight loss curve*

A weight loss curve enables visualization of the development of the dog's weight and is a motivating factor for the owner. During the first visit, it is advisable to establish an individual weight loss curve showing the initial weight and the curves for 1% and 2% of initial weight loss per week. There are computer programs for quickly visualizing projected weight loss. The owner's reference is to keep the dog's weight between the two curves. The prognosis depends almost exclusively on the owner's motivation *(Markwell & Butterwick, 1994)*.

In practice, the initial weight loss target is rarely achieved: the actual loss is generally lower than 1-2% of initial weight per week. In two control studies the weekly losses were 0.78% and 0.86% respectively. In a third study on 9 obese dogs the rate of loss varied between 0.8% and 3.1% (average: 1.9%) per week for a length varying from 4 to 38 weeks (average: 18). All the dogs achieved the target weight established at the start *(Diez et al, 2002)*.

CAUSES OF THE REBOUND EFFECT

- Absence of awareness that the maintenance of ideal weight is a long-term target
- Absence of long-term changes in dietary habits and the return to a certain laxness, due to either ignorance or ease. The owner starts to give the dog treats and leftovers or stops weighing the daily quantities.
- Absence of exercise: reduction in walks, reduction in available space after moving house, etc.
- Changes to the environmental conditions that favor a constant weight: the dog is put in a vacation kennel (absence of the owner), arrival of another animal in the home, absence of control of those that feed the animal (children, neighbors, friends, staff, etc.)
- Changes to the food initiated by the owner or the veterinarian: switch to a higher-energy food without adjusting quantities
- Changes in the dog's living or health conditions: appearance of anxiety, aging or disease.

The list above is not exhaustive. It would appear that maintaining the ideal weight is a target that necessitates the active involvement of the dog's owners.

There are many reasons that may explain these differences and they all deserve attention. The first is clearly the owner's lack of motivation when at home: giving the dog quantities in excess of the amounts agreed, as well as treats and leftovers. The complete lack of control with respect to total food ingestion is another problem: knowledge of the energy value of a staple is often poor. The lack of exercise is also to blame. Lastly, not adjusting the ration during the diet is a major factor for failure.

► Physical exercise

The aim of physical exercise is to increase energy expenditure and prevent the loss of muscle mass and bone mass. The effect of weight loss associated with physical exercise generally improves the animal's endurance; these are the positives for owners. There are pathological conditions, however, including an osteoarticular complaint or a torn cruciate ligament, that make exercise impossible, at least for a certain period of time.

4 - Post-diet monitoring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There have not been any studies published on the long-term development of body weight of companion dogs that have followed a low-calorie diet.

Once weight loss has been achieved, it is vital to monitor the dog's weight regularly and provide the owner with advice on the selection of a maintenance food and the quantity of rations. In dogs, ideally checkups should be scheduled every month until the dog's weight has stabilized over a period of three to four visits; fluctuations in weight must be limited to around 5% *(Burkholder & Bauer, 1998)*.

Generally speaking, at the end of the diet a gradual dietary transition is preferred, in terms of both quantities and type of food. The veterinarian has two options:

- Continuing with the same (low-calorie) type of food and gradually increasing the quantities to maintain the weight.
- Selecting a food with a little higher energy density while maintaining the same quantity as at the end of the diet. This will increase the energy intake. So if the energy density of a low-calorie food is 2800 kcal/kg for example, the same quantity of food with an energy density of 3200 kcal/kg will automatically lead to increased daily energy intake of 14%. This is a relatively simple option; it consists in changing the food without changing the quantities. It will be appropriate for the transition of a food that is a little energy-denser, but it is not recommended if the food selected is much richer in energy.

A rebound effect is generally observed in dogs in the absence of strict measures *(Kimura et al, 1991; Laflamme & Kuhlman, 1995)*. There are no precise figures relating to the scale of this rebound effect. In humans, long-term studies appear to show that the weight put back on in the twelve months following the end of the diet is between around 33% and 50% of the weight lost during a low-calorie diet. It is therefore advisable to consider obesity as a chronic disease that requires permanent monitoring *(Wadden, 1993)*.

From a practical perspective, the quantity of energy needed to maintain a constant weight must be known and, all things being equal (the dog's activity level and lifestyle, etc.), it must be adjusted when the food is changed. It is important to warn owners not to change the food without verifying the energy intake. This point is particularly important, because obese dogs are often older individuals and as a consequence it is highly likely that their food has been changed to respond to different physiological (aging) or pathological conditions. Lastly, it should be noted that there is a flagrant lack of data on weight monitoring after a diet.

After making huge efforts to achieve the targets set at the start of the process, at the end of the diet owners may lapse into old habits, in spite of their contentment at how their dog looks.

5 - Prevention of obesity

The best treatment for obesity is prevention

Knowledge of the epidemiology of obesity is a prerequisite for active lifelong preventative tools. Prevention is either passive or active.

Passive prevention consists in collecting as much data as possible throughout the animal's life and using the data to the fullest extent. In day-to-day veterinary medicine all dogs must be weighed and the data carefully noted in the patient's file and 'passport.' Passive prevention also involves the use of body condition scoring.

Active prevention goes further. It consists in taking responsibility for the dog's food and its energy ration, and continuing to monitor its diet throughout its life.

Conclusion

As we have progressed through this chapter, we have seen that canine obesity is a major pathology that affects approximately 25% of the dog population. Bearing in mind the knowledge we have today, it is unacceptable to ignore a disease that has so many harmful consequences for the animal's health and that reduces its life expectancy. When prevention proves ineffective the veterinarian must develop a systematic approach that takes account of diet, from a quality and quantity perspective, and the other environmental factors. All told, the owner's perception of the message will determine the success of the nutritional treatment and the subsequent maintenance of the body weight.

Behaviors or tools can be developed by veterinarians to encourage owners to prevent obesity

For puppy owners highlight which breeds that are predisposed to obesity, provide information on the expected adult weight, encourage the graphing of weight growth curves, discourage bad habits, emphasize the harmful effects of obesity and provide comprehensive and personalized information on food.

Generally speaking, provide precise information about food for dogs. Recommend quantities and types of food, behaviors to avoid, highlight every change in body weight, even minor, and establish a link with dietary habits in the home.

Limit the energy intake of animals immediately after neutering.

Encourage regular exercise and if possible, quantify it (minimum x hours per week).

Organize a multidisciplinary consultation for obese dogs together with an endocrinologist and a behaviorist.

Organize a dog health consultation in the form of an annual checkup and show an interest in monitoring the dog's weight and diet.

Provide a platform scale in the waiting room or a special room for example so that owners are encouraged to weigh their animals regularly.

Provide information on canine obesity in layperson's terms with posters in the waiting room, information sheets, 'before' and 'after' photos, etc.

Involve all staff in the veterinary clinic in the fight against obesity and encourage original initiatives, such as obesity awareness-raising days.

Owners' questions

Q	A
What should I do if my dog refuses to eat its diet food?	In any event, the food must be weighed and given in several small meals at fixed intervals. There is no use reducing the time of presentation and increasing the number of meals. Giving the dog 30 minutes to eat its food three or four times per day is a more effective way of stimulating ingestion than filling the bowl and letting to dog decide when it eats. Mixing the food with warm water may also increase palatability.
What should I do if my dog is hungry and keeps begging for food?	Never eat in the presence of your dog; have it leave the room when you eat or prepare the family meal. You could give the dog part of its daily ration in the form of kibbles as a reward. Instead of giving your dog food, take it for a walk, give it a stroke or lavish it with attention in some other way. There are behaviorists who recommend some original techniques, including keeping a container on the table for the food that you want to give your dog, be it snacks or leftovers. The aim is to stop the dog begging; behavior that is strengthened periodically when the owner gives the dog food extras. The container is then emptied into the dog's bowl at the dog's own meal time. In most cases, the container will remain empty after a few meals.
What should I do if I have two or more animals in my home?	There must be a strict separation at mealtimes. A cat's food can be placed somewhere high up, out of reach of an obese dog. The bowls must never be exchanged. If two animals have different needs they will obviously have to be fed differently, from the perspective of both quality and quantity. This aspect must be explained at the first consultation.
What should I do if it is impossible for me to feed my dog at least three times a day?	It is important to spread the ration throughout the day in order to increase the loss of energy. The daily ration must be spread over at least two meals.
Could a restrictive diet make my dog aggressive?	Never. Aggression due to energy restriction is a sign of a serious problem in the relationship between the owner and the dog.
Is it okay to give my dog just a few small treats?	No, it is totally inadvisable to give the dog treats. A low-calorie diet entails not only a drastic reduction in dietary intake but also a long-term change in habits to avoid a rebound effect. As a consequence, this type of behavior should be cut out. It is possible to reserve a portion of the weighed kibbles of the daily ration to give to the dog after exercises or at other times when treats are customarily given. But the owner must never be given the idea that after the diet it will be okay to revert to the old situation that made the dog obese in the first place. The veterinarian must be very clear on this matter before taking on the obese dog.

Questions veterinarians should ask themselves

Q	A
If the weight loss is negligible or non-existent after a few weeks of the diet what should I do?	Verify that the animal has been weighed on an empty stomach using the same scales as were used at the start of the diet. Check that the dog is not suffering from an endocrine disease or undergoing a course of medication that is slowing weight loss. Verify that the quantities of food given correspond to the quantities recommended and that they are weighed carefully. If in doubt, compare the dietetic food purchased with the length of the diet. Verify that the daily energy allocation is not greater than the pre-diet intake. If in doubt, calculate the energy allocation again **(Table 10)**. If the owner appears to be telling the truth and the intake is correct, a 10% reduction in quantities is advisable.
If the weight loss is greater than 2% of initial weight in the first week should I increase the quantity of food given?	No. During the first few weeks of the diet the weight loss may be greater than foreseen. Ideally, it should not exceed 3% of initial weight. But after this somewhat abrupt start a slowing down and eventual stabilization of the weight loss is generally observed. It has also been shown that the initial quantities often have to be restricted at the end of the diet for dogs that are very overweight. That is why it is sometimes advisable to wait a few weeks before increasing the quantities. On the other hand, owners appear to be very satisfied when the dog loses a lot of weight at the start of the diet. This could have an encouraging effect, but the reverse may also be true. An often observed reaction is a flagging of discipline, resulting in an attenuation of the weight loss. One way of preventing this is to check the dog frequently at the start of the diet to ensure that the diet is being followed.

References

Abel RM, Grimes JB, Alonso D et al. - Adverse hemodynamic and ultrastructural changes in dog hearts subjected to protein-calorie malnutrition. Am Heart J 1979; 97: 733-44.

Abraham S, Nordseick M. - Relationship of excess weight in children and adults. Public Health Rep 1960; 75: 263-73.

Allen TA - The effect of carnitine supplementation on body composition in obesity prone dogs. In: Proceedings of the Symposium "L-carnitine-What difference does it make?" 1998; 35.

Alonso-Galicia M, Dwyer TM, Herrera GA, et al. -Increased hyaluronic acid in the inner renal medulla of obese dogs. Hypertension 1995; 25: 888-92.

Andersen GL, Lewis LD - Obesity. In: Kirk RW (ed) - Current Veterinary Therapy. 7th edition. 1980; 1034-1039.

Anderson RS - Obesity in the dog and cat. Vet Ann 1973; 14: 182-6.

Anderson DB, Corbin JE - Estimating body fat in mature Beagle bitches. Lab Anim Sci 1982; 32 : 367-70.

Armstrong PJ, Lund EM - Changes in body condition and energy balance with aging. Vet Clin Nutr 1996; 3 : 83-87.

Astrup A, Vrist E, Quaade F - Dietary fibre added to very low calorie diet reduces hunger and alleviates constipation. Int J Obes 1990; 14: 105-12.

Azain MJ - Conjugated linoleic acid and its effects on animal products and health in single-stomach animals. Proc Nutr Soc 2003; 62: 319-28.

Baba E, Arakana A - Myocardial hypoxia in an obese Beagle. Vet Med 1984; 79: 788-91.

Bailhache E, Ouguerram K, Gayet C et al. - An insulin-resistant hypertriglyceridaemic normotensive obese dog model: assessment of insulin resistance by the euglycaemic hyperinsulinaemic clamp in combination with the stable isotope technique. J Anim Physiol Anim Nutr 2003a; 87: 86-95.

Bailhache E, Nguyen P, Krempf M et al. - Lipoprotein abnormalities in obese insulin-resistant dogs. Metabolism 2003b; 52: 559-64.

Bierer TL, Bui LM - The effect of high protein diets and conjugated linoleic acid on weight loss in dogs. In: Proceedings of the Waltham Symposium "Nature, Nurture and the case for Nutrition", Bangkok (Thailand), October 29-31, 2003: 27.

Blankson H, Stakkestad JA, Fagertun H et al. - Conjugated linoleic acid reduces body fat mass in overweight and obese humans. J Nutr 2000; 130: 2943-8.

Bodey AR, Michell AR - Epidemiological study of blood pressure in domestic dogs. J Small Anim Pract 1996; 37: 116-25.

Bomson L, Parker CHL - Effect of fenfluramine on overweight spayed bitches. Vet Rec 1975; 96: 202-3.

Boozer CN, Brasseur A, Atkinson RL - Dietary fat affects weight loss and adiposity during energy restriction in rats. Am J Clin Nutr 1993; 58: 846-52.

Borne AT, Wolfsheimer KJ, Truett AA et al. - Differential metabolic effects of energy restriction in dogs using diets varying in fat and fiber content. Obes Res 1996; 4: 337-45.

Bouché C, Rizkalla SW, Luo J et al. - Five-week, low-glycemic index diet decreases total fat mass and improves plasma lipid profile in moderately overweight nondiabetic men. Diabetes Cares 2002; 25: 822-8.

Brady LJ, Armstrong MK - Influence of prolonged fasting in the dog on glucose turnover and blood metabolites. J Nutr 1977; 107: 1053-61.

Branam JE - Dietary management of obese dogs and cats. Vet Tech 1988; 9: 490-3.

Brown DC, Conzemius MG, Shofer FS - Body weight as a predisposing factor for humeral condylar fractures, cranial cruciate rupture and intervertebral disease in Cocker Spaniels. Vet Comp Orthop Trauma 1996; 9: 38-41.

Brown JM, McIntosh MK - Conjugated linoleic acid in humans: regulation of adiposity and insulin sensitivity. J Nutr 2003; 133: 3041-46.

Burley VJ, Paul AW, Blundell JE - Sustained postingestive action of dietary fibre : effects of a sugarbeet fibre-supplemented breakfast on satiety. J Hum Nutr Diet 1993; 6: 253-60.

Burkholder WJ, Bauer JE - Foods and techniques for managing obesity in companion animals. J Am Vet Medic Assoc 1998; 5: 658-62.

Burkholder WJ - Precision and practicality of methods assessing body composition of dogs and cats. In: Proceedings of the 6th educational workshop in pet food labelling and regulations at The 2000 Purina Nutrition Forum, 2000, 15p.

Burrows CF, Kronfeld DS, Banta CA et al. - Effects of fibre on digestibility and transit time in dogs. J Nutr 1982; 112: 1726-32.

Butterwick RF, Markwell PJ, Thorne CJ - Effect of level and source of dietary fibre on food intake in the dog. J Nutr 1994; 121: 2695S-2700S.

Carroll MC, Côté E - Carnitine: a review. Comp Cont Educ Pract Vet 2001; 23: 45-52.

Cha BR, Chae JS, Lee JH et al. - The effect of a potential antiobesity supplement on weight loss and visceral fat accumulation in overweight women. Korean J Nutr 2003; 36: 483-90.

Chikamune T, Katamoto H, Ohashi F et al. - Serum lipid and lipoprotein concentrations in obese dogs. J Vet Med Sci 1995; 57: 595-8.

Clutton RE - The medical implications of canine obesity and their relevance to anaesthesia. Br Vet J 1988; 144: 21-8.

Crowell-Davis SL, Barry K, Ballam JM et al. - The effect of caloric restriction on the behavior of penhoused dogs: transition from unrestricted to restricted diet. Appl Anim Behav Sci 1995a; 43: 27-41.

Crowell-Davis SL, Barry K, Ballam JM et al. - The effect of caloric restriction on the behavior of penhoused dogs: transition from restriction to maintenance diets and long-term effects. Appl Anim Behav Sci 1995b; 43: 43-61.

Daminet S, Jeusette I, Duchateau L et al. - Evaluation of thyroid function in obese dogs and in dogs undergoing a weight loss protocol. J Vet Med A 2003; 50: 213-8.

De Bruijne JJ, Lubberink AAME - Obesity. Current Veterinary Therapy VI, Kirk RW (ed) 1977; 1068-70.

De Rick A, De Schepper J - Decreased endurance as a clinical sign of disease in the dog. Vlaams Diergeneesk Tijdschr 1980; 49: 307-21.

Diez M, Leemans M, Houins G et al. - Les aliments à objectif nutritionnel particulier chez les carnivores domestiques: les nouvelles directives de la Communauté Européenne et leur application pratique dans le cadre du traitement de l'obésité. Ann Méd Vét 1995; 139, 395-9.

Diez M, Hornick JL, Baldwin P et al. - Étude des fibres alimentaires chez le chien: Présentation des résultats de 7 essais expérimentaux. Ann Méd Vét 1998; 142: 185-201.

Diez M, Nguyen P, Jeusette I et al. - Weight loss in obese dogs - Evaluation of a high protein and low carbohydrate diet. J Nutr 2002; 132: 1685S-1687S.

Diez M, Nguyen P - Clinical aspects of dietary fibres. In: Proceedings of the 13th ECVIM-CA Congress, 4-6 September 2003, Uppsala, Sweden, 100-1.

Diez M, Michaux C, Jeusette I et al. - Evolution of blood parameters during weight loss in experimental obese Beagle dogs. J Anim Nutr Anim Physiol 2004; 88(3-4):166-71.

Di Lorenzo C, Williams CM, Hajnal F et al. - Pectin delays gastric emptying and increases satiety in obese subjects. Gastroenterology 1988; 95: 1211- 15.

Dixon RM, Reid SW, Mooney CT - Epidemiological, clinical, haematological and biochemical characteristics of canine hypothyroidism. Vet Rec 1999; 145: 481-487.

Durrant ML, Garrow JS, Royston P et al. - Factors influencing the composition of the weight lost by obese patients on a reducing diet. Br J Nutr 1980; 44: 275-85.

Dzanis DA - AAFCO protocols for pet foods intended for weight loss. In: Proceedings of the 6th educational workshop in pet food labelling and regulations at The 2000 Purina Nutrition Forum, Saint Louis, Missouri October 19-22, 2000, 72-77.

Edney ATB - Management of obesity in the dog. Vet Med Small Anim Pract 1974; 69: 46-9.

Edney ATB, Smith PM - Study of obesity in dogs visiting veterinary practices in the United Kingdom. Vet Rec 1986; 118: 391-6.

Elliott DA, Backus RC, Van Loan MD et al. - Evaluation of multifrequency bioelectrical impedance analysis for the assessment of extracellular and total body water in healthy cats. J Nutr 2002a; 132: 1757S-1759S.

Elliott DA, Backus RC, Van Loan MD et al. - Extracellular water and total body water estimated by multifrequency bioelectrical impedance analysis in healthy cats: a cross-validation study. J Nutr 2002b; 132: 1760S-1762S.

Eriksson J, Forsen T, Osmond C et al. - Obesity from cradle to grave. Int J Obes 2003; 27: 722-7.

Ettinger SJ - Dyspnea and Tachypnea. In: Textbook of Veterinary Internal Medicine. Diseases of the dog and cat. 2nd ed, WB Saunders Company, Philadelphia, 1983, 97-99.

Fahey GC, Merchen NR, Corbin JE et al. - Dietary fibre for dogs: II. Iso-total dietary fibre (TDF) additions of divergent fibre sources to dog diets and their effects on nutrient intake, digestibility, metabolizable energy and digesta mean retention time. J Anim Sci 1990; 68: 4229-35.

Festa A, D'Agostino R Jr, Williams K et al. - The relation of body fat mass and distribution to markers of chronic inflammation. Int J Obes Relat Metab Disord 2001; 25: 1407-15.

Fiser RH, Rollins JB, Beisel WR - Decreased resistance against infectious canine hepatitis in dogs fed a high-fat ration. Am J Vet Res 1972; 33: 713-9.

Fisher A, Waterhouse TD, Adams AP - Obesity: its relation to anaesthesia. Anaesthesia 1975; 30: 633-47.

Flournoy WS, Wohl JS, Macintire DK - Heatstroke in dogs: pathophysiology and predisposing factors. Comp Cont Educ 2003; 6: 410-418.

Forbes DC, White DE - A case of marked and unresponsive obesity. Can Vet J 1987; 28: 187.

Ford SL, Nelson RW, Feldman EC et al. - Insulin resistance in three dogs with hypothyroidism and diabetes mellitus. J Am Vet Med Assoc 1993; 202: 1478-80.

Fukoda S, Ninomiya N, Asanuma N et al. - Production of conjugated linoleic acid by intestinal bacteria in dogs and cats. J Vet Med Sci 2002; 64 (11): 987-92.

Garaulet M, Perez-Llamas F, Canteras M et al. - Endocrine, metabolic and nutritional factors in obesity and their relative significance as studied by factor analysis. Int J Obes 2001; 25: 243-51.

Gayet C, Bailhache E, Martin L et al. - Hypersecretion of TNFα and IGF1 in the development of insulin resistance. In: Proceedings of the Joint Nutrition Symposium, Antwerp, August 2002: 27.

Gayet C, Leray V, Nguyen P et al. - Relationship between leptin, lipoprotein lipase (LPL) and insulin resistance (IR) in obese adult dogs. J Vet Int Med 2003a; 17: 744.

Gayet C, Bailhache E, Martin L et al. - Changes in plasma tumor necrosis factor (TNFα), insulin-like growth factor 1 (IGF1), non-esterified fatty acids (NEFA) and insulin sensitivity in overfed and food restricted dogs. J Vet Int Med 2003b; 17: 417-18.

Gayet C, Bailhache E, Dumon H et al. - Insulin resistance and changes in plasma concentration of TNFα, IGF1, and NEFA in dogs during weight gain and obesity. J Anim Physiol Anim Nutr 2004a; 88: 157-65.

Gayet C, Leray V, Siliart B et al. - PPARÁ, lipoprotein lipase, GLUT4, adiponectin and leptin expression in visceral adipose tissue and/or skeletal muscle in obese and insulin resistant dogs. Am J Physiol 2004b, submitted.

Gentry SJ - Results of the clinical use of a standardized weight-loss program in dogs and cats. J Am Anim Hosp Assoc 1993; 29: 369-75.

Glickman LT, Sonnenschein EG, Glickman NW et al. -Pattern of diet and obesity in female adult pet dogs. Vet Clin Nutr 1995; 2: 6-13.

Godi R, Marchini G, Cairella M - Clinical observations on the use of a dietary fibre supplement in the treatment of obese patients. Clinica Dietologica 1992; 19: 297-9.

Grandjean D, Paragon BM - Pathologie liée à l'alimentation chez le chiot. Rec Med Vet 1996; 172: 519-30.

Gregory SP - Developments in the understanding of the pathophysiology of urethral sphincter mechanism incompetence in the bitch. Br Vet J 1994; 150: 135-50.

Gross KL, Zicker SC - L-Carnitine increases muscle mass, bone mass, and bone density in growing large breed puppies. J Anim Sci 2000; 78: 176.

Hannah S - Role of dietary protein in weight management. Comp Cont Educ Pract Vet 1999; 21: 32S-3.

Hand MS - Effects of low-fat/high-fiber in the dietary management of obesity. Proceedings of the 6th Annual Veterinary Forum, Madison, Omnipress, 1988, 702-3.

Harel Z, Biro FM, Kollar LM et al. - Adolescents' reasons for and experience after discontinuation of the long-acting contraceptives Depo-Provera and Norplant. J Adoles Health 1996; 19: 118-23.

Hayamizu K, Ishii Y, Kaneko I et al. - Effects of Garcinia cambogia (hydroxycitric acid) on visceral fat accumulation: a double blind, randomized, placebo-controlled trial. Curr Ther Res Clin Exp 2003; 64: 551-67.

Henegar JF, Bigler SA, Henegar LK et al. - Functional and structural changes in the kidney in the early stages of obesity. J Am Soc Nephrol 2001; 12: 1211-1217.

Hess RS, Kass PH, Shofer FS et al. - Evaluation of risk factors for fatal acute pancreatitis in dogs. J Am Vet Med Assoc 1999; 214: 46-51.

Hoenig M - Comparative aspects of diabetes mellitus in dogs and cats. Molec Cell Endocr 2002; 197: 221-9.

Holt PE - Studies on the control of urinary continence in the bitch. PhD Thesis, Department of Veterinary Surgery, University of Bristol, 1987.

Hotasmisligil GS, Arner P, Caro JF et al. - Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest 1995; 95: 2409-15.

Houpt KA, Coren B, Hintz HF et al. - Effect of sex and reproductive status on sucrose preference, food intake, and body weight of dogs. J Am Vet Med Assoc 1979; 174: 1083-5.

Hu E, Liang P, Spigelman BM - AdipoQ is a novel adipose-specific gene dysregulated in obesity. J Biol Chem 1996; 271: 10697-10703.

Ishioka K, Soliman MM, Sagawa M et al. - Experimental and clinical studies on plasma leptin in obese dogs. J Vet Med Sci 2002; 64: 349-353.

Janicki AM, Sendecka H - Pathological rupture of the cranial cruciate ligament in dogs. Medycyna Weterynaryjna 1991; 47: 489-91.

Jenkins DJA, Wolever TMS, Taylor RH et al. - Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr 1981; 34: 362-6.

Jenkins DJA, Wolever TMS, Jenkins AL - Starchy foods and glycemic index. Diabetes Care 1988; 11: 149-59.

Jerico MM, Scheffer KC - Epidemiological aspects of obese dogs in the city of Sao Paulo. Clinica Veterinaria 2002; 37: 25-9.

Jeusette I, Shibata H, Saito M et al. - Effects of obesity and weight loss on plasma ghrelin concentrations in dogs. In: Proceedings of the 7th Conference of the European Society of Veterinary and Comparative Nutrition, 2003: 39.

Jeusette I, Detilleux J, Cuvelier C et al. - Ad libitum feeding following ovariectomy in female Beagle dogs: effects on maintenance energy requirements and on blood metabolites. J Anim Physiol Anim Nutr 2004a; 88: 117-121.

Jeusette I, Detilleux J, Shibata H et al. - Effects of chronic obesity and weight loss on plasma ghrelin and leptin concentrations in dogs. Res Vet Sci 2005; 79(2): 169-75.

Jeusette I, Biourge V, Nguyen P et al. - Energy restriction during a weight loss programme must be stricter in female than in male dogs. In: Proceedings of the ACVIM Forum 2004c, in press.

Jewell DE, Toll PW - Effects of fiber on food intake in dogs. Vet Clin Nutr 1996; 3: 115-118.

Jewell DE, Toll PW, Novotny BJ - Satiety reduces adiposity in dogs. Vet Therapeutics 2000; 1: 17-23.

Johnson G - Genetic factors in obesity. In: Proceedings of the 6th educational workshop in pet food labelling and regulations at The 2000 Purina Nutrition Forum 2000: 24-26.

Joles JA - Obesity in dogs: effects on renal function, blood pressure, and renal disease. Vet Quart 1998; 20: 117-120.

Joshua JO - The obese dog and some clinical repercussions. J Small Anim Pract 1970; 11: 601-606.

Kaelin S, Watson ADJ, Church DB - Hypothyroidism in the dog: a retrospective study of sixteen cases. J Small Anim Pract 1986; 27: 533-9.

Kamphuis MM, Lejeune MP, Saris WH et al. - The effect of conjugated linoleic acid supplementation after weight loss on body weight regain, body composition, and resting metabolic rate in overweight subjects. Int J Obes Relat Disord 2003; 27: 840-7.

Karczewski W, Ostrzeszewicz G, Nagajewski M - Analysis of factors predisposing to pyometra and the results of surgical treatment. Medycyna Weterynaryjna 1987; 43: 487-9.

Kealy RD, Olsson SE, Monti KL et al. - Effects of limited food consumption on the incidence of hip dysplasia in growing dogs. J Am Vet Med Assoc 1992; 201: 857-63.

Kealy RD, Lawler DF, Ballam JM et al. - Five-year longitudinal study on limited food consumption and development of osteoarthritis in coxofemoral joints of dogs. J Am Vet Med Assoc 1997; 210: 222-225.

Kealy RD, Lawler DF, Ballam JM et al. - Evaluation of the effect of limited food consumption on radiographic evidence of osteoarthritis in dogs. J Am Vet Med Assoc 2000; 217: 1678-80.

Kealy RD, Lawler DF, Ballam JM et al. - Effects of diet restriction on lifespan and age-related changes in dogs. J Am Vet Med Assoc 2002; 220: 1315-20.

Kienzle E, Rainbird A - Maintenance energy requirement of dogs: what is the correct value for the calculation of metabolic body weight in dogs? J Nutr 1991; 121: S39-S40.

Kienzle E, Bergler R, Mandernach A - Comparison of the feeding behaviour and the man-animal relationship in owners of normal and obese dogs. J Nutr 1998; 128: 2779S-2782S.

Kim SP, Ellmerer M, Van Citters GW et al. - Primacy of hepatic insulin resistance in the development of the metabolic syndrome induced by an isocaloric moderate-fat diet in the dog. Diabetes 2003; 52: 2453-60.

Kimura T, Ohshima S, Lida K - A clinical report of the diet therapy on an obese dog. J Jpn Vet Med Assoc 1991; 44: 933-8.

Koh-Banerjee P, Rimm EB - Whole grain consumption and weight gain: a review of the epidemiological evidence, potential mechanisms and opportunities for future research. Proc Nutr Soc 2003; 62: 25-9.

Kojima M, Hosoda H, Date Y et al. - Ghrelin is a growth hormone releasing acylated peptide from stomach. Nature 1999; 402: 656-60.

Koutsari C, Karpe F, Humphreys SM et al. - Plasma leptin is influenced by diet composition and exercise. Int J Obes Relat Disord 2003; 27: 901-6.

Kronfeld DS - Cutting down on canine obesity. Vet Pract 1988, 9-10.

Krook L, Larsson S, Rooney JR - The interrelationship of diabetes mellitus, obesity, and pyometra in the dog. Am J Vet Res 1960; 21: 120-4.

Krotkiewski M - Effect of guar gum on bodyweight, hunger ratings and metabolism in obese subjects. Br J Nutr 1984; 52: 97-105.

Kurzman ID, Panciera DL, Miller JB et al. - The effect of dehydroepiandrosterone combined with a low-fat diet in spontaneously obese dogs: a clinical trial. Obes Res 1998; 6: 20-28.

Laflamme DP - Body condition scoring and weight maintenance. In: Proceedings of The NA Vet Conf, 1993, 290-291.

Laflamme DP, Kuhlman G - Obesity management: it can work. In: Proceedings of The NA Vet Conf, 1993, 291-293.

Laflamme DP, Kealy RD, Schmidt DA - Estimation of body fat by body condition score. J Vet Int Med 1994a; 8: 154A.

Laflamme DP, Kuhlman G, Lawler DF et al. - Obesity management in dogs. Vet Clin Nutr 1994b; 1: 59-65.

Laflamme DP, Kuhlman G - The effect of weight loss regimen on subsequent weight maintenance in dogs. Nutr Res 1995; 15: 1019-28.

Le Roux PH - Thyroid status, oestradiol level, work performance and body mass of ovariectomised bitches and bitches bearing ovarian autotransplants in the

stomach wall. J South Afr Vet Assoc 1983; 54: 115-7.

Lebel C, Bourdeau A, Lau D et al. - Biologic response to peripheral and central administration of recombinant human leptin in dogs. Obes Res 1999; 7: 577-85.

Leblanc J, Diamond P - The effect of meal frequency on postprandial thermogenesis in dogs. Fed Proc 1985; 44: 1678.

Lekcharoensuk C, Lulich JP, Osborne CA et al. - Patient and environmental factors associated with calcium oxalate urolithiasis in dogs. J Am Vet Med Assoc 2000; 217(4): 515-9.

Leray V, Gayet C, Siliart B et al. - Modulation of uncoupling protein 1 and peroxisome proliferator activated receptor expression in adipose tissue in obese insulin resistant dogs. In: Proceedings of the Waltham International Science Symposium 2003 "Nature, Nurture and the case for Nutrition", Bangkok (Thailand), October 29-31, 2003: 54.

Lewis LD - Obesity in the dog. J Am Anim Hosp Assoc 1978; 14: 402-9.

Lewis LD, Morris ML Jr, Hand MS - Small animal clinical nutrition III. Mark Morris Associates, Topeka, Kansas, 1987.

Lhoest E - Assessment of nutritional intakes in hospitalised carnivorous. Mémoire présenté en vue de l'obtention du Diplôme d'Etudes Approfondies en Sciences Vétérinaires, 2004: 28 p; Faculty of Veterinary Medicine, University of Liège, Belgium.

Lonnqvist F, Nordfors L, Schalling M - Leptin and its potential role in human obesity. J Int Med 1999; 245: 643-52.

Louis-Sylvestre J - Toutes les protéines ont-elles le même pouvoir satiétogène? Cah Nutr Diet 2002; 37: 313-21.

Lund EM, Armstrong PJ, Kirk CA et al. - Health status and population characteristics of dogs and cats examined at private veterinary practices in the United States. J Am Vet Med Assoc 1999; 214: 1336-41.

MacEwen EG, Kurzman ID - Obesity in the dog: role of the adrenal steroid dehydroepiandrosterone (DHEA). J Nutr 1991; 121: S51-S55.

Mahlow JC - Estimation of the proportions of dogs and cats that are surgically sterilized. J Am Vet Assoc 1999; 215: 640-643.

Malarewicz JA, Reynaud M - La souffrance de l'homme. Albin Michel Paris 425 p, 1996.

Manner K - Energy requirement for maintenance of adult dogs. J Nutr 1991; 121: S37-S38.

Manson JE, Stampfer MJ, Hennekens CH et al. - Body weight and longevity. A reassessment. J Am Med Ass 1987; 257: 353-58.

Markwell PJ, Van Erk W, Parkin GD et al. - Obesity in the dog. J Small Anim Pract 1990; 31: 533-8.

Markwell PJ, Butterwick RF - Obesity. In: The Waltham book of clinical nutrition of the dog and cat. Ed. JM Wills & KW Simpson 1994: 131-48.

Martin L - Principe des régimes hyper protéiques, notion d'énergie nette. Le Livre blanc de l'obésité féline; Royal Canin, 2001: 6-9.

Massabuau P, Verwaerde P, Galinier M et al. - Left ventricular repercussion of obesity-induced arterial hypertension in the dog. Arch Mal Coeur Vaiss 1997; 90: 1033-5.

Mason E - Obesity in pet dogs. Vet Rec 1970; 86: 612-6.

Mattheeuws D, Rottiers R, Kaneko JJ et al. - Diabetes mellitus in dogs: relationship of obesity to glucose tolerance and insulin response. Am J Vet Res 1984a; 45: 98-103.

Mattheeuws D, Rottiers R, Bayens D et al. - Glucose tolerance and insulin response in obese dogs. J Am Anim Hosp Assoc 1984b; 20: 287-93

Mawby D, Bartges JW, Moyers T et al. - Comparison of body fat estimates by dual-energy X-ray absorptiometry and by deuterium oxide dilution in client-owned dogs. In: Proceedings of the 6th educational workshop in pet food labelling and regulations at The 2000 Purina Nutrition Forum, Saint Louis, Missouri October 19-22, 2000: 127.

Meyer H, Drochner W, Weidenhaupt C - Ein Beitrag zum Vorkommen und zur Behandlung der Adipositas des Hundes. Deutsche Tierärztliche Wochenschrift 1978; 85: 133-6.

Mizelle HL, Edwards TC, Montani JP - Abnormal cardiovascular responses to exercise during the development of obesity in dogs. Am J Hypert 1994; 7: 374-8.

Miyake YI, Kaneda Y, Hara S et al. - Studies on the effects of spaying in small animals: results of a questionnaire survey. J Jpn Vet Med Assoc 1988; 41: 267-71.

Morooka T, Niiyama M, Uchida E et al. - Measurement of the back fat layer in beagles for estimation of obesity using two-dimensional ultrasonography. J Small Anim Pract 2001; 42: 56-59.

Munday HS, Booles D, Anderson P et al. - The repeatability of body composition measurements in dogs ans cats using dual energy X-ray Absorptiometry. J Nutr 1994; 124: 2619S-2621S.

Newberne PM - Overnutrition and resistance of dogs to distemper virus. Fed Proc 1966; 25: 1701-10.

Newberne PM - The influence of nutrition response to infectious disease. Adv Vet Sci Comp Med 1973; 17: 265-89.

Norris MP, Beaver BV - Application of behavior therapy techniques to the treatment of obesity in companion animals. J Am Vet Med Assoc 1993; 202: 728-30.

NIH (National Institute of Health) - Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. The evidence report. NIH Publication, N° 98-4083. September 1998, 228 pp.

NRC (National Research Council) - Nutrient requirements of dogs, 1974, National Academy Press, Washington DC; 71 pp.

NRC (National Research Council of the National Academies) - Nutrient requirements of dogs, 2006 (in press), The National Academies Press, Washington DC; 447 pp.

O'Brien JA, Buchanan JW, Kelly DE - Tracheal collapse in the dog. J Am Vet Radiol Soc 1966; 7: 12-20.

Panciera DL - Hypothyroidism in dogs: 66 cases (1987-1992). J Am Vet Med Assoc 1994; 204: 761-7.

Panciera DL - Conditions associated with canine hypothyroidism. Vet Clin North Am Small Anim Pract 2001; 31: 935-50.

Pak-Son IL, Youn-Hwa Young, Pak SI et al. - Risk factors for Malassezia pachydermatis-associated dermatitis in dogs: a case-control study. Kor J Vet Clin Med 1999; 16: 80-5.

Parkin GD - Management of obesity - the practitioner's experience. Int J Obes 1993; 18: S36-S38.

Pasanisi F, Contaldo F, de Simone G et al. - Benefits of sustained moderate weight loss in obesity. Nutr Metabolism Cardiov Dis 2001; 11: 401-6.

Pasquali R, Pelusi C, Genghini S et al. - Obesity and reproductive disorders in women. Hum Repr Update 2003; 9: 359-72.

Pedersen GJ - Elbow osteoarthrosis. 2. A study of a cross section of the dog population. Dansk Veterinaertidsskrift 1993; 76: 353-8.

Perez Alenza MD, Rutteman GR, Pena L et al. - Relations between habitual diet and canine mammary tumors in a case-control study. J Vet Intern Med 1998; 12: 132-9.

Perez Alenza MD, Pena L, Del Castillo N et al. - Factors influencing the incidence and prognosis of canine mammary tumours. J Small Anim Pract 2000; 41: 287-291.

Philibert JC, Snyder PW, Glickman N et al. - Influence of host factors on survival in dogs with malignant mammary gland tumors. J Vet Intern Med 2003; 17: 102-6.

Piatti PM, Monti F, Fermo I et al. - Hypocaloric highprotein diet improves glucose oxidation and spares lean body mass: comparison to hypocaloric high-carbohydrate diet. Metabolism 1994; 43: 1481-7.

Picavet S, Le Bobinnec G - Utilisation de la prolingestérone chez la chienne: à propos de 160 cas. Prat Méd Chir Anim Comp 1994; 29: 313-320

Pouteau E, Dumon H, Nguyen P et al. - Whole-body, peripheral and intestinal endogenous acetate turnover in dogs using stable isotopes. J Nutr 1998; 128: 111-5.

Prochaska J, DiClemente C - The Transtheoretical approach: Crossing traditional boundaries of therapy. Homewood Ill, Dow Jones-Irwin: 1984.

Prosky L, Asp NG, Schweizer TF et al. - Determination of soluble dietary fiber in foods and food products: collaborative study. J AOAC Int 1994; 77: 690-4.

Raben A, Jensen ND, Marckmann P et al. - Spontaneous weight loss during 11 week's ad libitum intake of a low fat/high fiber diet in young, normal weight subjects. Int J Obes 1995; 19: 916-23.

Remillard RL - Clinical aspects of obesity management. In: Proceedings of the 6th educational workshop in pet food labelling and regulations at The 2000 Purina Nutrition Forum 2000: 50-53.

Robertson ID - The association of exercise, diet and other factors with owner-perceived obesity in privately owned dogs from metropolitan Perth, WA. Preventive Veterinary Medicine 2003; 58: 75-83.

Rocchini AP, Moorehead C, Wentz E et al. - Obesity-induced hypertension in the dog. Hypertension 1987; 9: III64-III68.

Roche EA, Roseler BJE, Mason KV et al. - Observations on five cases of canine hypothyroidism. Aust Vet Pract 1991; 21: 114-20.

Royal Canin - Telephone survey on canine obesity with 400 veterinarians from France, Germany, Spain and UK. May-July 2000. Non-published data.

Rubner M - Die Gesetze des Energieverbrauchs bei der Ernährung. Deuticke F, Leipzig und Wien, 1902, 426 pp.

Russell J, Bass P - Canine gastric emptying of fibre meals: influence of meal viscosity and antroduodenal motility. Am J Physiol 1985; 249: G662-G667.

Ryttig KR, Tellnes G, Haeg L et al. - A dietary fibre supplement and weight maintenance after weight reduction: a randomized, double-blind, placebo-controlled long-term trial. Int J Obes 1989; 13: 165-71.

Schalling M, Johansen J, Nordfors L et al. - Genes involved in animal models of obesity and anorexia. J Int Med 1999; 245: 613-9.

Singh R, Laflamme DP, Sidebottom-Nielsen M - Owner perceptions of canine body condition score. J Vet Int Med 2002; 16: 362.

Solum TT, Ryttig KR, Solum E et al. - The influence of a high-fibre diet on body weight, serum lipids and blood pressure in slightly overweight persons. A randomized, double-blind, placebo-controlled investigation with diet and fibre tablets. Int J Obes 1987; 11, Suppl 1: 67-91.

Son HR, d'Avignon DA, Laflamme DP - Comparison of dual x-ray absorptiometry and measurement of total body water content by deuterium oxide dilution for estimating body composition in dogs. Am J Vet Res 1998; 59: 529-32.

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

Spain CV, Scarlett JM, Houpt KA - Long-term risks and benefits of early-age gonadectomy in dogs. J Am Vet Med Assoc 2004; 224: 380-7.

Speakman JR, van Acker A, Harper EJ - Age-related changes in the metabolism and body composition of three dog breeds and their relationship to life exspectancy. Aging Cell 2003; 2: 265-75.

Spearman JG, Little PB - Hyperadrenocorticism in dogs: a study of eight cases. Can Vet J 1978; 19: 33-9.

Sunvold GD, Bouchard GF - The glycemic response to dietary starch. In: Recent advances in canine and feline nutrition. Iams Nutrition Symposium Proceedings Vol II 1998a: 123-31.

Sunvold GD, Tetrick MA, Davenport GM et al. - Carnitine supplementation promotes weight loss and decreases adiposity in the canine. In: Proceedings of the XXIII Congress of the World Small Animal Veterinary Association, October 1998, Buenos Aires, Argentina, p 746.

Truett AA, Borne AT, Monteiro MP et al. - Composition of dietary fat affects blood pressure and insulin responses to dietary obesity in the dog. Obes Res 1998; 6: 137-46.

Valtonen MH, Oksanen A - Cardiovascular disease and nephritis in dogs. J Small Anim Pract 1972; 13: 687-97.

Van Goethem BEBJ, Rosenveldt KW, Kirpensteijn J - Monopolar versus bipolar electrocoagulation in canine laparoscopic ovariectomy: a nonrandomized prospective, clinical trial. Vet Surg 2003; 32: 464-70.

Van Winckle TJ, Bruce E - Thrombosis of the portal vein in eleven dogs. Vet Pathol 1993; 30: 28-35.

Verwaerde P, Galinier M, Fourcade J et al. - Anomalies du système nerveux autonome à la phase initial du syndrome d'insulino-résistance. Arch Mal Cœur Vaiss 1997; 90: 1151-4

Wadden TA - Treatment of obesity by moderate and severe caloric restriction. Results of clinical research trials. Ann Intern Med 1993; 119: 688-93.

Westerterp-Plantenga MS, Kovacs EM - The effect of α-hydroxycitrate on energy intake and satiety in overweight humans. Int J Obes Relat Metab Disord 2002; 26: 870-2.

Westerterp-Plantenga MS, Lejeune MPGM, Nijs I et al. - High protein intake sustains weight maintenance after body weight loss in humans. Int J Obes 2004; 28: 57-64.

White RAS, Williams JM - Tracheal collapse in the dog - is there really a role for surgery? A survey of 100 cases. J Small Anim Pract 1994; 35: 191-6.

World Health Organization - Obesity: Preventing and managing the global epidemic. Report of a WHO Consultation on Obesity, Geneva, 3-5 June 1997.

Williams GD, Newberne PM - Decreased resistance to salmonella infection in obese dogs. Fed Proc 1971; 30: 572.

Wolever TMS, Jenkins DJA - Effect of dietary fiber and foods on carbohydrate metabolism. In: Handbook of Dietary Fiber in Human Nutrition 1986, ed. by GA Spiller, CRC Press, 87-119.

Wolfsheimer KJ - Problems in diabetes mellitus management. Probl Vet Med 1990; 2: 591-601.

Wolfsheimer J, West DB, Kiene J et al. - Differential metabolic effects of caloric restriction using high-fat vs low-fat diets in dogs. J Vet Int Med 1994a; 8: 154.

Wolfsheimer KJ - Obesity in dogs. Comp Cont Educ Small Anim Pract 1994b; 16: 981-98.

Yamauchi T, Kamon J, Waki H et al. - The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 2001; 7: 941-6.

EXAMPLES OF HOME-PREPARED DIETS

Example 1

COMPOSITION
(1000 g diet)

Haddock . . . . . 765 g
Rice, cooked . . . . . 150 g
Carrots (boiled, drained) . . . . . 50 g
Cellulose* . . . . . 15 g
Rapeseed oil . . . . . 20 g

**Long-fiber purified cellulose (200-300 µm); 10 g of cellulose replaces 70 g of bran.*

Add a well-balanced mineral and vitamin supplement

ANALYSIS

The diet prepared in this way contains 24% dry matter and 76% water

	% dry matter	g/1000 kcal
Protein	60	147
Fat	11	26
Available carbohydrate	17	43
Fiber	7	18

Key Points

- **Reduce the fat content** to restrict the energy density
- **Increase the protein content** to favor the maintenance of muscle mass
- **Increase the fiber content** to encourage satiety

INDICATIVE RATIONING

Energy value (metabolizable energy) 960 kcal/1000 g diet prepared (4070 kcal/1000 g DM)

Weight of the dog (kg)*	Daily amount (g) (covering 100% of MER)**	Daily amount (g) (covering 60% of MER)**	Daily amount (g) (covering 40% of MER)**
2	225	140	90
4	370	230	150
6	520	310	210
10	750	460	300
15	1020	620	410
20	1270	770	510
25	1520	910	610
30	1690	1040	690
35	1720	1170	780
40	1860	1290	860
45	2150	1410	940
50	2550	1530	1020
55	2720	1640	1090
60	2920	1750	1170
65	3100	1860	1240
70	3270	1970	1310
75	3450	2070	1380
80	3620	2170	1450
85	3800	2270	1520
90	3950	2370	1580

**The diet must be prescribed in accordance with the ideal weight and not the real weight of the dog. The energy allocation level (40-100% of maintenance energy requirement or MER) varies according to the degree of obesity and the response of the dog (see preceding chapter).*
***Dividing of the daily amount into two or three meals is recommended to increase expenditure related due to postprandial thermogenesis.*

FOR THE TREATMENT OF OBESITY

Example 2

Composition
(1000 g diet)

Turkey, breast without skin . . . . . .620 g
Rice, cooked . . . . . .150 g
Lentils, cooked . . . . . 175 g
Wheat bran . . . . . 50 g
Rapeseed oil . . . . . 5 g

Add a well-balanced mineral and vitamin supplement

Indicative rationing

Energy value (metabolizable energy) 1090 kcal/1000 g diet prepared (3670 kcal/1000 g DM)

Weight of the dog (kg)*	Daily amount (g) (covering 100% of MER)**	Daily amount (g) (covering 60% of MER)**	Daily amount (g) (covering 40% of MER)**
2	200	120	80
4	320	200	130
6	450	270	180
10	670	400	270
15	900	550	360
20	1120	680	450
25	1320	800	530
30	1520	920	610
35	1720	1030	690
40	1900	1140	760
45	2070	1240	830
50	2250	1350	900
55	2400	1450	960
60	2570	1540	1030
65	2720	1640	1090
70	2870	1730	1150
75	3050	1820	1220
80	3200	1910	1280
85	3350	2000	1340
90	3470	2090	1390

Analysis

The diet prepared in this way contains 30% dry matter and 70% water

	% dry matter	g/1000 kcal
Protein	58	159
Fat	5	13
Available carbohydrate	23	61
Fiber	10	29

Contra-indications

Gestation
Lactation
Growth

Examples of home-made diets are proposed by Pr Patrick Nguyen
(Nutrition and Endocrinology Unit; Biology and Pathology Department, National veterinary School of Nantes)

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The Labrador has a greater fat mass than other dogs of similar weight. The Labrador is one of the breeds ;at risk of developing obesity.

Key points
to remember:

When estimating the energy need of a dog in good physical condition

There are many equations that attempt to describe the determination of energy need as a function of weight. In the canine species, the body weight range is so wide that the maintenance energy requirement (MER) cannot be directly expressed as a function of body weight (BW): a 50-kg dog clearly consumes less than two 25-kg dogs. The MER must be calculated on the basis of metabolic weight, using an allometric equation of the type:

Maintenance energy requirement (MER) = a x Body Weight (kg) ^{b}

(kcal of metabolizable energy / day).

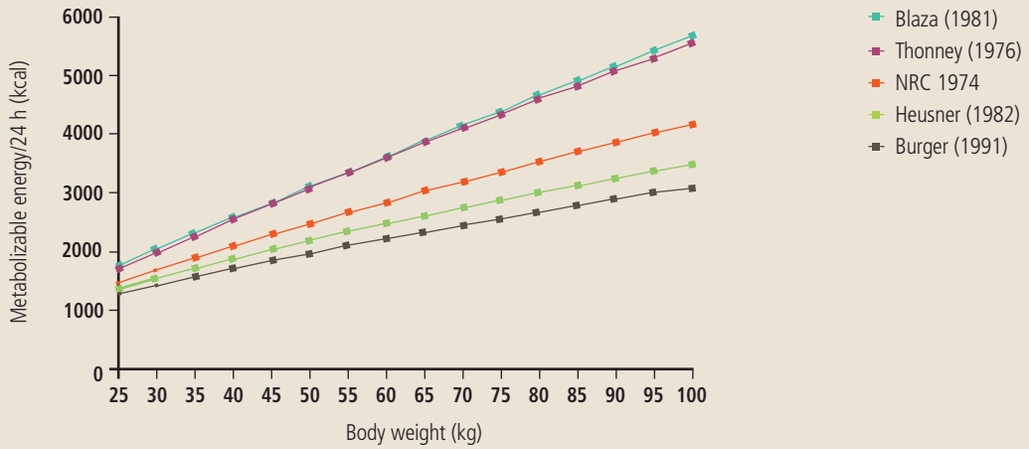
The problem is inherent in the evaluation of coefficients a and b, and the results differ slightly depending on the experimental conditions and the size of the groups: a few examples are shown in the table below.

EXAMPLES OF EQUATIONS PROPOSED FOR THE CALCULATION OF MER IN DOGS

MER in kcal BW in kg	BW = 30 kg (kcal/24 h)	BW = 50 kg (kcal/24 h)	BW = 70 kg (kcal/24 h)
(Blaza) *MER = 121.9 x BW $^{0.83}$*	2050	3175	4145
(Thonney) *MER = 100 x BW $^{0.88}$*	1980	3100	4170
(NRC 1974) *MER = 132 x BW $^{0.73*}$*	1670	2480	3195
(Heusner) *MER = (132 to 159) BW $^{0.67}$*	1550	2190	2760
(Burger) *MER = 162 x BW $^{0.64}$*	1430	1980	2460

**The coefficient of 0.73 is often rounded up to 0.75 (= 3/4) to facilitate the calculation of the metabolic weight.*

DEVELOPMENT OF THE MAINTENANCE ENERGY REQUIREMENT DEPENDING ON WEIGHT ACCORDING TO DIFFERENT AUTHORS



The differences in the results are often clearer as the weight increases. In the literature, the most frequently used equation is given by the NRC 1974. It represents a good compromise between the various equations proposed. No single mathematical model is truly satisfactory. Indeed, even at a constant weight, the energy requirement varies considerably according to age, breed, sexual status, climate conditions, level of activity and lean body mass. For an equal weight, the maintenance requirement of two dogs can vary depending on their body composition.

EXAMPLES OF THEORETIC MER VARIATIONS IN DOGS IN GOOD PHYSICAL CONDITION			
MER adjustment coefficient	0.9	1.1	1.4
Age	Mature dogs (from 5-8 years according to size)		
Breed	Labrador, Newfoundland, etc	Boxer, German Shepherd, etc	Great Dane, Irish Wolfhound, etc
Sexual status	Neutering		
Climate conditions	The homeothermic zone is 10-20 °C in dogs		MER increased 20-40% at 0-10 °C
Level of activity	**Every hour of activity increases the maintenance energy requirement by approximately 10%**		

Whatever the basis used for the calculation, it is only a starting point: the precise adaptation of intake to actual energy expenditure can only be realized based on observation of fluctuations in body weight and body condition score. The MER actually varies considerably from one individual to another. While it is sometimes difficult to weigh a large-breed dog when it has reached its adult weight, there are parameters that allow its physical condition to be estimated. Ideally, the ribs and the vertebral column are not visible, but easily palpable, and the waist is also clearly discernable.

Key Points
to remember:

In the estimation of the energy value of the food

In its 1974 and 1985 editions, the NRC proposed two different equations for calculating the metabolizable energy (ME) value of a food:

1. Equation proposed by the NRC in 1974 for the calculation of the energy for simple ingredients (also known as the Atwater equation). This equation has been used in human nutrition since 1902.

ME (kcal/100 g) = (4 x % proteins) + (9 x % fats) + (4 x % nitrogen-free extract*).

1. Equation advised by the NRC in 1985 (modified Atwater equation)

ME (kcal/100 g) = (3.5 x % proteins) + (8.5 x % fats) + (3.5 x % nitrogen-free extract*)

* Nitrogen-free extract (NFE) roughly represents total digestible carbohydrate. It is obtained by the difference:

NFA = 100 - (% moisture + % protein + % fat + % mineral + % crude fiber)

The differences between the coefficients used reflect the different hypotheses with respect to the digestibility of the categories of nutrients:

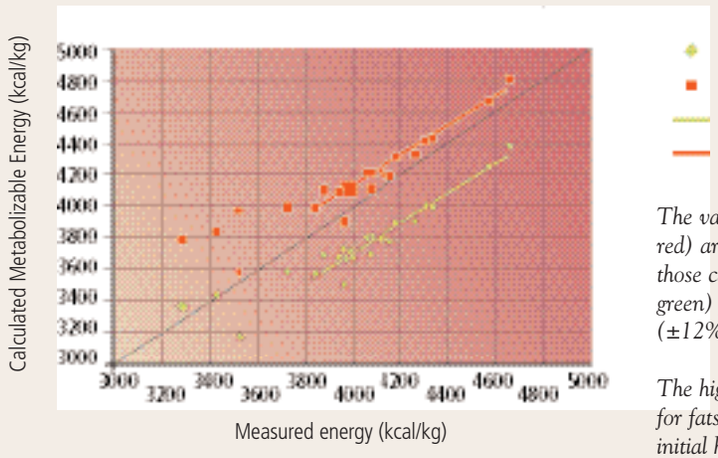
- The Atwater equation estimates the digestibility of protein at 91%, and those of fat and NFE at 96%.
- The modified Atwater equation estimates the digestibility of protein, fat and NFE at 80%, 90% and 85%, respectively.

What is the best equation?

The ideal equation depends on the dietary content, as shown by the graph below, which compares the energy value measured and the theoretical energy value calculated with the two equations.

- The Atwater equation gives values close to the values measured, albeit slightly overestimated, when the food contains low levels of fiber and is consequently characterized by high digestibility.
- The modified Atwater equation is a better reflection of the reality in the case of food containing a high level of fiber that is consequently characterized by low to medium digestibility.

CORRELATION BETWEEN CALCULATED AND MEASURED METABOLIZABLE ENERGY



The values measured with the Atwater equation (in red) are closer to the values measured (black line) than those calculated with the modified Atwater equation (in green) for food containing more than 3800 kcal of ME (±12% of fats, 5-7% of total fiber).

The high digestibility coefficients of the food (95-97% for fats; 84-87% for proteins) are actually close to the initial hypotheses of the Atwater equation.

French Mastiff puppy.

Conclusion

The lowest metabolizable energy level of a food is the value obtained after digestibility measurements are taken in dogs. In the absence of measured values, the Atwater equation should be reserved for highly digestible foods and home-prepared diets.

The daily ration for a dog is obtained by dividing the daily energy requirement by the metabolizable energy value of the food.

References

Blaza SE - Energy requirements of dogs in cool conditions. Canine Pract 1982; 9: 10-15.

Burger IH - Dogs large and small : the allometry of energy requirements within a single species. J Nutr 1991; 121: S18-S21.

Heusner AA - Energy metabolism and body size. I- is the 0.75 mass exponent of Kleiber's equation a statistical artefact? Respi. Physiol 1982; 48: 1-12.

National Research Council (NRC) - Subcommittee on Dog Nutrition - Nutrient requirements of dogs, 1974; National Academy Press, NW, Washington DC: 71 pp.

National Research Council (NRC) - Subcommittee on Dog Nutrition - Nutrient requirements of dogs, 1985; National Academy Press, NW, Washington DC: 71 pp.

Thonney ML et al - Intraspecies relationship between fasting heat production and bodyweight: a reevaluation of W75. Journal of Animal Science 1976; 43: 690-704.

- *Provocation*

There are two options: either the previous diet is given or a new protein source is introduced every one or two weeks. The latter option will identify the foods responsible for the hypersensitivity.

3 - Nutritional therapy in dermatology

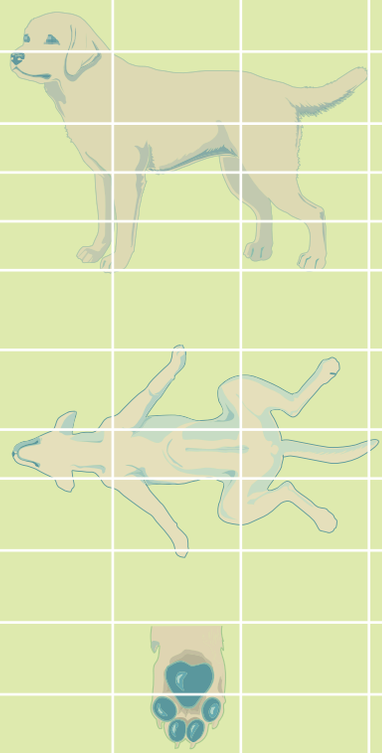
► Dull coat, xerosis

TABLE 16 - EXAMPLE OF PRURITUS SCORES

Score	Description
0	Absence of pruritus
1	Discrete pruritus, not spontaneously described by the owner, less than one hour per day
2	Moderate pruritus, spontaneously described by the owner, one to three hours per day
3	Significant pruritus, three to six hours per day
4	Very significant pruritus, permanent, observed in consultation, sleeping problems

TABLE 17 - SIMPLIFIED CADESI*

Clinical signs:		Erythema	Lichenification	Excoriations	Spontaneous Alopecia	Total
Region of the body						
Face	Periocular region Perilabial region					
Ears	Left internal surface Right internal surface					
Neck	Ventral surface					
Armpit	Left					
	Right					
Inguinal region	Left					
	Right					
Abdomen	-					
Forelimbs	Left (fold of the elbow) Right (fold of the elbow)					
Fore feet	Left Right					
Hind legs	Left: fold of the hock Right: fold of the hock					
Hind feet	Left Right					



** Atopic Dermatitis Extent and Severity Index "(CADESI) adapted from the SCORing Atopic Dermatitis (SCORAD)".*

The coat's sheen is connected to the composition of sebum, a natural wax secreted by the sebaceous glands and stored in the hair follicles. Sebum also has the role of preventing the felting of the hairs by eliminating the relief of the hair scale. Sebum makes the keratin in the hair more elastic and more flexible. The lipids in the composition of the sebum are species and breed specific *(Dunstan et al, 2000)*, but the production and the quality of the sebum is also influenced by the food. Some essential nutrients given in higher quantities than the strict recommended minimal quantities produce a significant improvement in the appearance of the dog's coat. This is notably so with PUFA from vegetable sources (omega 6) and zinc. A combined zinc/linoleic acid supplement improves the coat's brilliance and reduces scale *(Marsh et al, 2000)*.

The sensitivity of PUFA sources to oxidation demands close monitoring of their resistance to oxidation, and increased quantities of vitamin E in the food.

► Excessive shedding

Shedding experienced by dog owners as excessive may be physiological, whether it is continuous or seasonal. The intensity of this shedding depends on many factors including the genetic potential, the hormonal balances, the photoperiod and nutrition.

When excessive shedding leads to a veterinary consultation, an attempt must be made to identify the potential causes of anomalies in the pilary cycle:
- endocrinopathy
- unadapted environment
- relative deficiency of PUFA, biotin, tyrosine, tryptophan, cystine, vitamin E, vitamin A, choline or folic acid.

Many nutrients are used to stimulate hair growth, including biotin *(Fromageot & Zaghroun, 1990)* and paprika. The addition of paprika (*Capsicum tetragonum*) to the food increases the intensity of hair coloration and stimulates the hair growth, particularly during shedding *(Greer, 1981)*.

However, no studies have yet proved that shedding in a dog on a balanced diet can be controlled by nutritional or pharmacological measures.

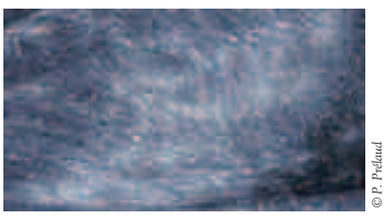

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Figure 20 *- Abundant scaling, showing major xerosis in an atopic Labrador.*

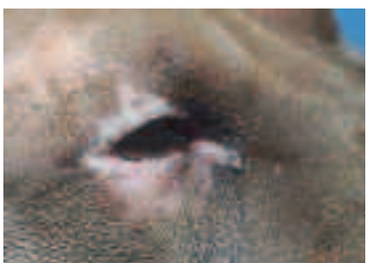
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Figure 21 *- Depigmented vitiligo lesions in a Shar Pei.*

► Black coat with red reflex

It is possible to prevent the reddening of the coat of dogs with black coats by enriching the diet with tyrosine. The response time varies according to the hair cycle. If the majority of hairs are in the telogen phase they are replaced more quickly. The hairs that redden during shedding remain red even after supplementation of aromatic amino acids.

► Vitiligo

Vitiligo is characterized by depigmented lesions preferentially in the mucocutaneous junctions **(Figure 21)**. Depigmentation is due to the absence of melanocytes. The causes of vitiligo are highly varied and few effective treatments have been identified at this time. In humans, L-phenylalanine is regularly used *(Antoniou & Katsambas, 1992; Camacho & Mazuecos, 2002)* and has produced good results in dogs *(Guaguère, personal communication)*.

► Skin wound healing

Nutritionists have studied the nutrients that improve the healing of wounds, so as to be in a position to propose nutritional supplements in the pre- and post-surgery period. Human medicine has a great number of enteral preparations in liquid form. The sought-after properties are stimulation of re-epithelialization and stimulation of the immune system to limit infection. They could potentially be used in adult dogs, but the protein concentration is insufficient for puppies.

Dogs suffering from a **protein** deficiency (e.g. during a fast due to hospitalization) have delayed wound healing. It is essential to safeguard nitrogen balance to facilitate tissue regeneration, paying particular attention to glutamine and arginine contents in the food. The production of nitric acid from arginine stimulates the expression of the endothelial vascular growth factor.

Zinc deficiency is associated with delayed wound healing. Zinc is essential to cell replication and proliferation.

Iron and vitamin C are involved in hydroxylation of proline, a major amino acid in the structure of collagen. Iron deficiency affects the quality of the scar tissue.

Omega 3 fatty acids have a positive effect on the inflammatory reaction at the site of wound healing. A vitamin E supplement helps protect PUFA's from oxidation.

The positive role of curcumin, aloe vera and bromelaine has been shown in the wound healing process *(Fray et al, 2004)*.

Ideally, these nutrients should be administered 8 weeks before surgery. This period is needed for the PUFA to act effectively in the skin. The treatment must be continued for at least four weeks after surgery, depending on the required length of wound healing.

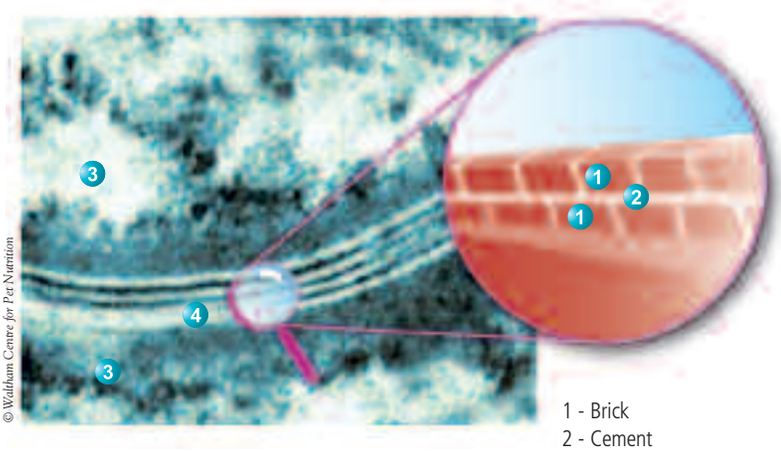
► Atopic dermatitis

Canine atopic dermatitis, like human atopic dermatitis, is a multifactorial disease in which nutrition can be used at three levels.

- Re-establishment of the skin barrier function

Atopic dogs have problems with function of the skin barrier, especially defects in the intercellular cement formed by the ceramides **(Figure 22)** *(Inman et al, 2001)*. This allows water loss, increased transcutaneous penetration by antigens and increased adherence of staphylococci to the surface of the corneocytes.

FIGURE 22 - STRUCTURE OF AN INTERCELLULAR JUNCTION



1 - Brick
2 - Cement
3 - Skin cell
4 - Ceramides (skin lipids)

As cement holds together the bricks in a wall, the ceramides are responsible for the cohesion of the skin cells.

- Reduction in inflammation

By using nutrients acting on the inflammatory (long-chain omega 3 polyunsaturated fatty acids: EPA and DHA) or immune response (probiotics) *(Baillon et al, 2004)*.

- Prevention or control of dietary hypersensitivities

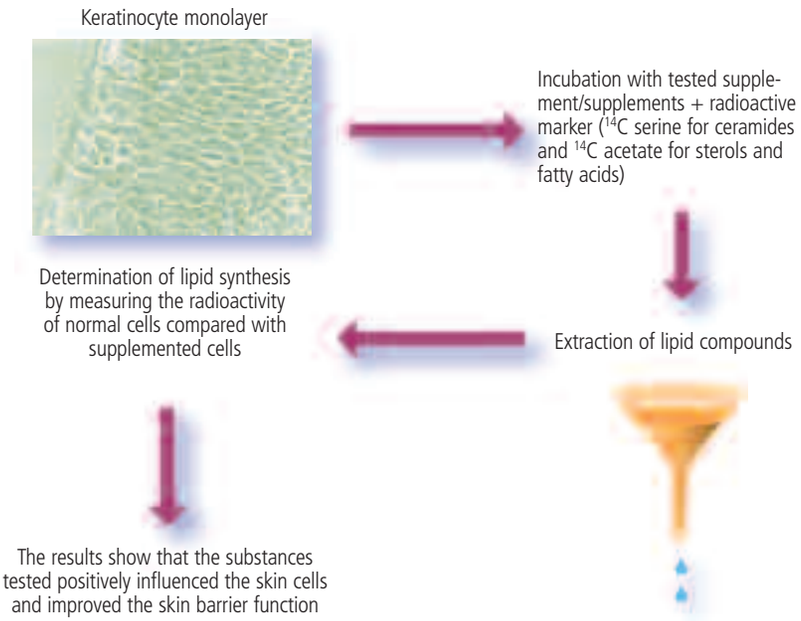
Due to highly digestible and/or hypoallergenic foods.

> Reinforcement of the skin barrier function

In vitro studies (keratinocytes cultures) conducted by the Waltham Research Centre have shown that some nutrients (in particular: nicotinamide, pantothenic acid, histidine, inositol and choline) improve the structure and the function of the skin. Others (pyridoxine and proline) stimulate the synthesis of ceramides **(Figure 23)** *(Watson et al, 2003)*.

In vivo studies have confirmed this approach. After nine weeks of supplementation with a supplement composed of nicotinamide, pantothenic acid, histidine, inositol and choline, the cutaneous water loss was significantly reduced in atopic dogs. The reduction in water loss and so xerosis can have a positive effect of reducing allergen penetration, and also limit bacterial and fungal colonization, which may cause the development of atopic dermatitis.

FIGURE 23 - MEASURING THE SYNTHESIS OF SKIN LIPIDS
(From Watson, 2003)



> Polyunsaturated fatty acids (PUFA)

In the case of pruriginous dermatitis caused by an allergy, omega 3 and omega 6 PUFA may be used to limit skin inflammation, restore the integrity of the hydrolipidic film and limit the transcutaneous penetration of allergens and bacterial and fungal infections. Various studies show that the use of supplements high in PUFA reduces skin inflammation, but does not have any obvious effect on pruritus. They also reduce the dose of long-term corticosteroid therapy when this is necessary *(Saevik et al, 2004)*. The efficacy of such a therapeutic approach in the case of canine atopic dermatitis is more significant in the early stages of the disease *(Abba et al, 2005)*.

In human medicine the preventive use of PUFA is envisaged in the mothers of atopic children. A mother's food is high in omega 3 and omega 6 PUFA and impacts the immune response of breastfed children, favoring a Th1-type response *(Das, 2004)*. Such an approach has not been used in dogs, but it could be tried in dogs of high-risk breeds, like the Shar-Peï and the West Highland White Terrier.

> Curcumin

The addition of curcumin can also benefit dogs suffering from atopic dermatitis, through mechanisms that are focused on the immune response (inhibition of mast cell activation, inhibition of lipoxygenase and cyclooxygenase synthesis, immunoglobulins, etc) *(Cuendet & Pezzuto, 2000)*.

The presence of borage oil in food provides interesting results in various allergic manifestations *(Quoc & Pascaud, 1996)*. Borage oil is frequently used in human dietetics and cosmetology and is the only oil that contains more than 20% gamma linolenic acid (GLA).

The efficacy of borage oil is improved when it is used in association with fish oils, which have high EPA and DHA contents *(Sture & Lloyd, 1995)*.

These very long-chain omega 3 fatty acids act in the same way as gamma linolenic acid, albeit through different metabolic processes. They inhibit the synthesis of arachidonic acid and its derivatives, which are responsible for inflammatory manifestations.

► Keratoseborrheic states

Table 18 - Doses of retinoids in dogs

Retinods	Dose	Daily intake
Vitamin A (retinol)	1000 IU/kg/day	1
Acitretin	1-2 mg/kg/day	1
Isotretinoin	1-2 mg/kg/day	1

> Primary keratinization disorders

Many primary keratinization disorders justify the use of PUFA or retinoids. Retinoids control the proliferation of keratinocytes by reducing the synthesis of sebum and the inflammatory reaction (inhibition of the expression of chemokines). They are much more effective than vitamin A and produce fewer secondary effects. Their use however, is not without risk and they must be part of a prescription in which the owner is informed and monitoring is provided **(Table 18)**.

• *Vitamin A responsive dermatoses*

Vitamin A regulates the growth of epidermal cells and the production of sebum. It helps combat seborrhea and the pellicles that often form after a pruritic episode. It acts in synergy with zinc and sulfated amino acids.

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Figure 24 *- Attached scaling lesions in a Cocker Spaniel presenting with vitamin A responsive dermatosis.*

Vitamin A responsive dermatosis is a rare and much discussed keratinization disorder described only in the Cocker Spaniel. It is clinically characterized by dull hair and thick, foul-smelling scaling **(Figure 24)**. The diagnosis is based on histopathology that reveals major follicular orthokeratotic hyperkeratosis. Vitamin A supplementation (1000 IU/kg/day) leads to a recovery, although the response is fairly slow. In case of failure or partial remission, retinoids may be used.

• *Ichthyoses*

Ichthyoses are genetic keratinization problems. Patients present with thick scaling around the pads and over the body from a very early age **(Figure 25)**. Predisposed breeds include Cavalier King Charles Spaniels, Cocker Spaniels, Retrievers, Soft Coated Wheaten Terriers, West Highland White Terriers, Jack Russell Terriers and Rottweilers. Histopathology helps identify the diagnosis. Treatment is based on the combined use of keratolytic shampoos and PUFA or synthesized retinoids **(Table 18)**.

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Figure 25 *- Perinipple ichthyosis lesions in a Cavalier King Charles.*

• *Idiopathic seborrheas*

The primary seborrheas will appear at a very early age in some predisposed breeds (particularly American Cocker Spaniels). This is a genetic anomaly caused by the accelerated regeneration of the epidermis. The lesions are generalized (oily scaling), sometimes with major localized thickening (on the ventral surface of the neck or in the fold of the elbow, for instance). The diagnosis is based on the elimination of all causes of seborrhea and skin biopsies.

Treatment includes an anti-infection treatment, localized care (clipping and keratolytic shampoos) and synthetic retinoids. They are administered every day for 3-5 months. If control is satisfactory, intake is reduced to once every two or three days.

> Zinc responsive dermatosis

Several zinc salts are available for the treatment of zinc responsive dermatoses **(Table 7)**. The very cheap zinc sulfate can be poorly tolerated (vomiting) and must be administered with meals. Zinc gluconate is generally better tolerated *(Guaguère & Bensignor, 2002)*. Zinc methionine is probably the best absorbed, but it is available only in a preparation in which it is associated with vitamin A and it is expensive. The length of treatment varies from three to eight weeks depending on the animal and must often be life long.

• *Secondary seborrheas*

Many keratinization disorders may be accompanied by inflammatory dermatoses caused by an allergen or a parasite. They do not justify retinoid treatment. The treatment of the associated infection or the primary cause will control it. Some authors consider that the nutritional requirements are greater during the keratoseborrheic state and that it is accordingly necessary to provide an appropriate diet, enriched with PUFA, vitamin E, zinc and trace elements.

► Granulomatous sebaceous adenitis

Granulomatous sebaceous adenitis is a genetic disease characterized by destruction of the sebaceous glands, which gradually disappear, causing keratinization disorders in the hair follicle with alopecia and the formation of hair flanges. The lesions appear gradually and can be localized in any region of the body **(Figures 26 A & B)**.

All breeds can contract this disease, but there are some clear breed predispositions: Akita Inus, Poodles, Samoyeds and Lhassa Apsos. The diagnosis is based on the examination of multiple biopsies that confirm the destruction of the sebaceous glands. The treatment requires localized care (keratin modulation shampooing) and general treatments: essential fatty acids, corticotherapy, cyclosporine, synthetic retinoids **(Table 19)**. The prognosis is always guarded. Given the potential secondary effects (retinoids, corticoids) or the cost (cyclosporin A) of alternative therapeutics, the administration of PUFA must be attempted first, in association with keratin modulating shampoo.

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Figure 26A *- Granulomatous sebaceous adenitis in an Akita Inu: irregular alopecia over the whole trunk, associated with a keratoborrheic state.*

► Various immune dermatoses

Vitamin E, due to its antioxidant action, and PUFA are commonly used on their own or as an adjuvant for immune mediated dermatoses.

Vitamin E (400-800 IU BID) is used as an adjuvant for lupus *(Scott et al, 2001)* and dermatomyositis *(Hargis & Mundell, 1992)*. Used on its own, it is only effective in a very limited number of cases.

PUFA are used for their anti-inflammatory or immunomodulating action in the treatment of lupoid onychodystrophies with excellent results in one in three cases *(Mueller et al, 2003)*.

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Figure 26B *- Same dog as in Figure 26A, after two months' treatment with polyunsaturated fatty acids and keratin modulating shampoo.*

► Recurring bacterial infections

Nutrition can play an essential role in controlling recurring infections by helping to reestablish the skin barrier (skin barrier-type nutrients, PUFA) or by helping to control allergic inflammation (PUFA, hypoallergenic foods).

► Prophylactic nutrition

In canine dermatology, nutritional interventions continue to be almost exclusively devoted to therapeutic functions. In human dermatology however, especially allergic dermatology, nutrition is used preventively **(Table 19)**.

TABLE 19 - EXAMPLES OF NUTRITIONAL RECOMMENDATIONS FOR LIMITING THE RISK OF FOOD ALLERGIES IN CHILDREN
(Sampson, 2004)

- Breastfeeding for three to six months
- Use of hydrolysates if breastfeeding is not possible
- Avoidance of peanuts and seafood during pregnancy and breastfeeding
- Avoidance of high-risk foods (peanuts, hazelnuts, seafood) before three years of age

Such an approach could be interesting, the more difficult problem is the identification of individuals at risk. This is problematical in humans *(Osborn & Sinn, 2003)*, but is much easier in dogs, as certain breeds and lines are predisposed to nutritional or immune dermatoses *(Scott et al, 2001)*.

> Hypoallergenic and highly digestible foods

Hypoallergenic and highly digestible foods are used in dermatology for therapeutic purposes. In human medicine these foods are mainly used in the prevention of food allergies in high-risk children, or even breastfeeding mothers. Hydrolysates are used for high-risk children that cannot be breastfed to significantly reduce the risk that clinical manifestations of atopy will develop *(Osborn & Sinn, 2003)*. Such an approach could be useful in canine medicine, but it must undergo controlled clinical studies.

> Probiotics

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In high-risk breeds, with respect to dermatology it would be useful to try to prevent hypersensitivity phenomena by modifying the mother's food during gestation, as occurs in human medicine.

In humans, there is a correlation between the use of antibiotics in infancy or in the mother during the perinatal period and the development of atopic dermatitis. Conversely, random double-blind studies show that the administration of probiotics to mothers at risk limits the occurrence of manifestations of atopic dermatitis (extrinsic form) in children *(Flohr et al, 2005)*.

In dogs, the addition of probiotics in the food presents technical problems *(Weese & Arroyo,2003)*. It is however possible to include them in a dry food and to observe their effect on immune response *(Baillon et al, 2004)*. If the goals of feeding such a food are aimed at the gastrointestinal tract, preventive or curative use in atopic dogs could also be practical.

> Polyunsaturated fatty acids

Recurring bacterial infections are most often caused by allergic dermatopathies (dietary hypersensitivity, atopic dermatitis) or non-specific skin defense problems. In both cases PUFA supplementation or a skin barrier cocktail may limit the risks of a relapse. It is essential however that the causes of recurring pyodermititis be identified before diagnosing an idiopathic recurring pyodermititis **(Table 12)**.

PUFA supplementation in human mothers during pregnancy and lactation helps limit the dietary hypersensitivity phenomena in children *(Korotkova et al, 2004)*. Such an approach could be useful in bitches of high-risks breeds like Shar-Peis or West Highland White Terriers.

Conclusion

Food plays a fundamental role in cutaneous homeostasis and in the treatment of many inflammatory dermatoses. The study of the diet is therefore an integral part of the dermatological history. The correction of dietary imbalances (with respect to zinc and essential fatty acids in particular) is a necessary factor in good dermatological therapy.

It is important to challenge ideas that impede the management of chronic pruriginous dermatitis on a daily basis. These include the harmfulness of food based on their origin, the value of IgE doses of dietary allergens, the absence of flea infestation opportunities and the harmfulness of short-term corticosteroid therapy.

The treatment of keratinization disorders or allergenic dermatites involves the use of nutrients that reinforce the skin barrier function, or even play an anti-inflammatory role. The future is open to the possible use of food for prophylactic purposes (probiotics, essential fatty acids, etc) in animals at risks of skin disease.

Frequently asked questions – Influence of food on dermatology

Q	A
Which nutritional deficiencies are most commonly implicated in dermatology?	The nutrients involved in skin diseases that are caused by deficiencies are zinc and essential fatty acids.
How can a zinc deficiency be identified?	It can be tempting to measure the zinc level in the blood or in the hair, but these methods are unsatisfactory. The diagnosis is based histopathology of the skin lesions (parakeratotic hyperkeratosis) and the response to supplementation or correction of the diet.
What should you do when a Siberian Husky showing signs of zinc responsive dermatosis does not respond to the administration of zinc?	First the zinc salt should be changed, for example, prescribe zinc gluconate or zinc methionine instead of zinc sulfate. The prescription of a low dose of corticosteroids (prednisolone: 0.2 mg/kg/day) generally leads to a very significant improvement in zinc absorption and the control of dermatosis.
Which foods are the most likely to cause allergenic reactions?	The data provided in the literature do not permit the identification of sources of more allergenic proteins. The knowledge of the very nature of allergens may permit definition of the high-risk foods in the near future.
Is white meat less allergenic than red meat?	This belief is incorrect. The color of the meat does not have any influence on its potential allergenic or hypoallergenic character. Indeed, the origin and the color of the meat are not implicated in the studies on the etiopathogenesis of food intolerances in dogs. On the other hand, the risk increases with the quantity of meat ingested. A very red meat like venison is very widely and successfully used as a basis for elimination diets.
Can atopic dermatitis be controlled simply with PUFA supplementation?	Yes, but if the response is unsatisfactory after two months of treatment other therapeutics should be used.
Can dietary imbalance create an immune deficiency?	Only serious protein or fatty acid deficiencies can cause an immune deficiency. This has been observed only in cases of debilitating diseases or serious chronic digestive problems.

References

Abba C, Mussa PP, Vercelli A et al. - Essential fatty acids supplementation in different-stage atopic dogs fed on a controlled diet. J Anim Physiol Anim Nutr (Berl) 2005; 89(3-6): 203-7.

Antoniou C, Katsambas A - Guidelines for the treatment of vitiligo. Drugs 1992; 43(4): 490-8.

Baillon ML, Marshall A, Jones ZV et al. - Effects of probiotic Lactobacillus acidophilus strain DSM13241 in healthy adult dogs. Am J Vet Res 2004; 65(3): 338-343.

Biourge VC, Fontaine J - Exocrine pancreatic insufficiency and adverse reaction to food in dogs: a positive reaction to a high fat, soy-isolate hydrolysate-based diet. J Nutr 2004; 134: 2166S-2168S.

Biourge VC, Fontaine J, Vroom MW - Diagnosis of adverse reactions to food in dogs: efficacy of a soy-isolate hydrolysate-based diet. J Nutr 2004; 134(8 Suppl): 2062S-2064S.

Biourge V, Sergheraert R - Dietary tyrosine and red hair syndrome in dogs. Proc 18th ESVD-ECVD Annual congress, Nice Sept 2002: 204.

Breiteneder H, Mills EN - Molecular properties of food allergens. J Allergy Clin Immunol 2005; 115(1): 14-23.

Busch-Kschiewan K, Zentek J, Wortmann FJ et al. - UV light, temperature and humidity effects on white hair color in dogs. J Nutr 2004; 134: 2053s-2055s.

Camacho F, Mazuecos J - Oral and topical L-phenylalanine, clobetasol propionate, and UVA/sunlight - a new study for the treatment of vitiligo. J Drugs Dermatol 2002; 1(2): 127-31.

Campbell KL, Lichtensteiger CA - Cutaneous markers of hepatic and pancreatic diseases in dogs and cats. Vet Med 2000: 306-314.

Cave NJ, Marks SL - Evaluation of the immunogenicity of dietary proteins in cats and the influence of the canning process. Am J Vet Res 2004; 65(10): 1427-33.

Chehade M, Mayer L - Oral tolerance and its relation to food hypersensitivities. J Allergy Clin Immunol 2005; 115: 3-12.

Chesney CJ - Systematic review of evidence for the prevalence of food sensitivity in dogs. Vet Rec 2001; 148(14): 445-448.

Chesney CJ - Food sensitivity in the dog: a quantitative study. J Small Anim Pract 2002; 43(5): 203-207.

Credille KM, Lupton CJ, Kennis RA et al. - What happens when a dog loses its puppy? Functional, developmental and breed related changes in the canine hair follicle. Advances in Veterinary Dermatology 2002; Thoday KL, Foil CS & Bond R eds, Blackwell Publishing; 4: 37-42.

Cuendet M, Pezzuto JM - The role of cyclooxygenase and lipoxygenase in cancer chemoprevention. Drug Metabol Drug Interact 2000; 17(1-4): 109-57.

Das UN - Breast-feeding, atopy, and asthma. J Allergy Clin Immunol 2004; 113:1002.

Day MJ - Clinical Immunology of the Dog and Cat. Manson Publishing; London, 1999.

Dickinson PJ, Anderson PJB, Williams DC et al. - Assessment of the neurologic effects of dietary deficiencies of phenylalanine and tyrosine in cats. Amer J Vet Res 2004; 65(5): 671-680.

Dunstan RW, Herdt TH, Olivier B et al. - Age- and breed-related differences in canine skin surface lipids and pH. In: Advances in Veterinary Dermatology 2000; Thoday KL, Foil CS & Bond R eds, Blackwell publishing; 4: 37-42.

Ermel RW, Kock M, Griffey SM et al. - The atopic dog: a model for food allergy. Contemp Top Lab Anim Sci 1997; 47: 40-49.

Feldman EC, Nelson RW - Canine and feline endocrinology and reproduction. Saunders; Philadelphia, 2004.

Flohr C, Pascoe D, Williams HC - Atopic dermatitis and the 'hygiene hypothesis': too clean to be true? Br J Dermatol 2005; 152(2): 202-16.

Foster AP, Knowles TG, Moore AH et al. -Serum IgE and IgG responses to food antigens in normal and atopic dogs, and dogs with gastrointestinal disease. Vet Immunol Immunopathol 2003; 92(3-4): 113-124.

Fray TR, Watson AL, Croft JM et al. - A combination of aloe vera, curcumin, vitamin C, and taurine increases canine fibroblast migration and decreases tritiated water diffusion across canine keratinocytes in vitro. J Nutr 2004; 134(8 Suppl): 2117S-2119S.

Fromageot D, Zaghroun P - Intérêt potentiel de la biotine en dermatologie canine. Rec Méd Vét 1990; 166(21): 87-94.

Fujimura M, Ohmori K, Masuda K et al. - Oral allergy syndrome induced by tomato in a dog with Japanese cedar (Cryptomeria japonica) pollinosis. J Vet Med Sci 2002; 64(11): 1069-1070.

Greer PT- Colour and growth enhancement of the coats of feline and canine. US patent Document, 1981.

Guaguère E, Bensignor E - Thérapeutique dermatologique du Chien. Paris: Masson - AFVAC; 2002.

Hargis AM, Mundell AC - Familial canine dermatomyositis. Compend Contin Educ Pract Vet 1992; 14(7): 855-862.

Hillier A - Inability to demonstrate food antigen-specific IgE antibodies in the serum of food allergic dogs using the PK and oral PK tests. In: Proceedings of the AAVD/ACVD Meeting, Charleston; 1994: 28.

Hillier A, Griffin CE - The ACVD task force on canine atopic dermatitis (X): is there a relationship between canine atopic dermatitis and cutaneous adverse food reactions? Vet Immunol Immunopathol 2001; 81: 227-231.

Hogen-Esch H, Dunham AD, Scott-Moncrieff C et al. - Effect of vaccination on serum concentrations of total and antigen-specific immunoglobulin E in dogs. Am J Vet Res 2002; 63(4): 611-616.

Inman AO, Olivry T, Dunston SM et al. -Electron microscopic observations of stratum corneum intercellular lipids in normal and atopic dogs. Vet Pathol 2001; 38(6): 720-3.

Jackson HA, Hammerberg B - Evaluation of a spontaneous canine model of immunoglobulin E-mediated food hypersensitivity: Dynamic changes in serum and fecal allergen-specific immunoglobulin E values relative to dietary change. Comp Med 2002; 52(4): 316-321.

Jackson HA, Jackson MW, Coblentz L et al. - Evaluation of the clinical and allergen specific serum immunoglobulin E responses to oral challenge with cornstarch, corn, soy and a soy hydrolysate diet in dogs with spontaneous food allergy. Vet Dermatol 2003; 14(4): 181-187.

Jackson HA, Murphy KM, Tater KC et al. - The pattern of allergen hypersensitivity (dietary or environmental) of dogs with non-seasonal atopic dermatitis cannot be differentiated on the basis of historical or clinical information: a prospective evaluation 2003-2004. Vet Dermatol 2005; 16: 200.

Jeffers G, Shanley KJ, Meyer EK - Diagnostic testing of dogs for food hypersensitivity. J Am Vet Med Assoc 1991; 198: 245-250.

Johanson SGO, Hourihane OB, Bousquet J - A revised nomenclature for allergy: an EAACI position statement from the EAACI nomenclature task force. Allergy 2001; 56: 813-824.

Korotkova M, Telemo E, Yamashiro Y et al. - The ratio of n-6 to n-3 fatty acids in maternal diet influences the induction of neonatal immunological tolerance to ovalbumin. Clin Exp Immunol 2004; 137(2): 237-244.

Kunkle GA, Horner S - Validity of skin testing for diagnosis of food allergy in dogs. J Am Vet Med Assoc 1992; 200: 677-680.

Leistra MHG, Markwell PJ, Willemse T - Evaluation of selected-protein-source diets for management of dogs with adverse reactions to food. J Am Vet Med Assoc 2001: 1411-1414.

Leistra M, Willemse T - Double-blind evaluation of two commercial hypoallergenic diets in cats with adverse food reactions. J Feline Med Surg 2002; 4: 185-188.

Loeffler A, Lloyd DH, Bond R et al. - Dietary trials with a commercial chicken hydrolysate diet in 63 pruritic dogs. Vet Rec 2004; 154(17): 519-522.

Lowe JA, Wiseman J - A comparison of the bioavailability of three dietary zinc sources using four different physiologic parameters in dogs. J Nutr 1998; 128(12 Suppl): 2809S-2811S.

March PA, Hillier A, Weisbrode SE et al. - Superficial necrolytic dermatitis in 11 dogs with a history of phenobarbital administration (1995-2002). J Vet Intern Med 2004; 18(1): 65-74.

Marsh KA, Ruedisueli KL, Coe SL et al. - Effects of zinc and linoleic acid supplementation on the skin and coat quality of dogs receiving a complete and balanced diet. Vet Dermatol 2000; 11: 277-284.

Martin A, Sierra MP, Gonzalez JL et al. - Identification of allergens responsible for canine cutaneous adverse food reactions to lamb, beef and cow's milk. Vet Dermatol 2004; 15(6): 349-56.

Mueller RS, Rosychuk RAW, Jonas LD - A retrospective study regarding the treatment of lupoid onychodystrophy in 30 dogs and literature review. J Am Anim Hosp Assoc 2003; 39(2): 139-150.

Mueller RS, Tsohalis J - Evaluation of serum allergen-specific IgE for the diagnosis of food adverse reactions in the dog. Vet Dermatol 1998; 9: 167-171.

Mundt HC, Stafforst C - Production and composition of dog hair. In: Edney ATB, ed. Nutrition, Malnutrition and Dietetics in the Dog and Cat. British Veterinary Association, 1987: 62-65.

Ohmori K, Masuda K, Maeda S et al. - IgE reactivity to vaccine components in dogs that developed immediate-type allergic reactions after vaccination. Vet Immunol Immunopathol 2005; 104(3-4): 249-56.

Osborn DA, Sinn J - Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. Cochrane Database Syst Rev 2003(4): CD003664.

Outerbridge CA, Marks SL, Rogers QR - Plasma amino acid concentrations in 36 dogs with histologically confirmed superficial necrolytic dermatitis. Vet Dermatol 2002; 13(4): 177-186.

Prélaud P - Allergologie canine. Masson; Paris, 1999.

Prélaud P - Diagnostic clinique des dermatites allergiques du chien. Rev Méd Vét 2004; 155(1): 12-19.

Prélaud P, Guaguère E, Alhaidari Z et al. - Réévaluation des critères de diagnostic de la dermatite atopique canine. Rev Méd Vét 1998; 149: 1057-1064.

Prélaud P, Olivry T - Etiopathogénie de la dermatite atopique canine. Prat Méd Chir Anim Comp 1998; 33: 315-329.

Qhoc KP, Pascaud M – Effects of dietary gamma-linolenic acid on the tissue phospholipids fatty acid composition and the synthesis of eicosanoids in rats. Ann Nutr Metab 1996; 40(2): 99-108.

Roudebush P, Wedekind KJ - Zinc-responsive dermatosis in dogs. Vet Dermatol 2002; 13(1): 63.

Saevik B, Bergvall K, Holm BR et al. - A randomized, controlled study to evaluate the steroid sparing effect of essential fatty acid supplementation in the treatment of canine atopic dermatitis. Vet Dermatol 2004; 15(3): 137-145.

Sampson HA - Update on food allergy. J Allergy Clin Immunol 2004; 113(5): 805-19; quiz 820.

Scott DW, Miller Jr WH, Griffin CE - Muller & Kirk's Small Animal Dermatology. 6th ed. Saunders WB; Philadelphia, 2001.

Scott DW, Sheffey BE - Dermatosis in dogs caused by Vitamin E deficiency. Comp Anim Pract 1987; 1: 42-46.

Sture GH, Lloyd DH – Canine atopic disease: therapeutic use of an evening primrose oil and fish combination. Vet Rec 1995; 137:169-170.

Turek MM - Cutaneous paraneoplastic syndromes in dogs and cats: a review of the literature. Vet Dermatol 2003; 14(6): 279-286.

Vaden SL, Hammerberg B, Davenport DJ et al - Food hypersensitivity reactions in Soft Coated Wheaten Terriers with protein-losing enteropathy or protein-losing nephropathy or both: Gastroscopic food sensitivity testing, dietary provocation, and fecal immunoglobulin E. J Vet Intern Med 2000; 14(1): 60-67.

Vroom MW - A prospective study of a commercial hypoallergenic diet in 18 dogs. Vet Quat 1994; 16: 60S-61S.

Watson AL, Baker CD, Bailey J et al – Dietary constituents can improve canine epidermal barrier function in vitro. Waltham International Symposium, Oct 2003; Bangkok, Thailand: 11.

Weese JS, Arroyo L - Bacteriological evaluation of dog and cat diets that claim to contain probiotics. Can Vet J 2003; 44(3): 212-215.

White SD, Bourdeau P, Rosychuk RAW et al - Zinc-responsive dermatosis in dogs: 41 cases and literature review. Vet Dermatol 2001; 12(2): 101-109.

Wiberg ME, Lautala HM, Westermarck E - Response to long-term enzyme replacement treatment in dogs with exocrine pancreatic insufficiency. J Am Vet Med Assoc 1998; 213: 86-90.

Wilhelm S, Favrot C - Futtermittelhypersensitivitäts-Dermatitis beim Hund: Möglichkeiten der Diagnose. Schweiz Arch Tierheilkd 2005; 147(4): 165-71.

Yu S, Rogers QR, Morris JG - Effect of low levels of dietary tyrosine on the hair colour of cats. J Small Anim Pract 2001; 42(4): 176-80.

Zentek J, Meyer H - Investigations on copper deficiency in growing dogs. J Nutr 1991; 121: 83-84.

EXAMPLES OF NOVEL PROTEIN

Example 1

COMPOSITION
(1000 g diet)

Venison, back . . . . . 475 g
Potato, cooked, with skin . . . . . 500 g
Rapeseed oil . . . . . 25 g

Add a well-balanced mineral and vitamin supplement.

ANALYSIS		
The diet prepared in this way contains 27% dry matter and 73% water		
	% dry matter	**g/1000 kcal**
Protein	43	102
Fat	16	37
Available carbohydrate	29	68
Fiber	3	7

INDICATIVE RATIONING			
Energy value (metabolizable energy) 1140 kcal/1000 g of diet prepared (4250 kcal/1000 g DM)			
Dog's weight (kg)**	Daily amount (g)*	Dog's weight (kg)**	Daily amount (g)*
2	190	45	1980
4	320	50	2140
6	440	55	2300
10	640	60	2460
15	870	65	2610
20	1080	70	2760
25	1270	75	2910
30	1460	80	3050
35	1640	85	3190
40	1810	90	3330

Key Points

- **Control raw ingredients used**
  - Use of a single source of highly digestible proteins, against which the dog is not sensitized (i.e. has not previously consumed)
  - Use of a single source of extremely digestible carbohydrate

- **Palatability** to facilitate the strict observation of the diet

**The rationing is offered in accordance with the dog's healthy weight. In case of obesity, the rationing must be prescribed in accordance with the ideal weight and not the real weight of the dog.*
***The quantities can be adapted as the dog's weight develops, but no other ingredients must be incorporated into the ration and no supplements must be given.*

HOME-PREPARED ELIMINATION DIETS

Example 2

COMPOSITION
(1000 g diet)

Duck ..... 500 g
Rice, cooked ..... 480 g
Cellulose ..... 10 g
Rapeseed oil ..... 10 g

Add a well-balanced mineral and vitamin supplement.

INDICATIVE RATIONING			
Energy value (metabolizable energy) 1325 kcal/1000 g of diet prepared (4480 kcal/1000 g DM)			
Dog's weight (kg)**	Daily amount (g)*	Dog's weight(kg)**	Daily amount (g)*
2	170	45	1700
4	280	50	1840
6	380	55	1980
10	550	60	2120
15	750	65	2250
20	930	70	2370
25	1100	75	2500
30	1260	80	2620
35	1410	85	2750
40	1560	90	2870

ANALYSIS		
The diet prepared in this way contains 30% dry matter and 70% water		
	% dry matter	**g/1000 kcal**
Protein	37	82
Fat	14	31
Available carbohydrate	43	95
Fiber	4	9

Contra-indications

For a puppy a commercial low-allergenic diet is preferable until the end of the growth phase

Examples of home-made diets are proposed by Pr Patrick Nguyen
(Nutrition and Endocrinology Unit; Biology and Pathology Department, National veterinary School of Nantes)

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The beauty of the coat obviously depends on the genetic data selected by the breeders, but these natural qualities are only realized if the food provides the nutrients essential to growth and regeneration.

Key Points
to remember:

The role of nutrition in preventing and treating skin diseases in dogs

Objective #1: strengthening the effectiveness of the skin barrier

The Waltham Research Center has screened 27 substances that are likely to have a beneficial effect on skin barrier function. The selection criteria were based on limiting water loss through the epidermis and the synthesis of skin lipids.

Four group B vitamins and one amino acid acting synergistically were identified *(Watson et al, 2006)*. Group B vitamins are water soluble and are not stored in the body. In general, a balanced diet and synthesis by the intestinal bacteria guarantee sufficient intake, although intake can become marginal in situations of major water loss or antibiotic treatment.

- **Niacin** (or nicotinamide) is synthesized from tryptophan. It is essential for cellular respiration. With deficiency, pruriginous dermatitis of the abdomen and the hind limbs occurs in dogs (termed pellagra in human medicine).

- **Pantothenic acid** is involved as a coenzyme in many metabolic pathways, including those of fatty acids.

- **Choline and inositol** work together in the formation of cell membranes. Combined with phosphorus, choline forms phospholipids.

- **Histidine** is essential to the growth and maturation of the epidermal cells (keratinocytes).

Administration of these nutrients has a beneficial effect after approximately two months, due to the time needed for the epidermal cellular differentiation process.

Objective #2: controlling inflammation with essential fatty acids

Some fatty acids are termed essential because the organism is incapable of synthesizing them. In the case of deficiency, the skin undergoes major desquamation with alterations in the skin barrier function.

The essential fatty acids have a dual action: they rebalance the composition of the superficial lipid film to limit skin drying phenomena *(Fray et al, 2004)* and they decrease the synthesis of inflammation mediators. The anti-inflammatory properties of long-chain omega 3 fatty acids (EPA/DHA) are widely used in human and veterinary dermatology *(Byrne et al, 2000)*.

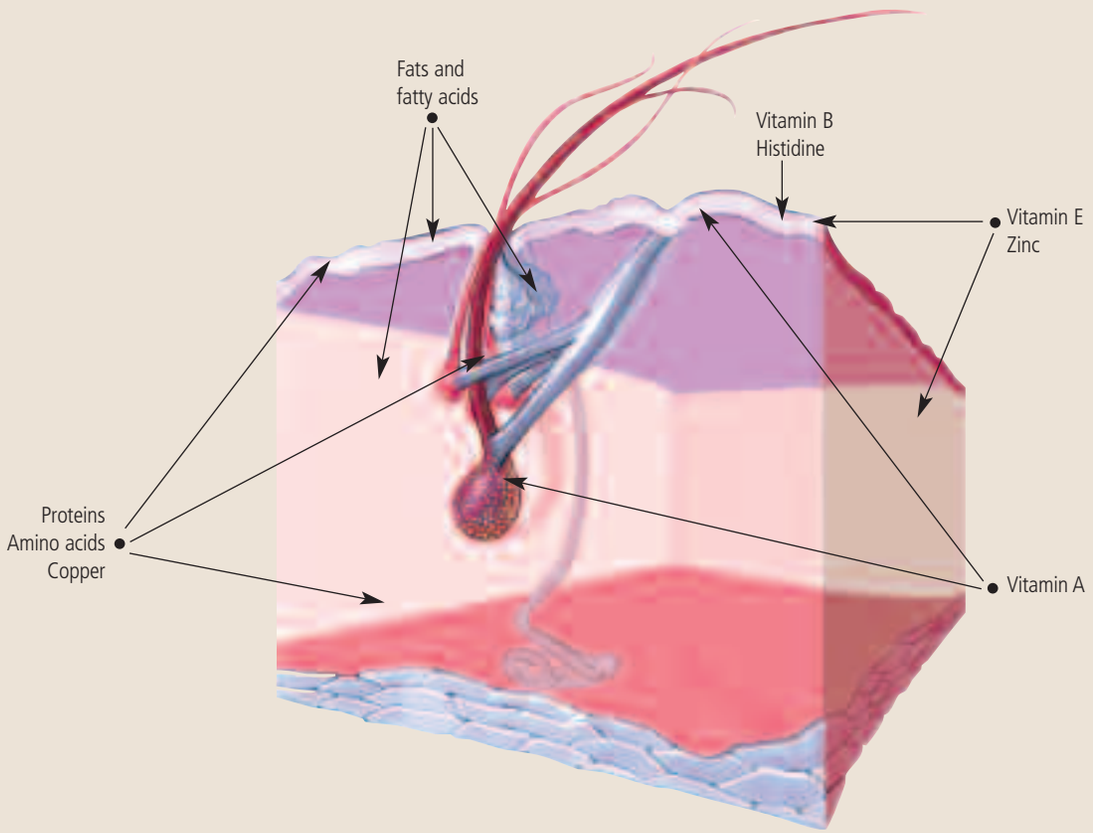
Objective #3: ensuring the vitamin intake meets the major requirements of the coat

Vitamin A regulates the growth of epidermal cells and the production of sebum. It helps combat seborrhea and the dandruff that often forms after pruritus. It acts synergistically with zinc and sulfated amino acids.

The sensitivity of polyunsaturated fatty acids to oxidation requires close monitoring of their resistance to oxidation and an increase in the quantities of vitamin E in the food.

Biotin (vitamin H) is essential to skin integrity. Biotin deficiency can lead to mild or severe hair loss.

ACTION OF NUTRIENTS IN THE SKIN



Many nutrients are essential to the complex organ that is the hair and skin. This figure only briefly summarizes the many essential elements that permit normal skin function.

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Focus on:
BORAGE OIL

Borage (*Borago officinalis*) is a plant from Asia that is also grown in North Africa and various European countries, including the UK, Germany, France and the Netherlands. The oil is obtained by pressing the grains.

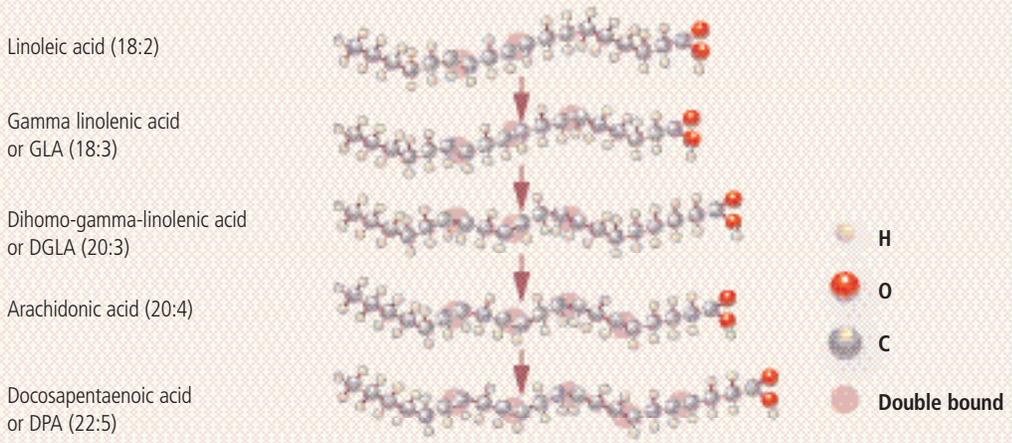
Borage oil is characterized by large quantities of fatty acids, especially those of the omega 6 family such as gamma linolenic acid or GLA. Most vegetable oils have high linoleic acid content, but the only oils that provide significant quantities of GLA are: borage oil, evening primrose oil and blackcurrant seed oil. Of course, borage oil contains the highest GLA content.

The diagram below illustrates the successive transformations linoleic acid goes through to produce the whole omega 6 fatty acid family. Each step in the transformation is characterized by the facilitation of a specific enzyme.

COMPARISON OF GLA CONTENTS FOR VARIOUS VEGETABLE OILS

Vegetable sources	Linoleic acid %	Gamma-linolenic acid %
Borage	35-40	20-25
Blackcurrant seeds	45-50	15-20
Evening primrose	70-80	8-12
Soy	50-55	-
Olive	8-10	-

STEPS IN THE SYNTHESIS OF POLYUNSATURED FATTY ACIDS OF THE OMEGA 6 SERIES

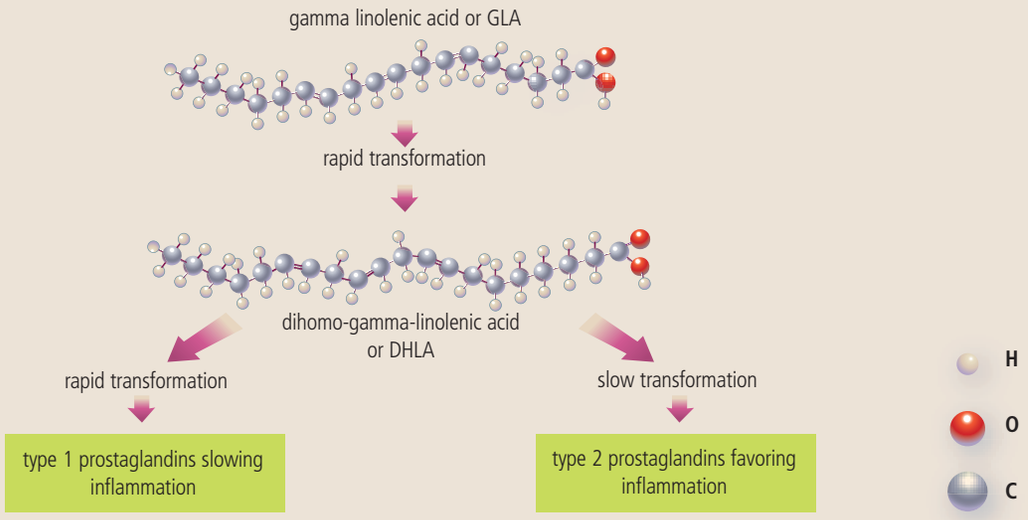


The addition of GLA to the diet favors the incorporation of GLA into tissues including the liver, red blood cells, and the vessel walls. The efficacy of this supplementation in the cell membranes is much clearer than that obtained from the transformation of linolenic acid. The dietary intake of GLA therefore prevents the risk of deficiency in animals at highest risk such as aging dogs or dogs suffering from enzyme deficiencies.

Borage oil has potential for the treatment of all inflammatory problems. The best studies into the beneficial effects of borage oil have been in dermatology. GLA supplementation favors an increase in the production of hormones with well known anti-inflammatory effects (type 1 prostaglandins). This production is at the expense of the synthesis of type 2 prostaglandins, which have a pro-inflammatory effect.

Decreasing the transformation of arachidonic acid limits the negative effects of its derivatives, type 2 prostaglandins and the excessive inflammatory phenomena associated with them.

ORIGIN OF THE BALANCE BETWEEN TYPE 1 & 2 PROSTAGLANDINS



The positive effects are significant in dogs presented with an inherited predisposition. The results are also promising with respect to problems with excessive sebum production by the skin (seborrhea).

Borage oil is also used in cosmetology where it is incorporated into products aimed at regenerating the flexibility and elasticity of the skin. It is indicated when the skin is dry.

References

Byrne K Campbell KL, Davis C et al - The effects of dietary n-3 vs n-6 fatty acids on ex-vivo LTB4 generation by canine neutrophils. Vet Dermatol 2000; 11: 123-131.

Fray TR, Watson AL, Croft JM et al - A combination of aloe vera, curcumin, vitamin C, and taurine increases canine fibroblast migration and decreases tritiated water diffusion across canine keratinocytes in vitro. J Nutr 2004;134 (8 Suppl): 2117S-2119S.

Watson AL, Fray TR, Bailey J et al - Dietary constituents are able to play a beneficial role in canine epidermal barrier function. Exp Dermatol. 2006;15 (1): 74-81.

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Nutricional dermatoses and the contribution of dietetics in dermatology

1 - Risk factors 63
2 - Nutritional dermatoses 66
3 - Nutritional therapy in dermatology 80

Frequently asked questions 87
References 88
Examples of home-prepared novel protein elimination diets 90
Royal Canin Nutritional Information 92

Nutritional dermatoses and the contribution of dietetics in dermatology

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The skin is a major organ both in terms of surface area ($1m^2$ for a 35-kg dog) and roles (social, maintenance of a stable internal environment, immune response, etc). In constantly rejuvenating itself the skin mobilizes a large part of the macro- and micronutrients provided by the food. An imbalanced intake of amino acids, fatty acids, vitamins or trace elements disrupts the barrier function (Table 1) and the immune protection provided by the skin. The dog may become more sensitive to infection and can develop allergic reactions more easily. The skin and the coat accordingly are the mirror of the dog's health and the quality of its food. There are many forms of nutritional dermatosis that frequently affect dogs (Table 2).

Nutrition has a special place in canine dermatology, not only as an essential factor in the prevention of skin diseases, but also as a therapeutic tool for allergy, keratoseborrheic and metabolic dermatopathies.

1 - Risk factors

The risks of developing nutritional dermatoses are not only related to the quality of the food, but also to individual factors in the animal such as the physiological stage, the type of hair and the predisposition to certain metabolic or allergic diseases.

► Breed specificities

There are many breed-related predispositions in canine dermatology that can be directly linked to nutrition (Table 3).

The two main groups of nutritional dermatoses (zinc or vitamin A responsive dermatoses) are the major causes of keratinization problems in predisposed breeds (e.g. Nordic breeds with respect to zinc).

Table 1 - Nutrients that can influence the skin barrier function

Polyunsaturated fatty acids (PUFA) (e.g. linoleic acid)	They belong to the lipids produced by the sebaceous glands that form the hydrolipidic surface film
Proteins	Sufficient intake of all essential amino acids is necessary for the synthesis of keratocytes
Vitamin A	Essential to the maturation of keratocytes and so the formation of the keratinous layer
Biotin	Essential to PUFA metabolism
Vitamin C	Plays a key role in the formation of the lipids of the keratinous film layer
Zinc	A zinc supplement helps reduce water loss and deficiency leads to corneogenesis problems
Nicotinamide	Increases the free fatty acid and ceramide concentrations in the keratinous layer
Water soluble vitamins	Participate in PUFA metabolism
Vitamin E	Excreted by sebaceous glands, helps limit the oxidation of fatty acids

Table 2 - Possible signs of nutritional dermatology

- dull hair
- widespread scaling
- localized or mucocutaneous keratoses
- pruritus
- recurring urticaria
- chronic otitis
- recurring pyoderma

Table 3 - Breeds predispositions to nutritional dermatoses

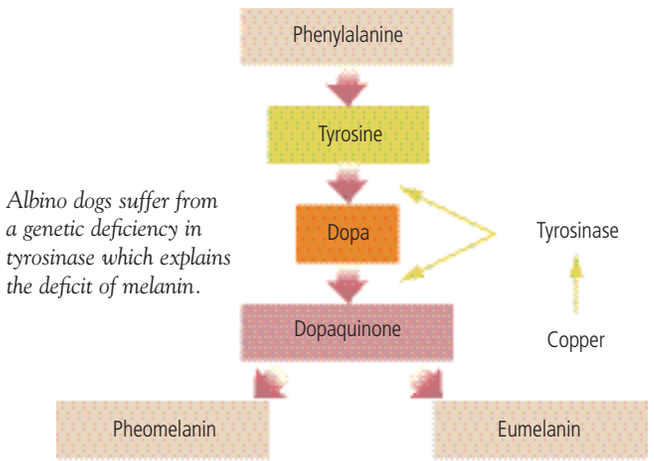
Deficiencies in intake or assimilation	
Zinc responsive dermatitis	Nordic breeds, large breeds
Vitamin A responsive dermatitis	Cocker Spaniel
Dietary hypersensitivity	
Predisposition or over-representation	Labrador Retriever
Predisposition associated with an atopic condition	American Staffordshire Bull Terrier, Beagle, German Shepherd, Boxer, Bulldog, Dalmatian, Fox Terrier, Bull Terrier Jack Russell Terrier, Labrador Retriever, Lhassa Apso, Pekingese, Shar-Pei, English Setters, Shi Tzu, West Highland White Terrier
Predisposition associated with malassimilations	German Shepherd, Irish Setters, Shar-Pei, Soft Coated Wheaten Terrier

There is a higher likelihood of dietary hypersensitivities in breeds suffering from malassimilation and atopy.

In dogs with a dense coat (e.g. Pomeranian, Spitz, Shih Tzu), the quantity of hair is such that skin and coat maintenance and rejuvenation of the skin and coat accounts for 30-35% of daily protein requirement *(Mundt & Stafforst, 1987)*. It is possible that the nutritional requirements of animals with a long coat and dense undercoat exceed that of shorthaired breeds.

► Coat

FIGURE 1 - SYNTHESIS OF MELANIN FROM PHENYLALANINE



Albino dogs suffer from a genetic deficiency in tyrosinase which explains the deficit of melanin.

The influence of nutrients on the color of the coat is well known. The coat's pigmentation depends on the presence and the distribution of pheomelanin (yellow-red) and eumelanin (black) pigment grains in the cortex and/or the medulla of hairs and along the pilary stem. The synthesis of these pigments depends on the intake of aromatic amino acids (phenylalanine [Phe] and tyrosine [Tyr]) and the activity of the tyrosinases (cupric enzyme) **(Figure 1)**.

Dietary imbalances in animals with a dark or black coat may provoke the reddening of the coat *(Busch-Kschiewan et al, 2003)*. This was initially shown in cats. In cats a slight imbalance in the aromatic amino acid intake may provoke the appearance of neurological problems (sensorial neuropathy) *(Dickinson et al, 2004)* and lightening of the coat in red cats, or the reddening of the coat in black cats *(Yu et al, 2001)*.

Reddening is also a common pigmentation anomaly in large dogs with a black coat. Work conducted on Newfoundland puppies and black Labrador puppies *(Zentek et al, 2003)* shows that, in canines too, the level of phenylalanine and tyrosine needed to guarantee optimal coat pigmentation is twice that of the minimum requirements to ensure the puppy's optimal growth. They also showed that tyrosine supplementation in food helps increase the intensity of coat color **(Figure 2)**. The nutritional recommendations based on the study of growth (NRC, AAFCO) do not allow estimation of the requirements necessary for some metabolically intense functions such as the production of melanine.

FIGURE 2 - INFLUENCE OF DIETARY TYROSINE INTAKE ON COLOR INTENSITY IN BLACK DOGS

Over a 6 month period, these dogs have consumed the same diet, differing only in tyrosine and phenylalanine content (Tyr + Phe). From the left to the right, the (Tyr + Phe) intake represents 3.2, 2.6 and 1.9 times the estimated AAFCO requirement for growth. The effect of the diet is obvious: the black color is more intense in the dog on the left whereas, on the right, the growing hair have a reddish color.

► Age and physiological condition

The age or the physiological condition may influence the relationship between skin homeostasis, coat quality and food.

In dogs, immaturity of the immune system and high intestinal permeability may to some degree explain the prevalence of dietary hypersensitivities in the young animal *(Day, 1999; Prélaud, 1999)* as it does in humans *(Chehade & Mayer, 2005)*. These phenomena may be more common during weaning.

Nutritional deficiencies appear more readily when the dogs' nutritional requirements exceed simple maintenance requirements: for example chronic disease, during gestation, lactation and growth, and especially in large-breed dogs. These deficiencies in protein, essential fatty acids and zinc, may result in keratinization defects.

In aging dogs, malassimilation is characterized by imbalances in the intake of polyunsaturated fatty acids.

► Concurrent diseases

Any disease that disrupts the assimilation of nutrients may have direct and indirect consequences on the quality of the coat and favor the development of concurrent diseases. Malassimilation is frequently associated with a dull and dry hair coat or even recurrent bacterial infections. Defective protein digestion may cause a decrease in immune tolerance as clearly demonstrated in human and murine models.

In dogs, this phenomenon is frequently described in German Shepherds with exocrine pancreatic failure *(Biourge & Fontaine, 2004; Wiberg et al, 1998)* and Soft Coated Wheaten Terriers suffering from protein-losing enteropathy *(Vaden et al, 2000)*, which often develop digestive hypersensitivities with cutaneous manifestations (pruritus, recurring pyoderma). Chronic digestive problems or prolonged use of antibiotics may also provoke a deficiency in B vitamins and a secondary deficiency in polyunsaturated fatty acids (PUFA).

At birth the skin is very supple and the number of hair follicles is low. The fragility of the skin and the coat means that the puppy is very susceptible to attacks on the skin by parasites or infections.
During growth the dermis thickens, the sebaceous glands increase in size and the hair follicles multiply: they increase by 50% in the Miniature Poodle between week 10 and 28 *(Credille et al, 2002)*. The composition of skin lipids is also modified *(Dunstan et al, 2002)*.

TABLE 4 - THE MOST COMMON DIETARY IMBALANCES WITH CONSEQUENCES FOR THE QUALITY OF THE SKIN AND COAT

Type of food	Particulars	Nutritional consequences	Dermatological consequences
Low-end generic food	Indigestible proteins	Protein deficiency	Xerosis Keratoseborrheic conditions
	Low fat content	Insufficient energy intake Essential fatty acid (EFA) deficiency	-
	Mineral excess (calcium and phytates)	Zinc deficiency	Generic dog food disease
Home-prepared diet (no supplementation)	PUFA deficiency	EFA deficiency	Xerosis Keratoseborrheic conditions
	Trace element deficiency	Zinc, vitamin E deficiency of water soluble vitamins	-
Vegetarian diet	Restricted protein intake	Sulfur amino acid deficiency	Dull, brittle coat
	PUFA deficiency	EFA deficiency	Xerosis Keratoseborrheic conditions
Excessive mineral supplements	Calcium excess	Zinc deficiency	Generic dog food disease

► Dietary balance

Poorly balanced nutritional intake may generate spectacular dermatological imbalances. The most common are due to generic foods that are low in fat with excessive mineral supplementation, the most common being surplus calcium which inhibits the absorption of zinc **(Table 4)**.

2 - Nutritional dermatoses

Nutritional dermatoses may be specific (identified deficiency of a particular nutrient or group of nutrients) or non-specific: associated with general underfeeding, poor digestibility of the food or a gastrointestinal absorption problem.

► Specific deficiencies

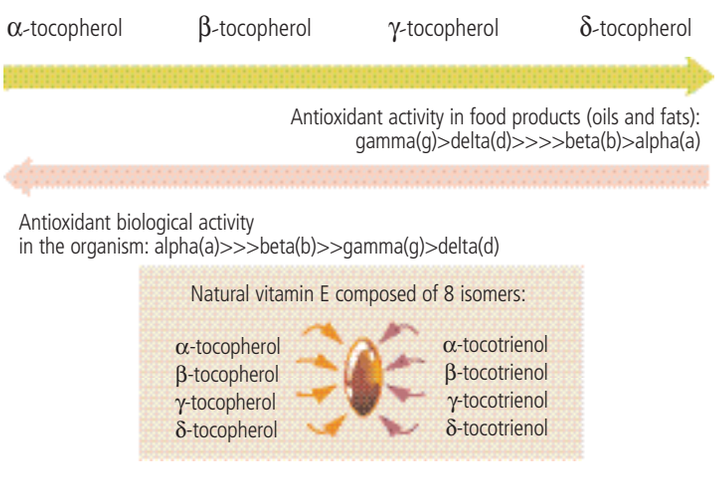
Nowadays, specific nutritional deficiencies are rare. They may, however, be observed in dogs fed with a poor-quality commercial food or an unbalanced homemade food.

> Vitamin deficiencies

• *Vitamin A*

Retinol, a fat soluble vitamin, is essential to the differentiation of epithelial cells. As a consequence, retinol deficiency causes a general keratinization problem, with scaling. In the only case in dogs described in the literature, these problems were associated with visual deficiencies and digestive problems *(Scott et al, 2001)*.

FIGURE 3 - TOCOPHEROL ISOMERS



• *Vitamin E*

Vitamin E is a generic term covering two classes of fat soluble molecules: tocopherols (α, β, γ, δ) and tocotrienols (α, β, γ, δ). Each of these eight different forms has a specific biological activity. α-tocopherol is the most widespread form of vitamin E in animal foods and organisms: it is the form with the greatest biological antioxidant activity in the cell membranes **(Figure 3)**.

Deficiencies of vitamin E are rare and usually due to foods whose fats are poorly stabilized *(Scott & Shelfey, 1987)*. Vitamin E is actually a natural antioxidant, being consumed during oxidation. An experimental deficiency in dogs provokes the appearance of dry seborrhea, diffuse alopecia, erythroderma, secondary pyoderma and anomalies of the immune system.

• *B vitamins*

B vitamins are water soluble and play a role as coenzymes for the cellular enzymes involved in energy metabolism and tissue synthesis. They are provided in food and some are synthesized by gastrointestinal flora. Deficiencies are rare. A correctly formulated commercial food stored in good conditions contains vitamins in sufficient quantities and supplementation is not necessary.

The dermatological manifestations of such deficiencies vary depending on the vitamin:
- **Riboflavin deficiency** (vitamin B_2), sensitivity to light: xerosis localized to the periorbital and abdominal regions

- **Niacin deficiency** (nicotinamide or vitamin PP), occurring with food low in animal nutrients: pruriginous dermatitis of the abdomen and hind limbs.
- **Biotin deficiency** (vitamin B_8 or H), mainly described in animals fed with an excess of egg whites, which contain avidin, a molecule that complexes the biotin and prevents its absorption in the intestine: erythema, facial and periorbital alopecia, generalized scaling, leukotrichia, dull and brittle hair.

> Trace element deficiencies

Trace elements are mineral substances that act at very low concentrations in the organism. The trace elements most directly related to the beauty of the coat are iron, zinc and copper.

• *Zinc*

Deficiencies in zinc intake are typically caused by foods high in phytates, which chelate zinc. These are most often foods of poor quality that are high in whole meal cereal containing a lot of bran. This intake deficiency is also observed with foods oversupplemented with calcium or in breeds with an inability to absorb zinc.

Zinc is a cofactor in a very large number of metabolic pathways, and a deficiency provokes immunity problems and keratinization with scaly, crusty periorificial thickening observed in the skin. The differential diagnosis is not always easy. Therefore it is important to confirm the clinical diagnosis in a histopathological biopsy. Zinc deficiency is characterized by major parakeratosis in the epidermis and the follicles.

In contrast to other types of dermatopathies related to metabolic disorders of zinc **(Table 5),** a simple deficiency can be controlled by rebalancing the diet and controlling secondary infection. In previous classifications, this deficiency is termed generic dog food disease or type-2 zinc responsive dermatitis (common in large-breed dogs) **(Figure 4)**.

TABLE 5 - CLASSIFICATION OF DERMATOSES IMPROVED BY ZINC
(Roudebush & Wedekind, 2002)

Abnormal nutritional intakes
- Primary zinc deficiency
- Secondary zinc deficiency
- Polyunsaturated fatty acid deficiency

Genetic abnormality
- Lethal acrodermatitis

Malabsorption of zinc

• *Copper*

Copper is a component of many carrier enzymes or proteins. A deficiency is observed mainly in puppies fed a homemade food without supplementation or with excessive zinc, calcium or iron content. The deficiency leads to changes in the coat with discoloration beginning in the face, and a thin coat with dull and brittle hairs **(Figure 5)** *(Zentek & Meyer 1991)*.

• *Iodine*

While an iodine deficiency could theoretically disturb the synthesis of thyroid hormones, these phenomena are unusual in dogs and generally without clinical consequence. The daily iodine requirement of a beagle is in the order of 140 µg. A reduction in total thyroxin is only observed when concentrations are under 20-50 µg/day, there is no however, in free thyroxin and no signs of a hypothyroidism *(Feldman & Nelson, 2004)*.

The quantity of trace elements provided in the food does not correspond to the quantity actually available to the organism. The level of absorption depends on the chemical form in which they are provided and their dietary environment. There are interactions between the different elements. So calcium absorption competes with the absorption of zinc, copper and iodine. The percentage of trace element absorption is often under 30%.

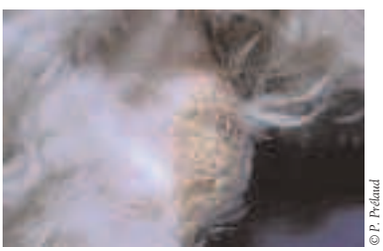

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Figure 4 *- Hyperkeratosis of the elbow in a Fox Terrier due to zinc deficiency.*


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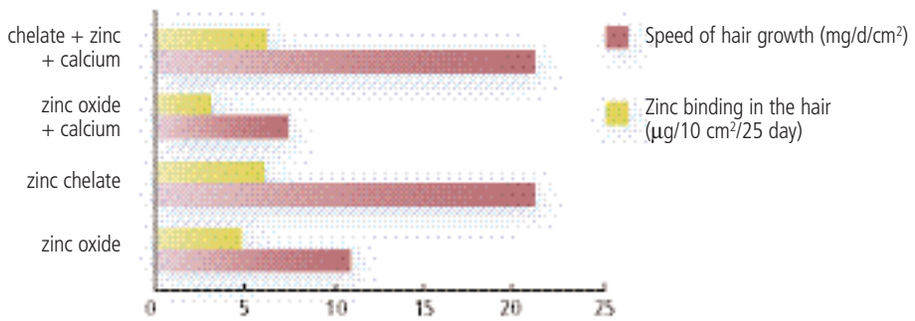
Figure 5 *- Leukotrichia (pilary depigmentation) in a Scottish Terrier puppy due to malnutrition.*

When the trace elements are provided in the organic form chelated with amino acids their absorption is clearly improved. Therefore they are better utilized by the organism. For example, in the presence of an excess of calcium in the ration, which inhibits zinc absorption, loss of zinc in the feces increases. Conversely with the chelated form, assimilation is not affected **(Figure 6)** *(Lowe & Wiseman, 1998)*.

A chelated trace element is made up of a metallic ion linked to three amino acids. This element weighs less than 1500 Daltons. Normal trace element absorption efficiency varies from 5% to 30%. When trace elements are chelated, the absorption efficiency can be in excess of 60%.

FIGURE 6 - INFLUENCE OF THE FORM OF ZINC INTAKE ON HAIR GROWTH

(From Lowe et al, 1998)



Chelated zinc binds to hair more avidly than zinc in mineral form (zinc oxide) and the speed of hair growth is significantly faster. Because calcium binds zinc, excessive calcium in the ration leads zinc oxide to bind to a lesser degree in the hair. Zinc binding is unaffected when zinc is provided in chelated form.

> Essential fatty acid deficiency

Essential fatty acids are so termed because they are not synthesized by the organism. As is the case with most vitamins they must be provided by the food. They are primarily the precursors of two families of PUFA, omega 6 fatty acids and omega 3 fatty acids.

- **Linoleic acid,** a precursor of fatty acids of the omega 6 family, is abundant in most vegetable oils. It represents more than 70% of the fatty acids in evening primrose oil and more than 50% in sunflower oil, wheat, corn and soy.

- **Alpha linolenic acid**, a precursor of fatty acids of the omega 3 family, is found in green vegetables, fruits, grasses and plankton, and is found in concentrated form in the oil of plants like soy and flax. The oils of fish from cold waters contain very high levels of two long-chain fatty acids derived from alpha linolenic acid: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These two fatty acids participate in the fluidity of the cell membranes.

PUFA fulfill four main functions:
- Incorporation in the structure of the cell membrane, which gives it its flexibility and permeability
- Production of eicosanoids (leukotrienes, prostaglandins)
- Maintenance of the skin barrier permeability (especially omega 6)
- Cholesterol metabolism and transport

PUFA deficiencies are observed only in animals suffering from malassimilation or animals fed with poor-quality diets or diets that have been overheated for a lengthy period. The cutaneous signs include xerosis, dull hair and a keratoseborrheic disorder. The response to PUFA supplementation is rapid.

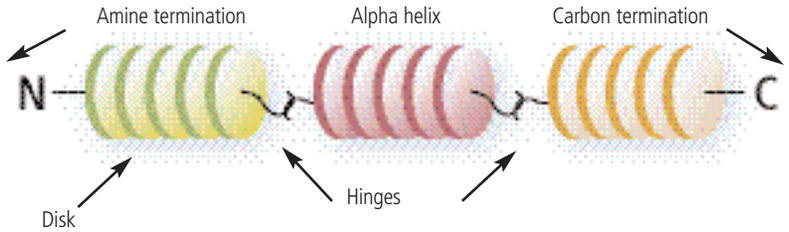
> Overall protein deficiency

Low-quality or overcooked food will undergo modification due to Maillard reactions and the digestibility will be reduced. Hair growth and the regeneration of the skin mobilizes almost 30% of protein intake and such protein deficiency leads to keratinization problems and diffuse alopecia with dull, brittle hair. Protein deficiencies are also observed in dogs presented with a chronic debilitating disease or bitches at the end of gestation or in lactation, if the dietary intake is not adapted.

The low digestibility of proteins may favor the development of dietary hypersensitivity *(Cave & Marks, 2004)*.

FIGURE 7 - STRUCTURE OF A KERATIN MOLECULE

(From Credille, 2002)



The word keratin comes from the Greek keratos, which means horn. There are several types of keratin, each with the same basic helicoidal structure. Inside the molecule, their hinges allow them to be flexible and to interconnect to form resistant filaments.

> Specific amino acid deficiencies

- ***Aromatic amino acids: tyrosine, tryptophan***

These amino acids are essential to the synthesis of the melanins responsible for hair pigmentation: pheomelanin (red, brown) and eumelanin (black). A dietary deficiency leads to a lightening of the coat or the reddening of black hairs **(see above)**.

- ***Sulfated amino acids: methionine, cystine***

Methionine and cystine are essential to the growth of hair, as they participate in the production of keratin **(Figure 7)**. These amino acids are abundant in animal proteins and are rarely deficient in dog food, with the exception of non-supplemented vegetarian diets.

Dogs are however less sensitive than cats to such deficiencies.

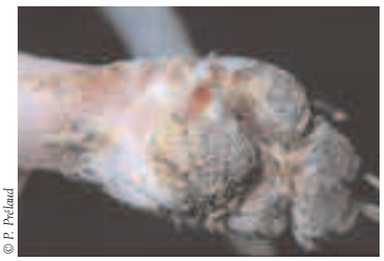
► Metabolic diseases

> Migratory necrolytic erythema

Migratory necrolytic erythema (or superficial necrolytic dermatitis, hepatocutaneous syndrome) is a serious dermatosis due to a severe amino acid deficiency. It originates from chronic liver dysfunction (tumor, cirrhosis, functional failure induced by the administration of Phenobarbital *(March et al, 2004)*) or less commonly from a pancreatic tumor (glucagonoma). It is most often a deficiency of amino acids, essential fatty acids and zinc *(Campbell & Lichtensteiger, 2000; Scott et al, 2001; Outerbridge et al, 2002; Turek, 2003)*.

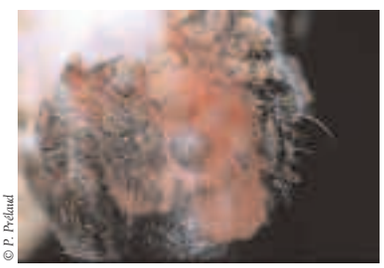
There is no breed or sex predisposition. The patients are usually old. Dermatological lesions are mucocutaneous and pedal in distribution, and are characterized by erythema associated with major, painful hyperkeratosis **(Figures 8 A-D)**. The diagnosis is based on skin biopsies and the identification of the cause of the deficiency (prolonged Phenobarbital intake, biochemical imbalance, liver and pancreatic ultrasound, biopsies). If the cause cannot be treated, the prognosis is poor.

FIGURES 8A TO D - MIGRATORY NECROLYTIC ERYTHEMA



8A - Hyperkeratosic, ulcerated foot lesions.

8B- Ulcerated, crusty perioficial lesions.



8C- Close-up of the lesions in figure 8B: wide ulcers on the face and firmly attached scabs.

8D- Perianal erosions.

TABLE 6 - SYMPTOMATIC AND NUTRITIONAL TREATMENT OF NECROLYTIC MIGRATORY ERYTHEMA

Amino acid intake
White cheese, egg yolk (1/10 kg body weight/day)
Slow intravenous infusions containing all essential amino acids at 10% every day

Polyunsaturated fatty acid intake
Egg yolk
Omega 3 fatty acids (fish oils, rapeseed oil)

Zinc intake
Zinc gluconate 10 mg/kg/day;
avoid zinc methionine

Multiple meals per day

Treatment of infectious complications
Empirical antibiotic therapy (e.g. cephalexin)

Analgesics
Opioid injections or patch

However, with appropriate nutrition intervention the condition of these animals can be quickly improved, and in some cases recovery or a very long remission is possible. Treatment involves intravenous infusion of amino acid solutions **(Table 6)** or administration of egg yolks and supplementation of essential fatty acids and zinc, at the same dosages as for zinc responsive dermatosis **(Table 7)**.

Zinc gluconate is preferable to zinc methionine complex, as it is less hepatotoxic. These nutritional measures are associated with a discontinuation of antiepileptics, antibiotic therapy and administration of analgesics (opioids), especially when the foot lesions affect locomotion.

> Lethal acrodermatitis in the Bull Terrier

Lethal acrodermatitis in the Bull Terrier is a rare autosomal recessive genetic dermatosis. It is probably a disorder of zinc metabolism, rather than a problem with zinc absorption. The animals present in poor general condition from a very early age (two weeks), with erythematous and keratoseborrheic lesions in the extremities of the limbs **(Figure 9)** and the face. The digits are thicker. There are serious systemic symptoms including bronchopneumonia, bone deformation, cataracts, and gastroenteritis. This disease is accompanied by a severe immune deficiency and is fatal in all cases.
The diagnosis is based on anamnestic data and histopathological confirmation. The supplementation of zinc is ineffective.

> Zinc responsive dermatosis

Type 1 Zinc responsive dermatosis is not a metabolic disease as such, but results from an abnormality in the intestinal absorption of zinc. It is mainly observed in Nordic breeds of dogs, but many other canine breeds can be affected, including Beaucerons, German Shepherd dogs, Boston Terriers, Bull Terriers and Great Danes.


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Figure 9 *- Erythema, scaling and ulcers on the extremities of a Bull Terrier puppy suffering from lethal acrodermatitis.*

The initial lesions are localized to the periorificial zones and the digits: erythema, scaling, which progress to firmly attached crusts **(Figures 10 & 11)**. Pruritus is present in the case of secondary infection. A febrile syndrome is sometimes associated with the condition. The diagnosis must be confirmed by histopathological examination of a biopsy. The differential diagnosis is sometimes difficult. It includes leishmaniasis in endemic areas, scabies, pemphigus foliaceous or dermatophysis *(White et al, 2001)*.

Zinc supplementation is generally sufficient and a clinical improvement follows in less than a month. In case of failure, the administration of low-dose glucocorticoid therapy for three weeks will achieve a rapid improvement in the clinical signs (e.g. oral administration of prednisolone at 0.1-0.2 mg/kg/day for three weeks). The treatment is usually lifelong *(White et al, 2001)*.


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Figure 10A *- Hyperkeratosis of the pads of a Siberian Husky presenting with zinc responsive dermatosis; note the cracking on one of the pads.*


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Figure 10B *- Periocular Hyperkeratosis (firmly attached crusty scaling) on a Siberian Husky presented with zinc responsive dermatosis.*

TABLE 7 - DOSAGE OF THE VARIOUS ZINC SALTS USED IN THE TREATMENT OF ZINC RESPONSIVE DERMATOSIS

Zinc (dosage by weight of zinc)	Dosage	Administrations per day
Zinc methionine	4 mg/kg/day	1
Zinc gluconate	5 mg/kg/day	1 to 2
Zinc sulfate	10 mg/kg/day	1 to 2

The various types of dermatitis due to zinc deficiency (food high in phytates or calcium and low in essential fatty acids) have several features in common including an identical histological appearance, hyperkeratosis of the mucocutaneous junctions and the pads. Treatment is based on balancing the diet and administering zinc for three to four weeks **(Table 7)**.

► Dietary hypersensitivities

The term dietary hypersensitivity covers all the dermatoses caused by the ingestion of a food that provokes a harmful reaction in a healthy individual. These hypersensitivities, also termed intolerances, can be of non-immunological or immunological origin *(Johanson et al, 2001)*. An immunological hypersensitivity is a dietary allergy. The clinical manifestations are highly diverse and include gastrointestinal, respiratory, cutaneous, renal or generalized involvement **(Figure 12)**.

***Figure 11A** - Crusty scaling in a Fox Terrier presented with generic dog food disease.*

***Figure 11B** - Crusty perioral scabs in a Basset Hound fed with a generic food (generic dog food disease).*

***Figure 11C** - Localized scrotal hyperkeratosis of zinc responsive dermatosis.*

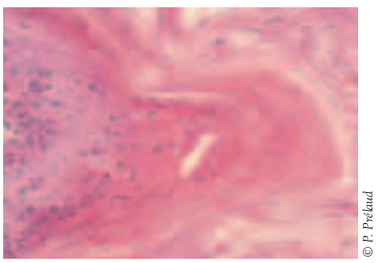
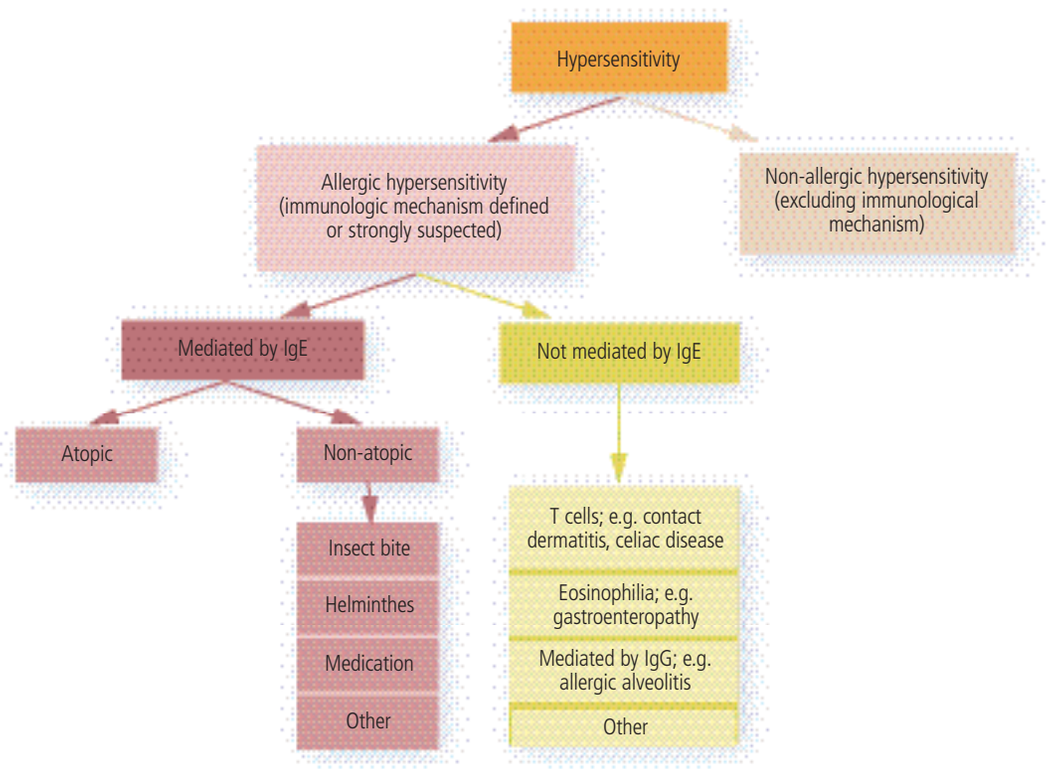


***Figure 11D** - Zinc responsive dermatosis: skin biopsy of crusty squama lesions (X 400, HE): note the major parakeratotic hyperkeratosis (persistence of knots in the corneocytes).*

FIGURE 12 - CLASSIFICATION OF HYPERSENSITIVITY REACTIONS DEFINED BY THE EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY (EAACI)



> Etiology

• *Non-immunological hypersensitivity*

The non-allergic reactions are highly diverse. Some foods may cause urticaria or aggravate an atopic dermatitis if they are high in:

- **histamine**: tomatoes, spinach, beef, pig liver, fresh crustacea, tuna, dry sausage, cheese
- **histamine liberator compounds**: chocolate, strawberries, fish, pork, ovomucoid
- **tryptamine**: chocolate, cooked cheese *(Prélaud, 1999)*.

• *Gastrointestinal allergies*

The development of an allergic reaction depends on the nature of the dietary antigens, their presentation to the digestive immune system and genetic factors.

Break in immune tolerance

The immune response to ingested antigens is generally an immune tolerance reaction. The immune reaction is inhibited when the antigens are present in low concentrations.

When the antigen concentration is high, anergy or even deletion phenomena may occur *(Chehade & Mayer, 2005)*. This immune tolerance is an active phenomenon that depends on several factors related to the individual and the antigen **(Table 8)**.

A hypersensitivity reaction may be triggered by the following factors: augmentation of intestinal permeability, chronic digestive problems, high insoluble antigen content, and individual predisposition to hypersensitivity reactions.

Dietary allergens

The foods most often implicated in the studies on dietary hypersensitivity in dogs are meat (beef, chicken, lamb), eggs, dairy products and soy, but any dietary protein is potentially allergenic. The very nature of the allergens implicated in these allergies is well known in human medicine, where the major allergens and their structural particularities have not been defined in the dog *(Breiteneder & Mills, 2005)*.

When it comes to dogs, our knowledge is very limited. The overwhelming majority of allergens identified in dogs are proteins of large molecular weight – 40-70 kD. The main allergens of beef and cow's mild for dogs may be heavy chains of immunoglobulin G *(Martin et al, 2004)*. There were however crossed sensitivities between cow's milk and beef in dogs. The allergy to casein in cow's milk has also been demonstrated in the animal models presenting spontaneous dietary allergies *(Jackson & Hammerberg, 2002)*. Lastly, some muscle enzymes common to many species of mammal could explain the crossed reactions between lamb's meat and beef in dogs. This is the case for phosphoglucomutases *(Martin et al, 2004)*.

TABLE 8 - FACTORS INVOLVED IN IMMUNE TOLERANCE
(Chehade & Mayer, 2005)

Antigen dose
Strong dose: lymphocytic deletion or anergy
Weak dose: activation of regulating T cells
Antigen form
Soluble antigens are more tolerogen than particulate antigens
Host genetics
Commensal floral
Age of the host
Newborns present stronger immune reactions.

In contrast to humans, there are no cross reactions between pollens and food (with the exception of the cross reaction between tomato and the Cryptomeria japonicum pollen) *(Fujimura et al, 2002)*.

> Predisposing factors

All the factors contributing to immune tolerance can favor the development of dietary hypersensitivity.

• *Maldigestion*

The great majority of dietary proteins, which are allergens or potential allergens, are broken down by the gastric and intestinal enzymes, although only amino acids or small peptides are normally assimilated by the mucosa of the small intestine. If digestion is defective, the quantity of antigens in the digestive immune system and their molecular weight is much greater, which is conducive to the break in tolerance. This explains why a chronic intestinal inflammatory disease or exocrine pancreatic failure is conducive to the development of dietary hypersensitivity.

• *Intestinal permeability problems*

An increase in intestinal permeability, by greatly increasing the quantity of allergens presented to the immune system, can break the condition of tolerance and induce deleterious immunological reactions. The inflammatory reaction increases the intestinal permeability and a vicious circle of maintenance of the phenomenon is maintained.

• *Vaccinations*

Vaccinations provoke an increase in the synthesis of IgE in dogs *(Hogen-Esch et al, 2002)*. This increase of IgE synthesis to dietary allergens in the experimental models of dietary allergy is however not accompanied by the appearance of symptoms.

Figure 13A *- Urticaria visible only after clipping in a Yorkshire Terrier.*

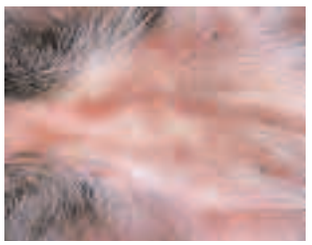


Figure 13B *- Chronic urticaria on the abdomen of a dog presented for dietary hypersensitivity.*

Figure 13C *- Facial angioedema due to a vaccine allergy in a French Bulldog puppy.*

• *Atopy*

By definition, an atopic condition predisposes the animal to the development of allergic reactions, be they aeroallergens or dietary allergens *(Prélaud & Olivry, 1998)*.

> Symptoms

The skin symptoms of dietary hypersensitivity are highly variable and sometimes rather vague. The clinical presentation may be that of atopic dermatitis, general or local pruritus, or major acute (skin rash, urticaria) or chronic keratinization problems **(Figures 13 A-C)**.

• *Urticaria and angioedema*

The most common causes of urticaria in dogs are allergies to medication (vaccines, anti-inflammatory drugs, anti-infection drugs including antibiotics, anti-viral, anti-fungal agents, allergens, etc) or reactions to anthropod bites **(Table 9)**. A dietary cause is less commonly identified. In this case, it may be due to an immunological phenomenon (immediate allergic reaction), the ingestion of a food that is high in vasoactive amines or anaphylactiod reactions (mastocyte degranulation without IgE intervention).

The allergic reactions to vaccines have some things in common with dietary allergies, in that, in the majority of cases, the allergy is due to residues of calf fetal serum in cell cultures (IgG bovines) or to protein additives (casein, gelatins) *(Ohmori et al, 2005)*. As a consequence, it is possible that these vaccine reactions are due to dietary sensitivities to these same proteins, as some vaccinal allergic reactions are observed during initial vaccination, so theoretically without prior sensitivity to the vaccine.

• *Atopic dermatitis and atopic-like dermatitis*

Atopic dermatitis is a chronic pruriginous dermatitis of the face and the extremities, characterized by a genetic predisposition to developing hypersensitive

TABLE 9 - MAIN CAUSES OF URTICARIA DESCRIBED AND SUSPECTED IN DOGS

Food
Medication: penicillin, ampicillin, tetracycline, cephalexin, vitamin K, oxopirvedine, vaccines, diethylcarbamazine, amitraz, doxorubicin
Radiolographic contrast agents
Antiserums
Allergenic extracts
Arthropod bites: bees, wasps, mosquitoes, caterpillars, termites, spider crabs, fleas
Plants
Intestinal parasites
Heat, cold
Dermographism
Aeroallergens


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Figure 14A *- Periocular erythema and alopecia in an atopic dog presented with dietary hypersensitivity.*


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Figure 14B *- Erythema of the surfaces of the concha auriculae showing the existence of otitis externa in an atopic Labrador.*

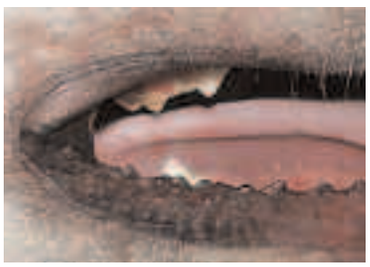
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Figure 14C *- Perioral erythema in an atopic dog.*


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Figure 14D *- Interdigital erythema in an atopic dog.*

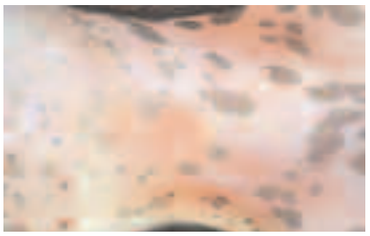
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Figure 15A *- Abdominal and stifle fold erythema in an atopic Fox Terrier (classic form of atopic dermatitis).*


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Figure 15B *- Erythema, papules and excoriations in the groins of a French Bulldog presented with a classic form of atopic dermatitis.*

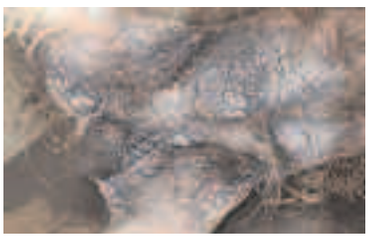
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Figure 15C *- Severe form of atopic dermatitis in a Cairn Terrier: major lichenification, and abdominal and inguinal hyperpigmentation.*


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Figure 15D *- Severe form of atopic dermatitis, with widespread alopecia, erythema and lichenification lesions in a Poodle (complication of Malassezia dermatitis).*

reactions to environmental allergens. The allergy to aeroallergens is not however demonstrated in 20-25% of referred or university atopic dermatitis cases.

This phenomenon, which is also described in humans, has led the European Academy of Allergy and Clinical Immunology (EAACI) to propose the term atopic dermatitis syndrome, covering all cases of atopic dermatitis of whatever cause, with or without a demonstrated allergy.

In canine medicine, the term atopic-like dermatitis was recently proposed by the International Task Force on Canine Atopic Dermatitis (ITFCAD) to designate cases of atopic dermatitis without a demonstrable allergy. All these variations of definition are the origin of confusion and controversy. If the results of allergological explorations are taken into account, as they are in human medicine, it is impossible to differentiate an atopic dermatitis due to aeroallergens from an atopic dermatitis due to dietary allergens *(Hillier & Griffin, 2001; Jackson et al, 2005)* **(Figures 14-16)**.

As a consequence, its diagnosis may be based on criteria tied to anamnesis and clinical signs comparables to those proposed in human medicine *(Prélaud et al, 1998)* **(Table 10)**.

In approximately 30% of atopic animals, the condition is significantly improved by an elimination diet. This suggests that dietary hypersensitivities could be considered as major factors in the etiology of canine atopic dermatitis *(Chesney, 2001 & 2002)*. As a consequence, when confronted with all the symptoms of canine atopic dermatitis, it is necessary to envisage the existence of dietary hypersensitivity in patients with the following clinical signs *(Prélaud, 2004)*:

- Bilateral otitis externa
- Bilateral cheilitis
- Bilateral pododermatitis
- Local or widespread Malassezia dermatitis

TABLE 10 - DIAGNOSTIC CRITERIA FOR CANINE ATOPIC DERMATITIS

The observation of more than three criteria in the following list enables a diagnosis with 80% discriminating firmness and 80% specific variance:

- Age of first symptoms: between 6 months and 3 years
- Steroid responsive pruritus
- Bilateral otitis externa
- Anterior erythematous pododermatitis
- Bilateral cheilitis

Table 11 - Various clinical forms of atopic dermatitis and therapeutic consequences

Clinical form	Clinic particularities	Common therapeutic bases	Therapeutic particularities
Benign	Localized lesions (e.g. otitis, pododermatitis, anitis) Moderate pruritus	- Complete and continued external anti-parasite treatment - Essential fatty acids if they lead to improvement - Hypoallergenic diet or highly digestible diet where possible	Local care often sufficient: emollients and anti-inflammatory drugs (corticoids or tacrolimus)
Classic	Multiple localizations Pruritus necessitating generalized treatment		- Early allergen immunotherapy - Control of secondary infections - Brief corticotherapy - Cyclosporin A
Serious	Very widespread localization of lesions, secondary infections Widespread pruritus		- Importance of local care (clipping and antiseptic shampoo and emollients) - Lengthy anti-infection treatments - Corticosteroid therapy most often contraindicated - Allergen immunotherapy - Cyclosporin A

Figure 16A *- Chronic recurring otitis externa in an atopic Poodle.*

- Erythematous or lichenified dermatitis of the large folds
- Hyperhidrosis

Regardless of whether the clinical form is benign, classic or severe **(Table 11)**, a hypoallergenic and highly digestible elimination diet is mandatory.

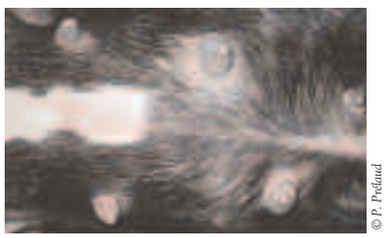

Figure 16B *- Perinipple lichenification, a minor form of atopic dermatitis in a French Bulldog.*

Figure 17A *- Local pruritus in the extremity of limbs leading to alopecia and erythema in a Collie presented with dietary hypersensitivity.*

• *Local or general pruritus*

Dietary hypersensitivity may also manifest itself in the form of local pruritus, which is most often bilateral. The lesions generally consist of erythema associated with a self-induced alopecia **(Figures 17 A-B)**.

Figure 17B *- Same dog as in figure 17A after a month-long elimination diet.*

Figure 18 *- Pyotraumatic furonculosis in a Retriever; note the papules and furuncles around the hot spot, which are visible only after clipping.*

• *Pyotraumatic dermatitis (hot spots)*

Dietary hypersensitivity is one of the causes of recurring pyotraumatic dermatitis. This diagnostic hypothesis must however be envisaged after the infection has been controlled **(Figure 18)** and the most common hypotheses such as demodetic mange (especially in Labrador Retrievers and Rottweilers), flea allergy dermatitis (FAD) and lack of hygiene in dogs with a dense undercoat have been eliminated.

• *Recurring superficial pyoderma*

Atopy and less often food allergy is the most common underlying cause of recurrent superficial pyoderma. No specific breed or age group is predisposed. Generally, the lesions (papules, pustules, crusts, epidermal collarettes) are first observed in the regions of predilection: abdomen and inguinal region **(Figures 19 A & B)**. They can spread all over the body. The response to antibiotic therapy is always good, but recurrence will be rapid after the antibiotic therapy has been stopped.

Figure 19A *- Papular lesions of recurring superficial pyoderma in a German Shepherd.*

Figure 19B *- Papular lesions of superficial pyoderma in an atopic French Bulldog.*

The diagnosis is based on identifying the lesions and conducting a cytological test to find neutrophilic leukocytes with some evidence of cocci phagocytosis. The differential diagnosis is that of all recurring superficial pyoderma and comprises at least the exclusion of an ectoparasitic or another allergic dermatitis (FAD, atopic dermatitis). Once all the causes of recurrence have been ruled out **(Table 12)**, an elimination diet must be initiated.

TABLE 12 - MAIN CAUSES OF RECURRING PYODERMA

Anatomical faults - Folds, excessive humidity **Pre-existing dermatoses** - Ectoparasitoses, keratinization problems, allergic dermatitis - Endocrinopathies	**Iatrogen causes** - Glucorticoid therapy - Irritating topical therapy - Unadapted or too brief antibiotic therapy **Immunodeficiency**

> Diagnosis

The diagnosis of dietary hypersensitivity is based on the elimination of other causes of pruritus (especially infections and parasites) and the beginning of an elimination diet.

It is tempting to measure specific dietary allergen IgE dosages to identify a dietary allergy or to eliminate some foods from the diet. At this time, such an approach is totally unjustified. The few studies that have been published show that allergy tests lack reliability in this capacity *(Jeffers et al, 1991; Kunkle & Horner, 1992; Hillier, 1994; Ermel et al, 1997; Mueller & Tsohalis, 1998; Jackson & Hammerberg, 2002; Foster et al, 2003; Jackson et al, 2003; Wilhelm & Favrot, 2005)*.

This approach is justified only in the case of an immediate pure allergy, as in human medicine. In humans, the positive result of measurement of specific IgE for peanuts, eggs or cow's milk is an excellent predictor in a patient presented with anaphylactic reactions. For the evaluation of atopic dermatitis, the value of these tests is as poor as it is in canine medicine *(Sampson, 2004)*.

> Practicalities of elimination diets

The principle of an elimination diet is based on the administration of a diet containing proteins that the animal has never previously ingested. It is vital that an elimination diet be rigorously followed. The compliance with such a diet is its main limitation.

TABLE 13 - EXAMPLE OF INGREDIENTS THAT CAN BE USED AS PROTEIN AND CARBOHYDRATE SOURCES IN A HOMEMADE DIET

Proteins	Carbohydrates
Venison	Rice
White fish	Corn
Duck	Tapioca (manioc)
Chicken	Potatoes
Lamb	Sweet potatoes
Rabbit	Bananas

• *Monitoring of dietary habits*

An elimination diet must be prescribed only after a highly detailed investigation and with the clear consent of the owner. The diet preparation phase conditions the subsequent implementation.

It is not easy to keep a log of the food ingested by the dog, because the dietary sources are highly varied. The questionnaire during the consultation should focus on describing the food itself and identifying all the extras and potential hidden sources of food consumption. If necessary, the owner must be asked to keep a log of all the food consumed over a two-week period. The diet supplements and medication that may contain protein palatability factors (e.g. liver) must also be taken into account.

• *Choice of food*

Protein sources

The ideal is to use sources of proteins and carbohydrates that the dog has never previously ingested. That is why venison, duck, rabbit and white fish are the most often used ingre-

dients (tuna, which is high in histamine, should be avoided). Protein hydrolysates with a low molecular weight to ensure low immunogenicity and high digestibility can be used whatever the source. (The available hydrolysates are generally extracted from poultry or soy proteins.)

Homemade preparations

Homemade preparations must be based on a limited number of sources of protein and carbohydrate **(Table 13)**. The significance of homemade preparations is connected with the control of raw ingredients. Dogs that are used to preparations of this type often find them more palatable than dry commercial foods.

The use of homemade diets is limited by the practicability of such a preparation, especially for large dogs. They are increasingly rare for companion dogs because even for a period of one or two months the preparation of the homemade diet can prove very difficult.

The imbalance of these diets can be easily compensated if the diet has to be followed for more than two months or if the dog is a puppy. However, the supplementary constraints imposed on owners may become limiting factors in the good observance of the diet **(Tables 14-15)**.

Commercial foods

There are a great number of commercial foods labeled "hypoallergenic" or "for allergic dermatitis". Three categories can be distinguished.

- Foods with proteins that **mostly** come from selected sources: they cannot be considered acceptable for an elimination diet as the protein sources are highly diverse.
- Foods with proteins that **exclusively** come from selected sources: these are more acceptable. This is the only category that has been subjected to controlled studies and the results are sometimes disappointing *(Vroom, 1994; Leistra et al, 2001; Leistra & Willemse, 2002)*.

TABLE 14 - THEORETICAL PROS AND CONS OF COMMERCIAL AND HOME-MADE FOODS

Homemade diets	Commercial Foods
Pros	
Involvement of the owner	Practicality
No additives	Nutritional balance
Control of protein sources	
Great diversity of protein sources	Digestibility (hydrolysates)
Effectiveness	Low allergenicity (hydrolysates)
Palatability	Palatability
Cons	
Difficult preparation	No control over protein sources
Often too high a protein content	Possible presence of additives
Necessity of balancing the ration for a puppy	Great diversity of foods available

The use of protein hydrolysates raises many questions in both human and veterinary medicine. Only the studies of cohorts in human medicine come close to answering any of them.

- Is a highly hydrolyzed food more effective than a traditionally hydrolyzed food? This has not been shown in either veterinary or human medicine *(Osborne & Sinn, 2003)*.
- Is a hydrolysate more effective than a homemade diet for dogs? There are no studies that demonstrate an advantage for any one type of food.
- Is it worthwhile using a hydrolyzed food on a patient at risk after the appearance of symptoms? This has been shown only in infants when they cannot be breastfed *(Osborne & Sinn, 2003)*.

- Foods formulated on the basis of **protein hydrolysates** are in principle less allergenic than non-hydrolyzed preparations. The purpose of the hydrolysate is to fractionate the proteins into small peptides of low molecular weight. So in practice these hydrolysate-based diets are the most suited to a commercial elimination diet *(Biourge et al, 2004; Loeffler et al, 2004)*.

Hydrolysis reduces the molecular weight and intrinsic antigenicity of the food, and also renders it more digestible. These two properties act in synergy to offer less stimulation of the gastrointestinal immune system.

The major advantage of hypoallergenic commercial foods is their ease of use. This however, does not mean that the owner should neglect the constraints of such a diet. The prescription of a commercial diet goes hand in hand with a warning against the possibilities of food consumption over and above the base diet.

• *Concomitant treatments*

Antibacterial and systemic steroid therapy may be required when an elimination diet is initiated. The prescription of flavored medication must be avoided. If the medication must be administered by mouth with a food, any potential source of protein must be avoided, such as butter, cheese, ice cream, and meat. Honey is preferred.

The effectiveness of the diet is interpreted six weeks after the end of the course of medication.

• *Special cases*

Multi-pet households

If more than one animal lives in the household, access to the other animals' bowls must be avoided or all animals must be given the elimination diet.

TABLE 15 - EXAMPLES OF POSSIBLE FOOD INTAKE OVER AND ABOVE THE DOG'S REGULAR FOOD INTAKE

Possible food sources	Special occasions
Toys	Breakfast
Leather bone	Appetizers
Trash	End of meal
Toothpaste	TV snacks
Flavored medication	
Treats used in the administration of medication	
Vitamin or trace element supplements	
Food given by well-intentioned neighbors	
Other animal's food	
Leftovers	
Dog or cat feces (in the home or outside)	

Puppies
Balancing a homemade ration for a growing animal requires special consideration (see the examples for homemade rations at the end).

Aging dogs
In older dogs, the fairly short length of the elimination diet should not pose any problems in the case of a commercial food or a balanced homemade ration **(see the examples for homemade rations at the end)**. On the other hand, the use of standard foods may be problematical: for example, meat as lean as venison may lead to weight loss. It is also important not to abruptly change the dog's habits.

Difficult dogs
For difficult dogs, two or three days may be needed to obtain normal consumption of the food. While feeding should begin with a palatable supplement, after four weeks a supplement of a different nature must be selected and used for the following four weeks (e.g. beef gravy, then fish).

Associated diseases
In cases with an associated disease, it is preferable to use a hydrolysate-based commercial food and to closely monitor the concurrent disease (e.g. serum fructosamine concentrations after 15 days of the diet in a diabetic dog).

- ***Monitoring the diet***

Compliance with the diet can be difficult, and information and motivational visits are often necessary. Every member of the family must be informed of forbidden foods that could affect the interpretation of the trial (**Table 15**).

Regular appointments are needed to monitor compliance with the diet. This will allow the potential secondary effects of the elimination diet to be identified, which are refusal to eat or digestive problems. A two-day fast is tolerated. In the case of failure, a new diet must be initiated. To limit the appearance of digestive problems, a period of gradual dietary transition from the previous diet of at least four days is recommended.

Depending on the food, weight gain or weight loss may ensue. Owners must be informed so that they can monitor the dog's weight and body condition score and adjust the quantities given when necessary.

- ***Length of the diet***

There is consensus on the duration of 6-8 weeks to 10-12 weeks at most. Continuing the diet after this period will be useless if no improvement has been observed.

- ***Interpretation of the results***

The appreciation of clinical improvement is simple when it is spectacular, but more difficult when it is partial. Photographs and lesional scores **(simplified CADESI: Table16)** or pruritus scores **(Table 17)** may prove highly useful.

More is needed if the food is to be identified as the cause of the genesis of pruritic dermatitis than the observation of a significant improvement. A certain number of dogs do not have any recurrence when they ingest the initial food again. As a consequence, a provocative test must be conducted in order to correctly interpret the effects of an elimination diet.

If a puppy has to follow an elimination diet it is important to ensure that the diet is properly formulated for the special needs of growth.

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The most common digestive diseases: the role of nutrition

1 - Digestive tract physiology 99
2 - Oropharyngeal and esophageal diseases 102
3 - Acute gastrointestinal diseases 109
4 - Chronic diseases of the stomach 112
5 - Gastric dilatation-volvulus 116
6 - Chronic diseases of the intestinal tract causing diarrhea 117
7 - Specific large intestinal conditions causing diarrhea 128
8 - Chronic diseases of the intestinal tract causing constipation 130

Frequently asked questions: diet in case of digestive complaints 132
References 133
Royal Canin Nutritional Information 134

The most common digestive diseases: the role of nutrition

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Gastrointestinal problems are a major concern for small-animal practitioners. Specifically chronic disorders of the digestive tract can be difficult to manage because of the limitations of the diagnostic procedures and the multiplicity of possible causes. The current chapter summarizes the basic facts on gastrointestinal physiology of dogs including the intestinal microflora and the immune system. The most frequent digestive disorders are presented in a problem orientated manner including diagnostic aspects and medical and dietary treatment. The role of dietetics is considered specifically for each of the different types of disease considered.

1 - Digestive tract physiology

The small intestine (SI) is the principal site for digestion and absorption of nutrients, and is key to electrolyte and fluid absorption. The villi and microvilli contribute to the huge surface area, which facilitates absorption and assimilation of nutrients. Enterocytes are highly specialized cells involved in absorption processes. A brush border (or microvillus membrane; MVM) is present on the luminal surface of the enterocytes, and contains enzymes necessary for digestion of nutrients. Carrier proteins assist in the transport of amino acids, monosaccharides and electrolytes. The turnover of both enterocytes and microvillar proteins is influenced by luminal factors such as pancreatic enzymes, bile salts and bacteria.

► Digestion and absorption of food

> Proteins

Protein digestion is initiated in the stomach by the enzyme pepsin. It is inactivated once it has passed into the duodenum. Protein digestion in the small intestine is carried out by pancreatic and MVM enzymes. Peptides and free amino acids are produced by the digestive processes and small peptides and amino acids are absorbed by specific carriers in the MVM **(Figure 1)**.

FIGURE 1 - DIGESTION AND ABSORPTION OF PROTEINS

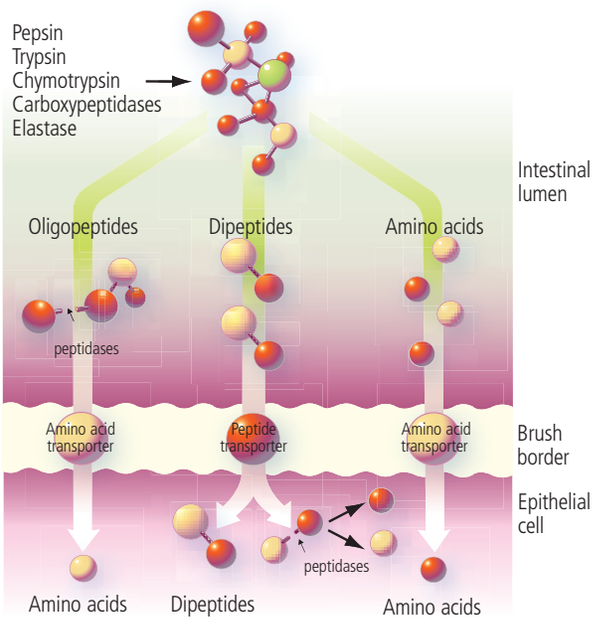
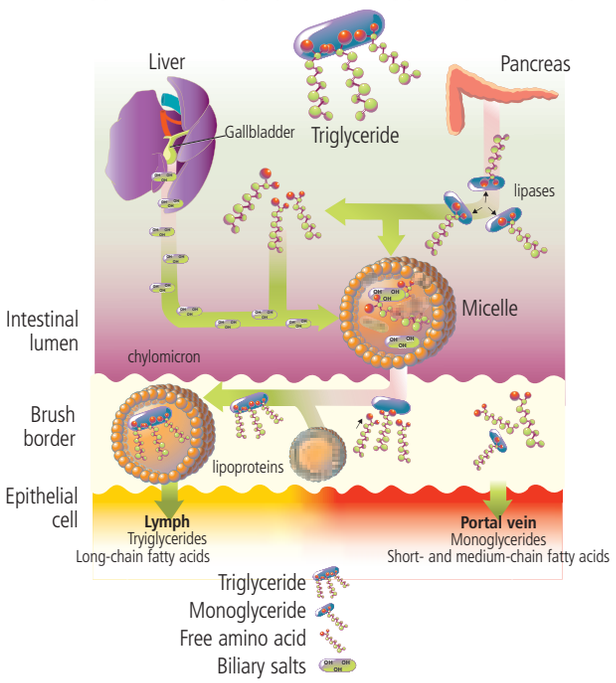


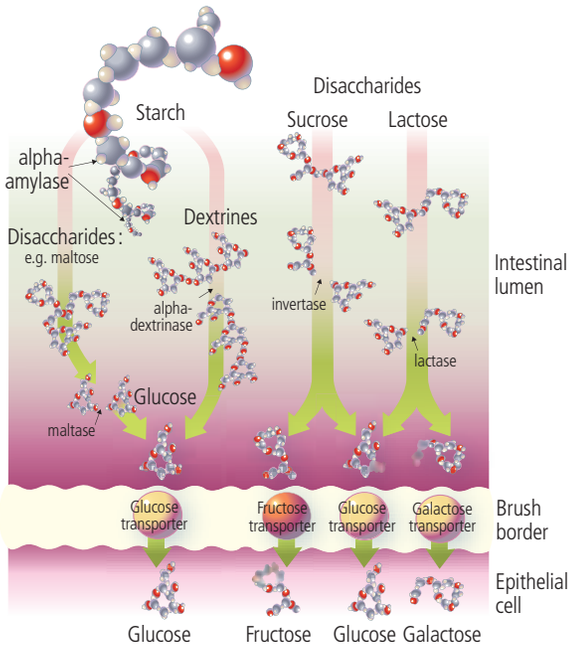
FIGURE 2 - DIGESTION AND ABSORPTION OF FATS



> Lipids

Dietary fats are emulsified by their interaction with bile acids in the small intestine, and subsequently digested by the pancreatic enzymes lipase, phospholipase and cholesterol esterase. Triglycerides are digested to monoglycerides and free fatty acids. In combination with bile acids, micelles are formed enabling absorption as monoglycerides and free fatty acids **(Figure 2)**. Bile acids are reabsorbed by a specific carrier mechanism in the ileum, and then recycled by the liver. After absorption, long-chain fatty acids are re-esterified to triglycerides, incorporated into chylomicrons and then enter the lymphatics. Medium and short chain fatty acids were originally thought to be absorbed directly into the portal circulation, but recent work has questioned this theory *(Sigalet et al, 1997)*.

Figure 3 - Digestion and absorption of carbohydrates



> Carbohydrates

Starch is the major digestible polysaccharide in common food and is degraded by pancreatic amylase to maltose. Maltose and other dietary disaccharides (lactose and sucrose) are digested by MVM enzymes to constituent monosaccharides, which are then absorbed by specific transporters or by facilitated transport. Monosaccharides are then transported across the basolateral membrane into the portal circulation **(Figure 3)**.

> Minerals

Macrominerals and trace elements are mainly absorbed from the small intestine, but the large intestine may also take part in the absorption processes. Active calcium absorption is subjected to regulatory mechanisms that are mediated by vitamin D, parathyroid hormone and calcitonin. These homeostatic mechanisms allow the organism to adapt to the different dietary intakes within certain limits. However, in dogs a fraction of dietary calcium is absorbed by passive processes. Phosphorus is less well studied and seems to be regulated by similar mechanisms. Magnesium is absorbed without homeostatic regulation so that the blood magnesium levels have a higher variation. Sodium, potassium and chloride are mainly absorbed in the small intestine and the absorption rates normally exceed 90 per cent. The trace elements are mainly absorbed from the small intestine, but the colon may also contribute to the absorption of trace elements. The absorption rates of zinc, iron and manganese are subjected to regulatory mechanisms. Active transport systems have been demonstrated for manganese and copper. Other elements are absorbed by passive diffusion.

> Vitamins

Lipid-soluble vitamins (A, D, E and K) are dissolved in mixed micelles, and passively absorbed across the MVM.

Water-soluble vitamins, most notably B vitamins, are absorbed by passive diffusion, facilitated transport or active transport. The absorptive mechanisms for folic acid and vitamin B12 are more complicated, and summarized in **Figure 4 and 5**.

► Intestinal microflora

The resident bacterial flora is an integral part of the healthy intestinal tract and influences development of microanatomy, aids in digestive processes, stimulates the development of the enteric immune system, and can protect against pathogen invasion. Healthy individuals are immunologically tolerant of this stable flora, and loss of tolerance may contribute to the pathogenesis of chronic enteropathies e.g. inflammatory bowel disease (IBD).

The populations of bacterial flora quantitatively increase from the duodenum to colon, and are regulated endogenously and by a number of factors, including intestinal motility, substrate availability, various bacteriostatic and bacteriocidic secretions (e.g. gastric acid, bile and pancreatic secretions). A functional ileocolic valve is the anatomical barrier between the colonic and small intestinal microflora. Abnormalities or dysfunction in any of these factors may lead to bacterial flora abnormalities, which may be quantitative or qualitative.

The normal SI flora is a diverse mixture of aerobic, anaerobic and facultative anaerobic bacteria. The total upper small intestinal bacterial counts reported in humans is less than 10^{3-5} CFU*/mL.

There is currently no consensus as to what constitutes a 'normal' SI population in healthy dogs; some studies suggest that healthy dogs can harbor up to 10^9 CFU/mL aerobic and anaerobic bacteria in the proximal SI. Therefore, the 'cut-off' for normal flora in dogs cannot be extrapolated from humans, and descriptions of small intestinal bacterial overgrowth (SIBO) in dogs using a cut-off value of 10^5 may be spurious. The intestinal microflora is subjected to endogenous and exogenous regulatory influences. Diet composition will impact the concentrations of bacteria in the gut. High protein diets favor the growth of proteolytic bacteria, especially clostridia, while certain fermentable fibers stimulate the saccharolytic bacteria, for instance bifidobacteria and lactobacilli.

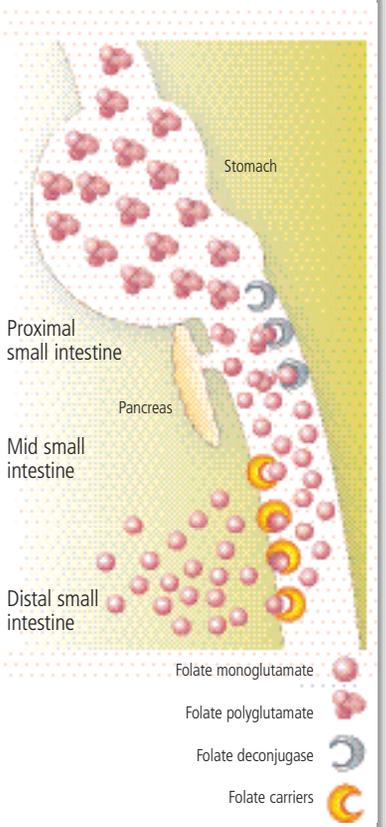
► Role of the mucosal immune system

The SI mucosa has a general barrier function, but must also generate a protective immune response against pathogens, whilst remaining 'tolerant' of harmless environmental antigens such as commensal bacteria and food. Yet despite recent advances in our understanding of the structure of and interactions in the immune system, it is still unclear as to how it decides to respond to or become tolerant of a particular antigen.

The gastrointestinal tract harbors the largest number of immune cells in the body. The gut-associated lymphoid tissue (GALT) consists of inductive and effector sites. Inductive sites comprise Peyer's patches, isolated lymphoid follicles, and the mesenteric lymph nodes, whilst effector sites comprise the intestinal lamina propria and epithelium.

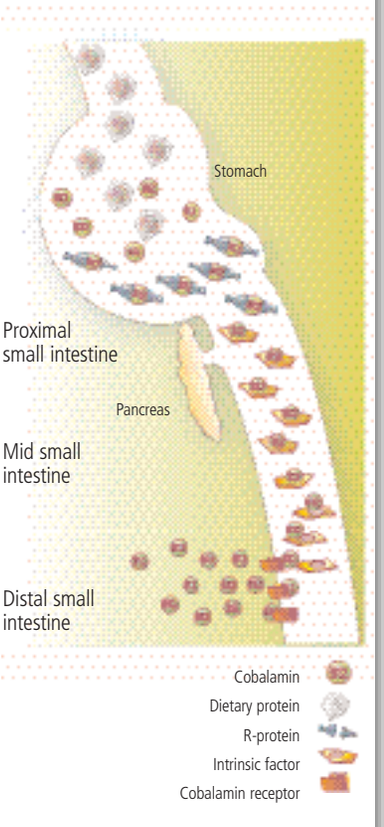
Such a distinction, however, is not absolute, and there is overlap between the functions of these different sites. The population of immune cells is diverse and includes T and B lymphocytes, plasma cells, dendritic cells, macrophages, eosinophils and mast cells. Protective immune responses are critical for guarding against pathogen invasion, and both cell-mediated (synthesis of cytotoxic cells) and humoral (immunoglobulin production) responses can be produced. However, of equal if not greater importance is maintenance of mucosal tolerance. This is not surprising, given that the majority of luminal antigens are derived from innocent dietary components or endogenous microflora. Generation of active immune responses to such ubiquitous molecules is both wasteful and potentially harmful, since it could lead to uncontrolled inflammation. Indeed, a break down in immunological tolerance to commensal bacteria is thought to be a critical step in the pathogenesis of inflammatory bowel disease.

FIGURE 4 - ASSIMILATION OF FOLATE



Dietary folate is present in the diet as a conjugated form (with glutamate residues). This conjugate is digested by folate deconjugase, an enzyme on the microvillar membrane, which removes all but one residue, before uptake via specific carriers situated in the mid-small intestine.

FIGURE 5 - ASSIMILATION OF COBALAMIN



Following ingestion, cobalamin is released from dietary protein in the stomach. It then binds to non-specific binding proteins (e.g. 'R-proteins'). In the small intestine cobalamin transfers onto intrinsic factor (IF), which is synthesized by the pancreas. Cobalamin-IF complexes pass along the intestine until the distal small intestine, where cobalamin is transported across the mucosa and into the portal circulation.

* *CFU: Colony Forming Unit*

Whilst the mechanisms by which mucosal tolerance actually occurs have been well characterized, the fundamental question of how the GALT decides when to and when not to become tolerant remains unresolved. Nevertheless, the critical cell in generating tolerance is the $CD4^+$ T-cell, either by down-regulatory cytokine synthesis (e.g. TGF-β, or IL-10) or via cell-cell interactions (e.g. through $CD25^+$, the IL-2 receptor). Interestingly, the cytokines that mediate tolerance (namely TGF-β, and IL-10) also facilitate IgA production, the most important mucosal immunoglobulin. Therefore, generation of mucosal tolerance could potentially occur in parallel to specific IgA responses. Interestingly, IgA 'coats' the mucosal surface and protects by immune exclusion (i.e. preventing antigens from crossing the mucosal barrier). Given that **immune exclusion** limits the amount of antigen to which the mucosal immune system is exposed, its effect is also 'tolerance-generating' because it minimizes immune responsiveness.

2 - Oropharyngeal and esophageal diseases

► Swallowing disorders and diseases of the esophagus

> Clinical signs associated with swallowing disorders

Dysphagia is defined as difficult or painful swallowing (odynophagia) and can result from conditions of the oral cavity, pharynx and esophagus. The complete swallowing sequence involves oropharyngeal, esophageal and gastro-esophageal phases. The oropharyngeal phase can be further subdivided into oral, pharyngeal and cricopharyngeal stages. Abnormalities of any of these stages can result in dysphagia. Disorders are usually functional or morphological; most functional disorders are the result of failure, spasm or incoordination of the normal neuromuscular activity. Regurgitation is almost effortless expulsion of food from either the oropharynx or esophagus. This should be differentiated from vomiting **(Table 1)**.

The main clinical signs associated with swallowing disorders are listed in **Table 2**.

TABLE 1 - DIFFERENTIATION OF REGURGITATION FROM VOMITING

Regurgitation	Vomiting
Passive event - No abdominal effort Not preceded by prodromal signs - But may drool saliva Can be associated with: - Undigested food covered by mucus/saliva - Neutral pH - Solids but not liquids if stricture or pointed foreign body - Fresh blood if ulcerated - Bolus in neck - Pain on swallowing Timing - Immediate or soon after swallowing - Delayed if dilated esophagus or diverticulum present	Reflex act with a coordinated reflex - Abdominal heaves - Retroperistalsis - Reflex closure of glottis Preceded by prodromal signs - Nausea - Unease - Anorexia - Hypersalivation - Swallowing - Retching Can be associated with: - Acid pH (<5) - Bile - Partially digested food - Digested or fresh blood Timing - Variable but rarely immediate

> Diagnosis of esophageal disease

For animals presenting with esophageal disease, a staged approach to diagnosis is usually required.

• *Signalment and history*

Breed, gender and age can all provide clues as to the likely diagnosis. In this regard, young dogs are more likely to suffer from congenital diseases. A thorough history is essential, in order to establish the pattern of clinical signs, in terms of duration, progression, frequency and severity. Further clues as to the underlying etiology may be evident e.g. ingestion of a foreign body.

TABLE 2 - SIGNS OF SWALLOWING DISORDERS

Primary Signs	Secondary Signs
Dysphagia Odynophagia Regurgitation Polypnea may be present	Malnutrition Dehydration Anorexia (pain, obstruction) or polyphagia (starvation) Regurgitation - reflux pharyngitis, rhinitis - nasal discharge Aspiration pneumonia - cough, dyspnea Tracheal compression - cough, dyspnea

• *Physical examination*

Physical examination is often normal although, if regurgitation is severe, body condition may be poor. Diseases of the oral cavity can often be directly visualized, but the pharynx and cricopharynx cannot be examined without sedation or general anesthesia. If the cervical esophagus is dilated, this can often be palpated or visualized.

• *Further diagnostic investigations*

History and physical examination confirms signs consistent with a swallowing disorder, and may give a clue as to the exact region involved **(Table 3)**. However, a definitive diagnosis can rarely be established at this stage and additional procedures are required.

TABLE 3 - DIFFERENTIATION OF OROPHARYNGEAL FROM ESOPHAGEAL DYSPHAGIA

Clinical Sign	Oropharynx	Esophagus
Dysphagia	Always present	Sometimes present (with esophagitis or obstruction)
Regurgitation	Present	Present
Hypersalivation	Usually present	Absent (except in case of foreign object), n.b. pseudoptyalism
Gagging	Often present	Usually absent
Ability to drink	Abnormal	Normal
Ability to form a solid bolus	Abnormal	Normal
Dropping of food from mouth	Yes	No
Time of food ejection	Immediate	Immediate in cranial obstruction
Character of food ejected	Undigested	Undigested
Odynophagia	Occasionally seen	Frequent, particularly with esophagitis due to foreign body
Number of swallowing attempts	Multiple	Single to multiple
Associated signs	Nasal discharge	Dyspnea, cough
Reluctance to eat	May be present	May be present

• ***Radiography (direct or indirect signs)***

Survey radiographs. Many swallowing disorders can be detected with plain radiography. A gas-filled esophagus can be seen with megaesophagus, sometimes evident as a tracheal stripe sign. Most foreign bodies (especially bone material) are also evident with plain radiography.

• ***Barium esophagram ± fluoroscopy***

In some cases contrast radiography is required, although this is unnecessary (and can even be dangerous e.g. inhalation of barium) if a diagnosis is evident on the plain radiograph. Barium mixed with food is preferable for esophageal studies; iodine-based contrast agents should be used if perforation is suspected. If available, fluoroscopic analysis is preferable because it provides dynamic information on oral cavity, pharyngeal and esophageal function. All swallowing phases can be examined and characterized.

• ***Endoscopy***

This is not essential for many esophageal diseases e.g. megaesophagus, but is the method of choice for most other conditions. This procedure is also essential for diagnosis of all organic causes (e.g. esophagitis – **Figure 6** –, gastro-esophagal reflux, stenosis, esophagal neoplasia). Flexible endoscopy is preferable to rigid endoscopy for viewing the esophagus. Endoscopy can also be therapeutic e.g. foreign body removal, esophageal stricture dilation, and placement of percutaneous esophagostomy tubes.

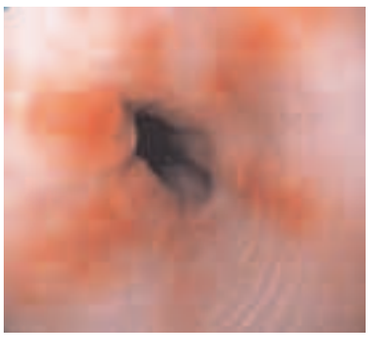


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Figure 6 - Esophagitis
Esophagial mucosa: secondary inflammatory aspect lesions in the presence of gastroesophageal reflux. Cardial incontinence is present.

► Specific swallowing disorders

The major swallowing disorders are listed in **Table 4**.

TABLE 4 - MAJOR DISEASES OF THE OROPHARYNX AND ESOPHAGUS

Oropharynx	Esophagus
Oropharyngeal neuromuscular dysphagia Cricopharyngeal achalasia Oropharyngeal neuromuscular granuloma Oropharyngeal trauma - Physical injury - Burns - Foreign bodies Oropharyngeal inflammation (various etiologies!) - Glossitis - Stomatitis - Pharyngitis	Megaesophagus Esophagitis Esophageal stricture Esophageal foreign body Vascular ring anomalies Hiatal hernia Gastro-esophageal intussusception Esophageal neoplasia Esophageal fistula Esophageal diverticulum Gastroesophageal reflux

> Oropharyngeal neuromuscular dysfunction

These can result in disruption of any of the oropharyngeal stages of swallowing (oral, pharyngeal or cricopharyngeal). Cricopharyngeal dysmotility can result either from failure of the cricopharynx to contract (chalasia) or relax (achalasia). The etiology of these disorders is poorly understood, but some cases are associated with neurological (brain stem disease, peripheral neuropathies), neuromuscular (myasthenia gravis, polymyositis) or metabolic (hypothyroidism) derangements. Cricopharyngeal achalasia is described in young dogs as a congenital failure.

Most of these disorders are treated medically. If a specific cause can be documented this should be treated. **Otherwise treatment is usually supportive e.g. nutritional support (via gastrostomy tube) or postural feeding.** If cricopharyngeal achalasia is present, this can be managed surgically e.g. by

cricopharyngeal myotomy. Given that in many cases, an underlying disorder is not found, the prognosis is usually guarded.

> Megaesophagus and esophageal dysmotility

Megaesophagus refers to esophageal global dilatation and dysfunction/paralysis, and has numerous possible causes **(Table 5)**. Pathogenesis is characterized by failure of progressive peristaltic waves. Esophageal dysmotility is the term used to describe defective esophageal motility without overt dilation of the esophagus (e.g. visible on radiography). The same diseases that cause megaesophagus are also responsible for esophageal dysmotility. Megaesophagus can be primary or secondary. The most important cause of acquired megaoesophagus is myasthenia gravis (MG). In focal MG, megaosophagus may be the only clinical sign.

The main clinical sign of megaesophagus is regurgitation (without pain), and a dilated cervical esophagus may be seen. Secondary signs (pyrexia, coughing, dyspnea, weight loss) may also be present and are usually due to nasal reflux, inhalation pneumonia, and malnutrition.

There is no effective medical or surgical therapy for idiopathic megaesophagus and all methods are supportive (see below). For secondary megaesophagus, treatment involves treating the underlying cause. Examples include using steroid replacement for hypoadrenocorticism, and using a combination of *anticholinesterases* (e.g. pyridostigmine) and *immunosuppressive medication* (glucocorticoids, azathioprine, mycophenolate or cyclosporin) to treat MG.

There is always a danger of aspiration and subsequent pneumonia and, therefore, prognosis is guarded. However, some idiopathic cases in young dogs recover spontaneously, whilst recovery of function occasionally occurs in secondary megaesophagus if the underlying cause is treated.

Table 5 - Major causes of Megaesophagus

Primary / Idiopathic	Secondary
Congenital e.g. - Great Dane, German Shepherd, Irish Setter (associated with pyloric stenosis) **Acquired**	**Focal or general myasthenia gravis** **Other neurological disorders** - Polymyositis - Polyneuropathies - Dysautonomia - Bilateral vagal nerve damage - Brain stem disease • Trauma • Neoplasia • Vascular disease • Botulism • Distemper • Dysautonomia • Tetanus - Systemic lupus erythematosus (SLE) **Toxicity** - Lead - Thallium - Anticholinesterase - Acrylamide **Various** - Mediastinitis - Hypoadrenocorticism - Pituitary dwarfism - Esophagitis - Hiatal hernia - Hypothyroidism (controversial)

> Esophagitis and esophageal ulceration

Esophagitis is defined as inflammation of the esophagus, and has a number of potential causes **(Table 6)**. Ulceration (and subsequent stricture formation) can develop if esophagitis is severe.

Table 6 - Major causes of esophagitis

Gastro-esophageal Reflux	Ingestion of Irritant Substances/Material
General anesthesia +++ Hiatal hernia Persistent vomiting: rare Natural reflux esophagitis (defective lower esophageal sphincter function) - Obesity - Upper airway obstruction (laryngeal paralysis)	Caustics Hot liquids Irritants Foreign bodies Drugs e.g. NSAIDs, antibacterials (doxycycline)

Clinical signs of esophagitis include chronic vomiting/regurgitation, hypersalivation and anorexia due to the pain associated with swallowing. Endoscopy is advisable and the stomach and the duodenum should be examined if chronic vomiting is present.

Treatment is symptomatic. In addition to nutritional support **(see below)**, attention must be given to providing adequate fluid therapy. Recommended drug therapy includes the use of broad-spectrum antibacterials, analgesics, mucosal protectants (sucralfate), gastric acid blockers (e.g. H_2 antagonists such as ranitidine, famotidine, or proton pump inhibitors such as omeprazole), and motility modifiers e.g. metoclopramide.

> Esophageal obstruction

Esophageal obstruction can be intraluminal, intramural or extramural, and can be partial or complete **(Table 7)**. If the obstruction is long-standing, the esophagus cranial to the obstruction can become dilated and hypomotile. Other complications of esophageal obstruction include esophagitis and esophageal rupture leading to mediastinitis (not often described in dogs).

TABLE 7 - MAJOR CAUSES OF ESOPHAGEAL OBSTRUCTION

Intraluminal	Mural	Extramural
Esophageal foreign body - Bones - Needles - Wood - Fish-hooks - Other	**Esophageal stricture** - Foreign body - Caustic material - Esophagitis - Gastric reflux - Drug therapy e.g. antibacterials, non-steroidals etc **Esophageal neoplasia** - Leiomyoma, leiomyosarcoma - Carcinoma - Fibrosarcoma - Osteosarcoma (associated with *Spirocerca lupi* infection) - Papilloma (rare)	**Thoracic neoplasia** - Thymoma - Lymphoma - Other **Enlarged bronchial lymph nodes** - Neoplastic - Infectious (e.g. granulomatous diseases) **Cardiac disease** - Congestive cardiac failure causing enlarged left atrium - Vascular ring anomalies **Persistent right aortic arch** **Double aortic arch** **Anomalous origin of the subclavian** **Anomalous origin of intercostal arteries** **Aberrant ductus arteriosis (PDA).** **Other thoracic and mediastinal diseases**

Esophageal strictures are the result of luminal narrowing caused by fibrosis. The fibrosis develops in the healing phase after esophageal ulceration, which is in turn caused by foreign bodies, ingestion of caustic material, esophageal burns (from ingestion of hot foodstuffs), diseases that cause esophagitis, gastric reflux (most common after general anaesthesia), and drug therapy (e.g. doxycycline). The diagnostic approach described above is applicable to esophageal strictures, with esophageal contrast studies and endoscopy most applicable.

Treatment involves widening dilation of the stricture, either by balloon dilation or bougienage. Nutritional support is often required during the period of therapeutic dilations **(see below)**.

Esophageal foreign bodies are relatively common in dogs and types include bones, needles, wood and fish-hooks. Foreign bodies occur most commonly in young animals, and Terrier breeds (e.g. West Highland White Terrier) are predisposed. Clinical signs are usually acute in onset and include dysphagia, regurgitation, ptyalism and anorexia (if the presence of the foreign body causes pain).

If obstruction is incomplete, ingestion of liquids but not solids is tolerated and there may be a delay before the animal is presented to the veterinarian. If perforation is present, mediastinitis can develop leading to signs of depression and pyrexia. A combination of plain radiography and esophagoscopy are suitable to make the diagnosis. Contrast studies are rarely required; barium may mask the foreign body and it should be avoided if perforation is suspected.

The majority of esophageal foreign bodies can be removed, perorally, under endoscopic guidance. On rare occasions, surgical esophagostomy is required to remove the foreign body, but this should be a last resort. Again nutritional support may be required during the convalescent phase (see below). If lesions are severe, a percutaneous gastrostomy tube (PEG) must be placed.

Vascular ring anomalies (VRA) are congenital malformations of the aortic arches, and constrict the esophagus at the level of the heart base. The esophagus cranial to the obstruction can then become dilated and aperistaltic. VRA are most common in Irish Setters and German Shepherds (e.g. same as for idiopathic megaesophagus).

Clinical signs include acute onset of regurgitation and poor weight gain, and are usually first noted at the timing of weaning (e.g. when solids are administered for the first time). Contrast radiographic studies are the best methods of diagnosis.

Surgical management is the treatment of choice, but success depends upon how longstanding the problem is. The more delayed the presentation, the greater the size of the associated esophageal dilatation and the less likely the signs are to resolve. Given that these animals are often poorly grown, nutritional support is required to improve condition prior to surgery **(see below)**. The prognosis is guarded; these patients are at poor surgical risk due to malnutrition and the potential for aspiration pneumonia. Further, the esophageal cranial dilatation may persist despite correction of the VRA.

> Hiatal hernia

A hiatal hernia is a herniation of part or all of the gastresophageal junction and stomach through the esophageal hiatus of the diaphragm into the thorax. The condition can sometimes be exacerbated by increased inspiratory effort due to upper airway obstruction (e.g. laryngeal paralysis). The most severe, but thankfully rare, form is the gastro-esophageal intussusception, which occurs in young dogs with a breed predisposition for Shar-pei dogs. Clinical signs include acute onset of vomiting, regurgitation and dyspnea, leading to shock and death. Paraesophageal hernia involves herniation of the stomach parallel to the esophagus. Sliding hiatal hernia often presents in an intermittent fashion.

Shar-pei puppies present a breed predisposition for gastro-esophageal intussusception.

© Bakeau

Fluoroscopy or endoscopy may be required to demonstrate the problem but, unless the hernia develops during visualization, it is often missed. Repeated evaluation may be required. This type of hernia may cause reflux esophagitis intermittent regurgitation and vomiting.

Many hernias can be successfully managed medically with modification of feeding behavior (small frequent meals, upright feeding) and drugs to treat associated reflux esophagitis. Surgical management is required for intussusception or persistent herniation.

Feeding from a height helps swallowing in esophageal disease.

> Esophageal neoplasia

Esophageal neoplasia is a rare cause of progressive regurgitation, often with blood. It has been reported to be associated with hypertrophic osteopathy (Marie's disease). The most common types of neoplasia in dogs include smooth muscle tumors, carcinoma, fibrosarcoma, and osteosarcoma (which is associated with *Spirocerca lupi* infection especially in South America, Africa or La Reunion Island). Esophageal neoplasia is invariably malignant, treatment options are limited and prognosis is grave (because the diagnosis is usually made too late).

> Esophageal diverticula

Esophageal diverticula are focal dilatations of the esophageal wall, and can either be congenital or can arise secondary to other esophageal diseases. Two types are described:

- **Pulsion diverticula**. These occur cranial to an esophageal lesion e.g. vascular ring anomalies.
- **Traction diverticula**. These develop as a result of inflammation and fibrosis within the esophagus, which distracts the esophagus causing a diverticulum.

Diverticula must be differentiated from esophageal redundancy e.g. kinking of the esophagus seen in young brachycephalic breeds and Shar-pei dogs. Diagnosis is made with radiography (+/- barium studies). Small diverticula rarely cause a problem, and conservative treatment is appropriate (e.g. soft diet fed from an upright position). Larger (multilobulated) diverticula are more problematic and may require surgery, although prognosis is poor.

NUTRITIONAL MANAGEMENT OF SWALLOWING DISORDERS

Feeding from a height. Food and water bowls can be placed in a high place. Small dogs can be fed 'over-the shoulder'. These patients can also be held vertical for a short while after feeding to encourage passage of food to stomach *(Guilford & Matz 2003)*. In patients that tolerate liquids poorly, fluid requirements can be fulfilled with ice cubes

Alter food consistency. The optimum type of food varies between cases. For some, liquidized high quality diets are best, for others, wet food or moisturized dry food is suitable. Diet viscosity should also be considered.

Diets may be applied either by syringe or as small solid boluses depending on the underlying disease or the preference of the patient or of the owner.

Ensure adequate nutrient intake. Patients with swallowing disorders need to be fed for shorter or longer times and depending on the duration of the disease the intake of fluid, energy and nutrients has to be balanced.

Ideally, the diet should deliver all required nutrients in a reasonable volume.
To maintain the energy balance of the patient, high fat diets are preferred because these diets provide high energy density so that the patients' energy requirements can be met in a smaller volume of food.

Assisted feeding e.g. gastrostomy tube - see Chapter 14. For many diseases (e.g. esophageal stricture and esophageal ulceration), a period of assisted feeding is required whilst the primary disease is treated. Short to medium term assisted feeding can sometimes be of benefit in patients with megaesophagus, since it enables improvements in body condition and gives the patient time to adjust to alterations in oral feeding *(Marks et al. 2000; Devitt et al. 2000; Sanderson et al. 2000)*.
Many owners readily accept to feed their dogs with feeding tubes.

Swallowing disorders and esophageal diseases are a significant problem for the affected individual, however, they occur less frequently in practice compared to the disorders of the gastrointestinal tract. Acute and chronic diseases of the stomach, the small and large intestine are of major practical significance and require thorough clinical workup of the patient to avoid misleading diagnosis and treatment.

3 - Acute gastrointestinal diseases

► Diagnosis

Acute gastroenteritis is a common reason for owners to seek veterinary advice; classification is shown in **Tables 8 and 9**. At the time of initial presentation, the veterinarian must quickly make a number of decisions about diagnosis and treatment **(Tables 10 and 11)**.

Table 8 - Classification of acute gastroenteritis on severity

Non-fatal, self-limiting acute gastroenteritis	Secondary to extraintestinal / systemic disease	Severe, potentially, life-threatening acute gastroenteritis
Uncomplicated parasitism **Dietary** - dietary indiscretion - dietary sensitivity - food poisoning - scavenging	**Systemic infections** - canine distemper - leptospirosis **Metabolic disorders** - uremia - hypoadrenocorticism	**Enteric infections** - enteroviruses - salmonellosis **Hemorrhagic gastroenteritis (HGE)** **Intestinal obstruction by foreign body** - intusssusception - volvulus

Table 9 - Classification of acute gastroenteritis on region affected

a) Acute gastritis	b) Acute enteritis	c) Acute colitis
• Predominant region affected is the stomach • Frequent vomiting • Often associated with acute diarrhea (i.e. acute gastroenteritis) • **Etiologies include:** - dietary indiscretions, garbage intoxication - ingestion of foreign material esp. in young, e.g. poisonous plants, hairballs (bezoars) - drug therapy e.g. corticosteroids, digoxin, erythromycin, chemotherapy - acute systemic disease (uremia, liver disease, sepsis)	• Predominant region affected is the small intestine • Profuse small intestinal diarrhea is the principle sign • Often associated with acute vomiting • **Etiologies include:** - dietary indiscretions, garbage intoxication - enteric infections e.g. bacterial, viral, protozoal, parasitic	• Predominant region affected is the large intestine • Frequent, small volume diarrhea predominates ± - tenesmus - mucoid feces - hematochezia • Fairly common in dogs • **Etiologies include:** - Dietary indiscretion e.g. garbage ingestion - Whipworm (*Trichuris vulpis*) infection - Protozoal infections e.g. *Giardia, Cryptosporidia* - Bacterial overgrowth

Table 11 - Database for emergency GI disease cases

Hematology	Biochemistry	Urinalysis	Additional (if available)
PCV Total Protein (refractometer) Blood smear examination	Urea Glucose Electrolytes	Urine sample - dipstick - specific gravity by refractometer	Blood gas analysis - acid-base - PCO_2, PaO_2*, HCO_3^-, etc. ** partial oxygen arterial pressure*

Table 10 Decision-making for acute gastroenteritis

Are the clinical signs non-specific, and will symptomatic treatment be sufficient?

• Most cases will fit this category

Are further investigations, hospitalization or treatment necessary?

• Diagnostic investigations are required:
- Potential underlying non-enteric cause of gastroenteritis
- Emergency database required for stabilization **(Table 11)**
- Abnormality in history requiring follow-up
- Physical examination finding requiring follow-up

• Intensive emergency treatment is required:
- Severe dehydration
- Electrolyte and/or acid/base disturbances
- Shock
- Severe blood loss or pale mucous membranes

• Surgical management is or may be required:
- Abnormality in history requiring follow-up
- Physical examination finding requiring follow-up

• An infectious cause is likely ± isolation is required

TABLE 12 - HISTORY AND PHYSICAL EXAMINATION FOR ACUTE CASES OF GI DISEASE

History. Relevant historical findings include:	Physical examination. Relevant findings on physical examination include:
• Age and vaccination status • Recent dietary history • Concurrent drug therapy • Possible exposure to toxins, plants, foreign bodies or infectious disease • Nature of signs e.g. - onset and severity - content of vomitus - stool characteristics -presence of blood (hematemesis, melena, hematochezia)	• General body condition • Hydration status (may also require PCV/TP) • Oral examination - mucous membranes etc. • Rectal examination • Abdominal palpation

Clinical signs usually include a combination of vomiting and diarrhea, the latter of which may have either small or large intestinal characteristics (depending on the region of the gastrointestinal tract affected). Other clinical signs include appetite changes, abdominal pain and tenesmus. For non-fulminating cases, history and physical examination are sufficient to allow an appropriate treatment to be formulated **(Table 12)**. Based on this preliminary information, the decision-making process can commence. In some cases further diagnostics will be required **(Table 13)**.

For cases that present as emergencies, with acute or peracute clinical signs diagnostic investigations should be performed in parallel to preliminary treatment to stabilize the condition of the patient. It is advisable to run an emergency database to allow decisions to be made about preliminary treatment (especially fluid therapy) **(Table 11)**.

TABLE 13 - DIAGNOSTIC INVESTIGATIONS FOR ACUTE CASES OF GI DISEASE

Hematology, serum biochemistry and urinalysis
Fecal examinations for parasites
Bacteriology. Bacterial culture is indicated if: - Febrile - Inflammatory leukogram / rectal cytology - GI bleeding - Young animal?
PCR for enteropathogenic *E. coli*?
Virology - *Fecal examination*, e.g. ELISA test for viral antigen (e.g. parvovirus) or electron microscopy (e.g. rotavirus, coronavirus) - *Serology*. Paired samples required to demonstrate recent infection.
Imaging - Plain radiographs are helpful to rule out gastrointestinal obstruction and other surgical diseases. - Abdominal ultrasonography is also useful for this purpose.
Response to empirical treatment Diagnosis can be confirmed by response to any of the following therapies: - Dietary restriction - Discontinuation of drugs - Avoidance of plants or other environmental agents - Anti-emetics - Anti-diarrheals - Parasiticides

► Treatment

If a primary cause can be identified this should be treated (e.g. antibacterials for infectious diarrhea). However, in most cases a cause is not obvious; nevertheless most will improve spontaneously in 2-3 days, suggesting that treatment is not always necessary. Prognosis for complete recovery is usually good. However, the animal should be reassessed if:
- Clinical signs persist for >48 hours, despite symptomatic treatment
- Clinical signs are deteriorating.

The mainstay of therapy is dietary management. Concurrent drug therapy is often prescribed empirically **(Table 14)**. Antimicrobials are often prescribed but have only occasional true indications **(Table 15)**.

Table 14 - Medical therapy for acute cases of GI disease

Anti-inflammatory medication (NOT recommended!)
- Glucocorticoids
- NSAIDs

Anti-emetic medication
- Metoclopramide
- Antihistamines e.g. chlorpromazine.
- Ondansetron (last recourse)
- Anticholinergics (not recommended)
  - Atropine
  - Methylscopolamine

Gastric mucosal protectants and antacids (only if persistent vomiting or GI ulceration is present)
- H_2-receptor antagonists
- Ranitidine
- Famotidine
- Nizatidine
- Sucralfate
- Antacids (not useful and not recommended)
- Aluminum hydroxide
- Magnesium hydroxide

Anti-diarrheals
- Absorbents / protectants
  - Kaolin-pectin
  - Montmorillonite
  - Aluminum hydroxide
  - Bismuth
  - Activated charcoal
  - Magnesium trisilicate

Motility modifiers
Opioids
Diphenoxylate
Loperamide
Kaolin-morphine

Anticholinergics
(not recommended for most cases)
- Atropine
- Hyoscine

Antispasmodics
(not recommended for most cases)
- Buscopan

Antibiotics
(not recommended for most cases)
(Table 15)

Table 15 - Indications for antimicrobial therapy in acute conditions

Specific bacterial infection documented (Note: NOT *Salmonella**)

Severe mucosal damage

GI ulceration/hemorrhage
- Hematemesis
- Melena
- Hematochezia

Pyrexia

Leukopenia or neutropenia.

* *Antibiotic treatment is not prescribed if* Salmonella *is isolated in a healthy dog. Such treatment risks the development of antibiotic resistance and/or chronic bacterial shedding.*

Dietary management of acute gastrointestinal diseases

The mainstay of therapy for acute gastrointestinal disease is dietary management. Two major approaches exist:

1."Resting the gut" i.e. restricted oral intake

If the patient is vomiting water, is dehydrated, or there is evidence of an electrolyte/acid-base disturbance, the patient should be maintained nil per os (NPO) and parenteral fluids should be administered *(Marks et al 2000; Devitt, et al 2000; Sanderson et al 2000)*. Suitable choices would include Hartmann's or 0.9% saline (both ± 10 mM/L KCl).

If the patient is not vomiting, oral glucose-electrolyte rehydration solutions can be administered. However, parenteral fluids should be administered if evidence of dehydration exists (>5%) or if the patient is exhausted or refuses to drink.

In both cases the animal should be fasted, i.e. food should be withheld for at least 24 hours. The patient should then be given frequent small, bland, low-fat meals for 24-72 hours. Examples would include boiled 1 part rice or pasta with 1 part boiled lean meat (chicken or turkey), eggs or low-fat cottage cheese.

Milk and milk products should be limited due to their high lactose concentration.
An alternative would be to use a proprietary food with low-fat concentration and a high digestibility.

The fiber content of diets for patients with acute intestinal problems should be limited to ensure high digestibility. Due to the expected losses of electrolytes the dietary levels of potassium, sodium and chloride should be increased. Assuming clinical signs resolve, the normal diet can be reintroduced gradually over 3-5 days.

2. "Feeding through diarrhea"

An alternative approach is to continue to feed the animal despite the clinical signs. Such an approach has been adopted for diarrhea in human infants, and may speed recovery. Further, there is preliminary evidence in dogs with parvovirus that such an approach may reduce morbidity *(Mohr et al, 2003)*. However, it is less practicable if vomiting is persistent or if diarrhea is profuse.

A certain risk may exist because the gastrointestinal tract is likely to have altered permeability that allows easier passage of dietary antigens. Therefore, the patient may be at risk of developing a hypersensitivity to the dietary proteins used in the enteral diet. It is often recommended to use a protein source that is not part of the normal diet (sacrificial protein).

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Enteral nutrition was associated with a shorter time to recovery, increased body weight gain, and improved gut barrier function in puppies with parvo-viral enteritis, compared to nil per os (Mohr et al, 2003).

4 - Chronic diseases of the stomach

Chronic diseases of the stomach result in a number of clinical signs **(Table 16)**, the most important of which is vomiting. Causes of vomiting include gastrointestinal and extra-gastrointestinal diseases **(Table 17)**. There are two main mechanisms that cause gastric vomiting: gastric outflow obstruction, gastroparesis and disruption of the mucosal barrier **(Table 18)**. Hematemesis is defined as vomiting blood. It usually results from the presence of gastric or gastro-duodenal ulceration. Blood can be fresh or partially digested blood ("coffee grounds").

► Diagnosis of gastric disease

The approach to the chronically vomiting patient depends upon the exact nature of the clinical signs. It is important to distinguish vomiting from regurgitation at an early stage **(Table 1)**, if possible by examining the act of vomition and/or the vomitus. Secondary causes of vomiting (metabolic, toxic) should then be eliminated with laboratory analyses (hematology, serum biochemistry, urinalysis) and diagnostic imaging. Contrast radiography is occasionally useful although most abnormalities can be seen on a survey radiograph. Gastroscopy (or exploratory laparotomy) and biopsy is necessary in most cases of gastric disease. This allows inspection of the gastric mucosa, biopsy procurement (which should be performed even if grossly normal as it is on **Figure 7**), and foreign body removal (where applicable).

Table 17- Causes of Vomiting

Primary gastric disease
- Chronic gastritis
- Gastric ulcers
- Gastric retention disorders
- Gastric neoplasia

Part of diffuse GI disease
- Inflammatory bowel disease
- Diffuse alimentary lymphoma

Secondary to intestinal disease (diarrhea usually predominates)
- Inflammatory bowel disease
- Intestinal neoplasia
- Small intestinal obstruction
- Peritonitis

Secondary to systemic disease
- Infectious diseases e.g. distemper, infectious canine hepatitis, leptospirosis
- Renal failure
- Hepatic disease
- Pancreatic disease e.g. pancreatitis, pancreatic neoplasia
- Other abdominal disease
  - Urogenital e.g. pyometra
  - Peritoneum e.g. peritonitis
  - Direct stimulation of emetic center
- CNS disease
- Stimulation of chemoreceptor trigger zone
  - drugs e.g. digoxin, erythromycin, morphine, cytotoxics
  - toxins
  - septicemia
- Stimulation of vestibular centre
  - motion sickness
  - vestibulitis
- Secondary to metabolic / endocrine disease
  - hypoadrenocorticism
  - ketoacidotic diabetes mellitus
  - thyroid disease
  - others!

Table 16 - Signs of gastric disease

Vomiting
Nausea
Anorexia
Weight loss
Belching
Bloating
Polydipsia
Hematemesis
Melena

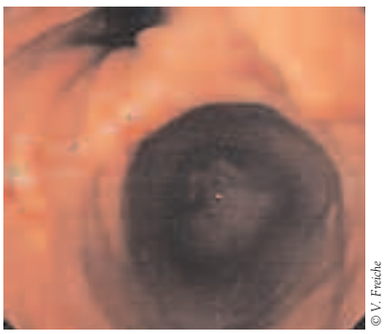

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Figure 7 - *Endoscopic image of the normal gastric mucosa in retrovision.*

Table 18 - Pathogenesis of vomiting caused by primary gastric disease

Gastric outflow obstruction	Disruption of mucosal barrier (gastritis, erosions, ulcers)
• Mechanical - fibrosis preventing receptive relaxation - chronic gastritis - schirrus adenocarcinoma ('leather bottle stomach') - foreign body - pyloric stenosis • Functional (gastroparesis) - hypokalemia - pylorospasm	Barrier disruption leads to back-diffusion of HCl. This in turn causes histamine release, then increased capillary permeability leading to hemorrhage, pain etc. • Ischemia - disturbance of mucosal microcirculation - acute energy deprivation of mucosal cells • NSAIDs • Corticosteroids • Neoplastic infiltration • Uremia • Bile acids • Spiral bacteria (unconfirmed hypothesis) • Hyperacidity caused by hypergastrinemia - gastrin-secreting tumor - chronic kidney disease

► Specific causes of chronic gastritis (± chronic enterocolitis)

The etiology of chronic gastritis is usually unknown, but possible causes include:
- Immune mediated
- Part of generalized inflammatory bowel disease
- Secondary to other metabolic diseases (chronic renal insufficiency, hepatic diseases, pancreatitis)
- Gastric spiral bacteria (*Helicobacter*) (controversial)

Laboratory changes are uncommon and/or often non-specific. Gastroscopy and biopsy is required for definitive diagnosis.

Treatment modalities include:
1. **Dietary management**
2. **Removal of the etiological agent** if known
3. **Corticosteroids** for some cases, especially if this forms part of a more generalized IBD, and only after biopsy samples have been analyzed.
4. **H_2 antagonists** and/or **proton pump inhibitors**
5. **Motility modifiers** e.g. metoclopramide, ranitidine and erythromycin.
6. **'Triple therapy' for spiral bacteria.**

> Anatomical outflow obstruction

Gastric outflow obstruction can have a number of causes including pyloric disease, foreign body and neoplasia. Pyloric stenosis can be congenital (e.g. brachycephalic breeds) or acquired. Surgical treatment is necessary e.g. pyloroplasty or pyloromyotomy. Pylorospasm is a functional rather than structural disorder. The cause is likely related to a gastric motility disorder. Foreign bodies (e.g. balls, peach stones, horse chestnuts, wine corks) can cause intermittent obstruction in a 'ballcock' manner. Other common pyloric diseases include polyp and chronic hypertrophic pyloric gastropathy (CHPG; reported in toy breeds).

> Delayed gastric emptying

This is defined as vomiting following retention of food within the stomach for more than eight hours. Clinical signs include chronic vomiting, which is usually delayed, whilst gastric distension may also be seen. Diagnosis can be inferred from clinical signs, but is confirmed with contrast radiography. Gastroduodenoscopy is also indicated to rule out other causes or define an underlying cause; exploratory laparotomy, may also be diagnostic and may or may not be necessary for treatment.

The underlying etiology may be a primary motility disorder, e.g. dysynergy between antral and pyloric motility, or secondary e.g. delayed motility resulting from inflammatory disease in the GI tract. Motility modifiers (e.g. metoclopramide, cisapride, ranitidine and erythromycin) can be used to increase the speed of gastric emptying. Surgery can be used as last resort (e.g. pyloromyotomy), and may benefit some cases. **Dietary management may also be helpful as adjunctive therapy e.g. low-fat, low-fiber easily digestible food, fed in small frequent meals.**

> Gastric ulceration

The causes of gastric ulceration are presented in **Table 19**. Clinical signs include hematemesis, melena, anemia, weight loss, pain (may demonstrate 'praying posture') **(Figure 8)**, and signs of peritonitis (if the ulcer perforates). Treatment for gastric ulceration involves correc-

DIETARY MANAGEMENT OF CHRONIC GASTRITIS

Patients with chronic gastritis should be fed multiple small feeds. Wet food should be warmed to body temperature. Dilution with water is often necessary and helps to reduce osmolality. Liquid low osmotic diets facilitate gastric emptying.

Diets must be highly digestible, reduced in fat (lower by at least 10% fat DMB, then increased depending on the individuals' tolerance), and should have a low fiber content (<3% crude fiber DMB or 6% total dietary fiber DMB). All of these factors help to increase the rate of gastric emptying.

ting the underlying cause if identified. Medical management involves the use of acid blocking agents (H_2-receptor antagonists, proton pump inhibitors), gastric mucosal protectants (sucralfate), and synthetic prostaglandin analogues (misoprostol). **Dietary management is designed to facilitate emptying from the stomach and minimize retention of contents within the gastric lumen. The dietary content should be optimal to assist the healing processes.**

> Gastric neoplasia

Primary neoplasia occurs infrequently in companion animals, and usually occurs in dogs more than cats. Furthermore older male dogs are often predisposed. Adenocarcinoma (75%), lymphoma, lymphosarcoma, leiomyoma and polyps are the most common gastric tumors in dogs. Response to treatment (e.g. chemotherapy) is usually poor, and most will have metastasized by the time of diagnosis. Prognosis is poor.

TABLE 19 - CAUSES OF GASTRIC ULCERATION

Drugs • NSAIDs • Corticosteroids* • Cytotoxics
Cranial and spinal injuries • Usually in combination with corticosteroid use • Can also cause colonic ulcers/perforation
Metabolic • Liver disease - Portal hypertension - Coagulation disorder • Uremia • Hypoadrenocorticism
Severe gastritis
Sharp/abrasive gastric foreign bodies
Mast cell tumor • Histamine release, gastric hypersecretion and then ulceration
Gastric spiral bacteria
Gastrinoma

* *On their own, corticosteroids are not typically ulcerogenic - even high (immunosuppressive) doses rarely cause any problems. However, steroids can exacerbate ulceration in a number of circumstances:*
- *If used in conjunction with NSAIDs*
- *If high doses are given to patients with spinal disease (mechanism unknown)*
- *In the presence of 'mucosal hypoxia' e.g. secondary to severe anemia.*
- *Another reason for a mucosa prone to injury e.g. primary hemostatic disorder such as immune-mediated thrombocytopenia.*
- *A concurrent disease which also increases the risk of GI ulceration e.g. mast cell tumor, gastrinoma, hypoadrenocorticism, liver disease, renal disease, hypovolemia/shock etc.*

> Bilious Vomiting Syndrome

The pathogenesis of this condition is poorly understood. It is thought to result from a combination of reflux of bile into the stomach and impaired gastric motility resulting in prolonged exposure of the gastric mucosa to bile. This causes a local gastritis and vomiting, usually in the early morning e.g. after a prolonged period without food.

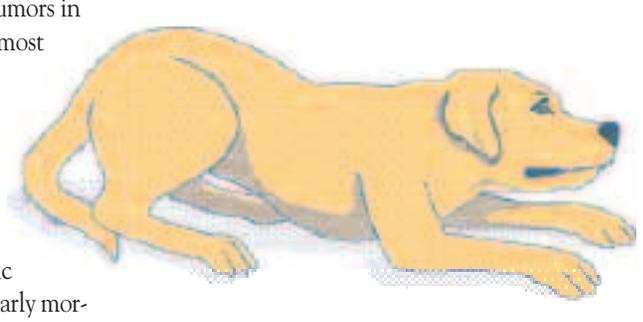

Figure 8 - *"Praying posture".*

Most diagnostic investigations are unremarkable. **Treatment involves altering the pattern of feeding e.g. increasing the frequency of feeding to 2-3 times daily, with one of these meals administered last thing at night.** Prokinetic drugs (metoclopramide, ranitidine) can also be of benefit in some cases.

5 - Gastric dilatation-volvulus

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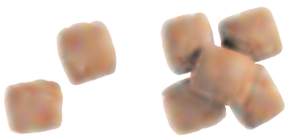
Feeding from a height is a risk factor for gastric dilatation and volvulus in high-risk dogs (Glickman et al, 2000).

Gastric dilatation-volvulus (GDV) is a sudden, dramatic and often fatal disorder. Overall mortality of up to 30% has been reported in some studies. Older dogs are most commonly affected, although GDV can potentially affect dogs of any age. The most important risk factor is body conformation and, in this regard, a narrow deep chest is associated with increased risk *(Glickman et al, 1994)*. Although many studies have incriminated diet (e.g. ingestion of dry, cereal based foodstuffs), no clear association has been proven. Other potential incriminating factors include single large meals, overeating, small kibble size, elevated feeding bowls, post-prandial exercise, anesthesia, aerophagia, and previous gastric 'injury'.

Gastric dilatation is the rapid distension of the stomach with food, fluid or air, and can rapidly progress to volvulus (e.g. rotation of the stomach along its long-axis). Rapid gastric dilation affects lower esophageal function, and impairs gastric motility and emptying. The gastric mucosa can later undergo ischaemic necrosis. Accumulation of gastric secretions and occlusion of venous return from the caudal body can lead to hypovolemic and cardiogenic shock. Splenic torsion with infarction is another common sequel.



Large kibbles (30 mm x 30 mm x 20 mm) help prevent aerophagia. Aerophagia increases the risk of gastric dilatation and volvulus (Theyse et al, 2000).

Most animals present with a history of progressive (often rapid) abdominal distension, non-productive retching/vomiting, and hypersalivation. On physical examination gastric tympany is usually obvious, but absence of clear symptoms does not exclude the possibility of a dilatation/volvulus of the stomach. Treatment involves emergency stabilization with aggressive intravenous fluid therapy, and gastric decompression (ideally by gastric intubation). If appropriate, corrective surgery (e.g. gastropexy) should be performed once the animal is stable (ideally within the first 3-6 hours). Other adjunctive treatments (many post-operatively) include antibacterials, H2 antagonists, sucralfate, intravenous fluid therapy, gastric intubation, lavage and decompression, and anti-arrhythmics (if appropriate).

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Gastric dilatation and volvulus particularly affects large breeds with a deep chest (St Bernards, Great Danes, Weimaraners, Gordon Setters, Irish Setters and Standard Poodles).

Dietary management of GDV

The dietary risk factors for the development of gastric dilatation and volvulus are not clear. In addition, there are no studies available on the dietary effects that would help to prevent gastric dilatation in predisposed dogs. Data available from clinical cases demonstrate increased microbial fermentation in the stomach of affected dogs with the accumulation of bacterial fermentation products (gas, lactic acid, volatile fatty acids) *(Van Kruiningen et al. 1974; Rogolsky et al, 1978)*. Gas composition in clinical patients was similar to atmospheric air, indicating that aerophagia could be a significant factor in the pathogenesis of the disease *(Caywood et al, 1977)*.

The stomach content of dogs is physiologically colonized with a large number and variety of microorganisms *(Benno et al, 1992a-1992b)*. Imbalance in the bacterial flora e.g. increased numbers of clostridia have been considered as one potential factor in the etiology of the disease. However, in one study comparing diseased and healthy dogs the authors were unable to demonstrate differences in the clostridial colonization of the stomach of these dogs *(Warner et al, 1978)*.

Although the pathogenesis is not yet understood, it is justified to recommend certain dietary measures.

- Dogs at risk should be fed three small meals and not one single meal a day *(Raghavan et al, 2004)*.
- Owners should be advised not to use elevated feeding bowels as this appears to be a risk factor for GDV.
- Food and feeding hygiene should not be ignored. Food bowls should be regularly cleaned and food should not be stored for excessive periods, especially when it is mixed with water.
- Owners of affected dogs should be advised to feed the dogs as regularly as possible because this consistency conditions the secretory and digestive functions of the gastrointestinal tract
- Stress should be avoided after food intake, because it can have negative effects on gastric secretion (avoid exercise post-feeding)
- Diets for dogs at risk of developing gastric dilatation and volvulus should not contain elevated mineral levels. Minerals have a high buffering capacity and may maintain the gastric pH at higher levels which allows the microorganisms to be more active compared to an acidic environment
- Fat and especially unsaturated fatty acids have a capacity to reduce microbial fermentation. Although not experimentally proven it seems to be advisable to feed patients at risk of GDV with diets containing higher fat levels *(Meyer & Zentek, 2001)*.

6 - Chronic diseases of the intestinal tract causing diarrhea

Diseases that affect the intestinal tract can cause a range of clinical signs **(Table 20)**. Diarrhea is the most common clinical signs and is defined as an increase in fecal water content with an accompanying increase in the frequency, fluidity or volume of feces.

Diarrhea may be due to SI, large intestinal (LI) or diffuse disease. Chronic diarrhea is rarely self-limiting and, in order to administer rational therapy, a definitive diagnosis is required. Diarrhea may be the result of a number of pathogenetic mechanisms **(Table 21)**.

TABLE 20 - CLINICAL SIGNS OF INTESTINAL DISEASE

Signs of Small Intestinal disease	Signs of Malabsorption	Signs of Large Intestinal Disease
• Diarrhea • Abdominal discomfort • Weight loss / failure to thrive • Borborygmi • Vomiting • Flatus • Dehydration • Altered appetite: inappetence, pica, coprophagia, polyphagia • Melena • Hypoproteinemia • Ascites • Edema	• Diarrhea • Weight loss • Polyphagia ± coprophagia, pica • Protein-losing enteropathy (PLE)	• Constipation or • 'Large intestinal' Diarrhea: small volume, mucoid, occasionally hematochezia • Increased frequency of defecation • Tenesmus • Dyschezia • Vomiting • Weight loss

TABLE 21 - PATHOGENETIC MECHANISMS OF DIARRHEA

• **Lack of pancreatic enzymes** e.g. exocrine pancreatic insufficiency
• **Impaired micelle formation** which could be the result of: - Decreased bile salt formation as a result of severe parenchymal liver disease - Decreased bile salt delivery as a result of cholestatic liver disease or bile duct obstruction - Increased intestinal bile salt loss e.g. as a result of ileal disease (or SIBO – **see below**)
• **Small intestinal bacterial overgrowth** which then causes: - Fatty acid hydroxylation leading to hydroxy-fatty acid formation which then stimulates colonic secretion. - Bile salt deconjugation which causes fat malabsorption and colonic secretion
• **Villus atrophy** which causes diarrhea because: - A decreased surface area is available for absorption - Immature enterocytes are present which have lower expression of brush border enzymes and carriers
• **Inflammatory infiltration** (NB also neoplastic or amyloid). This leads to: - Obstruction of nutrient uptake - Interference with enterocyte function - Impaired lymphatic flow
• **Impaired lymphatic drainage** e.g. lymphangiectasia
• **Abnormal motility** (which is often secondary to another process e.g. inflammatory disease). This then causes hypermotility or hypomotility and lack of segmentation.

► Diagnosis of chronic intestinal diseases

A staged approach to diagnosis is usually recommended **(Table 22)**.
- First, the diarrhea is defined as either small or large intestinal **(Table 23)**
- Intestinal parasitism is excluded (with fecal analyses)
- Empirical therapies are often used.

When a definitive cause has not been established, or cases do not respond, further diagnostics are justified **(Table 22)** including laboratory analyses (hematology, serum biochemistry, multiple fecal samples), diagnostic imaging and ultimately biopsy procurement.

TABLE 22 - APPROACH TO CHRONIC DIARRHEA

Stage 1	Stage 2
• Exclusion of dietary problems (e.g. by dietary modification) • Localization to SI or LI (or both) using history and physical exam (especially abdominal and rectal digital palpation) • Fecal exam and rectal cytology • Attempt response to therapy e.g. anti-parasiticides to eliminate the possibility of: **Roundworms, whipworms and hookworms which can be treated with:** - Fenbendazole - Febantel - Nitroscanate **Giardia** - Fenbendazole (50 mg/kg q 24 h for 3 days) - [Albendazole, but toxicity] - Febantel - requires 3-5 days of treatment. - Metronidazole (25 mg/kg q 12 h for 5 days) Many cases are resolved in this stage, and don't need in-depth workup.	• Initially preliminary laboratory tests should be performed e.g. hematology, serum biochemistry and urinalysis. These rarely give a definitive diagnosis, but rule out the presence of systemic disease. • A definitive etiological/histopathological diagnosis is usually made via an extended database of: **- Digestion and absorption tests** **- Diagnostic imaging** (which often guides which method of biopsy is chosen) - Plain and contrast radiography - Ultrasound - **Biopsy**, either: - Exploratory laparotomy [always take biopsies, even if grossly normal] - Gastroduodenoscopy (depends on the expertise of the operator) by flexible endoscopy (e.g. fiber-optic or video). Both the stomach and duodenum should be examined - Colonoscopy by flexible endoscopy to allow the examination of the ileo-coecal valvula. This requires prior preparation with prepare with warm water enemas or oral cleanser. It is important to rule out EPI prior to more detailed investigations.

Table 23 - Differentiation of SI diarrhea from LI diarrhea

	Clinical signs	Small intestinal diarrhea	Large intestinal diarrhea
Feces	Volume	Markedly increased	Normal or decreased
	Mucus	Rarely present	Common
	Melena	May be present	Absent
	Hematochezia	Absent except in acute hemorrhagic diarrhea	Fairly common
	Steatorrhea	Present with malabsorption	Absent
	Undigested food	May be present	Absent
	Color	Color variations occur e.g. creamy brown, green, orange, clay	Color variations rare; may be hemorrhagic
Defecation	Urgency	Absent except in acute or very severe disease	Usually but not invariably present
	Tenesmus	Absent	Frequent but not invariably present
	Frequency	2 to 3 times normal for the patient	Usually greater than 3 times normal
	Dyschezia	Absent	Present with distal colonic or rectal disease
Ancillary signs	Weight loss	May occur in malabsorption	Rare except in severe colitis and diffuse tumors
	Vomiting	May be present in inflammatory diseases	Uncommon? Probably occurs in ~30% of dogs with colitis
	Flatulence and borborygmi	May occur	Absent
	Halitosis in the absence of oral cavity disease	May be present with malabsorption	Absent unless perianal licking

► Specific small intestinal conditions

> Small Intestinal Bacterial Overgrowth (SIBO) and Antibiotic-Responsive Diarrhea (ARD)

SIBO is defined as an increased number of bacteria in the upper small intestine, and is the cause of much recent controversy. SIBO is well documented in humans and almost invariably develops secondary to an underlying cause.

Therefore, it should be viewed more as a sign than a specific diagnosis. Recently, the term secondary SIBO has been used for cases which arise as a result of an underlying disorder e.g. partial obstruction, EPI, motility disorder, reduced gastric acid production (gastric surgery, gastric achlorhydria or drug therapy with antacids), and possibly, IBD. The previously described 'idiopathic SIBO' is now more commonly referred to as 'antibiotic-responsive diarrhea ', given the uncertainty as to the underlying pathogenesis. This occurs in young dogs (especially German Shepherds) with a predominance of small intestinal diarrhea and weight loss/stunting. The clinical signs are antibiotic responsive.

© Hermeline

German Shepherds show a breed predisposition for idiopathic antibiotic-responsive diarrhea.

Diagnosis for secondary SIBO involves identifying the underlying cause; none of the currently available tests are ideal for the diagnosis of idiopathic ARD, and diagnosis is based upon exclusion of all other causes and response to antibacterial therapy. Secondary SIBO is best controlled by treating the underlying cause (if possible), though antibacterials may be required if response is suboptimal. Long courses (and some times lifelong) antibacterials is the mainstay of treatment for ARD. Other medical therapies include parenteral cobalamin supplementation, if cobalamin deficiency is identified.

• *Dietary management of SIBO/ARD*

In light of the unknown etiology of the disease, dietary treatment should be considered adjunctive rather than definitive therapy. The diet should have a high digestibility, so that can be effectively absorbed and utilized by the dog. High digestibility supports the patient by providing available nutrients, and reduces the potential load of antigenic material. By providing highly digestible diets, the flux of nutrients into the colon is reduced. These nutrients would be utilized by the colonic microflora with negative effects as gas formation, flatulence and diarrhea. In cases where dietary sensitivity or allergy cannot be excluded, an antigen-limited hypoallergenic diet is recommended. The diet can either contain a highly digestible protein source (e.g. chicken, fish, and wheat gluten) or any other highly digestible meats not normally used in commercial diets (e.g.rabbit, venison). Alternatively, a hydrolyzed protein diet may be suitable. Even in cases that are not etiologically linked with allergy or sensitivity a high digestible diet can be expected to support the patient.

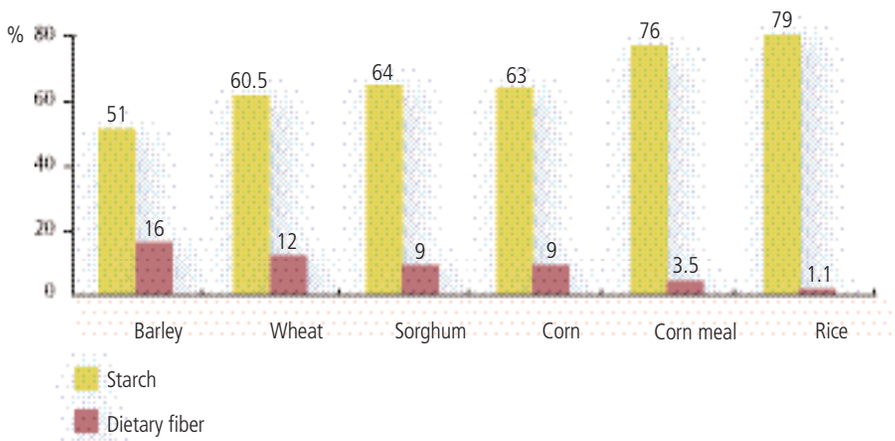
Psyllium grains are a source of non fermentable, soluble fiber with a strong hygroscopic power. These benefits are very useful for regulating intestinal transit in diarrhea or constipation.

Diets for patients with small intestinal bacterial overgrowth should contain carbohydrate sources that are highly digestible in the small intestine. Most carbohydrate sources will fulfill the requirements as long as the starch is adequately processed by thermal treatment (cooking, extrusion). Rice is the cereal that contains the lowest level of fiber and it is considered as the most digestible starch source **(Figure 9)**.

The concentration of dietary fiber has to be adjusted according to the requirements of the patient. Usually it is recommended to start with a low fiber type of diet (<3% crude fiber or 6% total dietary fiber DMB). Depending on the clinical outcome, it may be necessary to increase the fiber concentration by adding small amounts of insoluble or soluble fiber sources. Adequate feedstuffs are small amounts of cellulose, carrots, beet pulp or psyllium. **(See Chapter 1 for more on dietary fiber.)**

It may be advisable to adjust energy intake according to the needs of the patient. Many patients with small intestinal digestive problems suffer from malabsorption and resulting deficiencies. Weight loss and poor coat and skin quality are major problems that must be treated by increasing the density of certain nutrients in the diet. Fat concentration in a diet for patients with small intestinal disease has to be considered from two sides.

FIGURE 9 - COMPARISON OF STARCH AND DIETARY FIBER CONTENTS IN CEREALS USED IN DOG FOOD



The minimum indispensable fiber for good transit and to avoid prolonged stasis in the large intestine is provided by the combination of corn, purified cellulose and beet pulp.

- On the one hand, fat can be used effectively to increase dietary energy density.
- On the other hand fat can induce problems (due to the bacterial conversion of non absorbed fatty acids and bile acids into hydroxylated fatty acids and deconjugated bile acids, respectively) that may cause hypersecretion and aggravate clinical signs of diarrhea.

Therefore, the level of fat tolerated by dogs with SIBO/ARD needs to be evaluated according to individual needs. In cases that have experienced severe weight loss, it is justified to test increased intakes of dietary fat as long as the clinical condition is not negatively affected. In many chronic intestinal diseases, a high level of fat (20% of crude fat in a dry diet, supplying more than 40% of the calories) is very well tolerated by the dogs. This may be explained by the presence or absence of bacteria that are able to metabolize fatty acids and bile acids.

- ***Role of probiotics and prebiotics***

Probiotics and prebiotics have been suggested as treatment options for patients with intestinal problems.

A probiotic is a living organism that is administered orally, and exerts health benefits beyond those of inherent basic nutrition. In theory they are 'beneficial' bacteria that colonize the intestine at the expense of harmful bacteria. Their exact mechanism of action is not known and the identification of suitable bacteria for dogs is still in progress. However, two strains have been recently approved by the European authorities as feed additives in complete dog food: *Lactobacillus acidophilus* and *Enterococcus faecium*. A probiotic containing a strain of *Lactobacillus acidophilus* was successfully incorporated into canine diets, and improved recovery from clinical Campylobacter infection *(Baillon et al, 2004)*. More work would be required to determine whether there would be similar effects in SIBO/ARD.

Prebiotics are substrates for 'beneficial' bacterial species, which cause alterations in the luminal microflora. The aim is to offer a substrate to certain beneficial members of the gut flora and by this to achieve a shift in the composition of the gut bacteria in favor of a "healthy" flora. Therefore, they work in a similar or supportive way to probiotics. Prebiotics are non-digestible carbohydrates that can be used by several gut bacteria. Lactulose and certain types of dietary fiber with moderate bacterial fermentability can be used. Examples include several carbohydrates with different chain length: inulin and different oligosaccharides (fructo-oligosaccharides, galacto-oligosaccharides, mannan-oligosaccharides). There is currently no convincing evidence that such feed additives and feed compounds are beneficial in dogs with SIBO/ARD, and further work is required before their use can be recommended *(Willard et al, 1994; Zentek et al, 2002; Guilford & Matz, 2003)*.

> Adverse reactions to food

Adverse food reactions are an extremely common cause of chronic gastrointestinal disease and can be divided into non-immunologically mediated 'food intolerance' and immunologically mediated 'food allergy' (or hypersensitivity) **(Table 24)**. Clinical signs may effect more than one body system, but most common are dermatological signs (e.g. pruritus) **(See chapter 2)**, and gastrointestinal signs (e.g. vomiting and diarrhea). The gold standard of diagnosis involves response to exclusion diet and subsequent challenge **(See Chapter 2)**.

The gut mucosa is exposed to numerous exogenous factors and has differentiated regulatory mechanisms which enable selective permeability for nutrients and certain macromolecules but also exclusion of potentially harmful dietary, environmental or bacterial antigens. Discrimination of absorption and exclusion, tolerance and reactivity results from complex regulatory processes that depend on the age of the individual, the functional and regulatory mechanisms of the immune system and the influence of exogenous factors. The interaction between luminal factors of dietary or bacterial origin and the gut wall is of particular importance. Exogenous food antigens, e.g. pep-

TABLE 24 - CATEGORIES OF ADVERSE REACTIONS TO FOOD

Immunologically mediated (food hypersensitivity)	Non-immunologically mediated (food intolerance)
• Type I • Other? (e.g. type IV) * *Several immunological mechanisms of hypersensitivity would be involved but this hypothesis needs to be confirmed.*	• Idiosyncratic (e.g. enzyme deficiency) • Pharmacological effect (e.g. caffeine, tyramine, chocolate) • Pseudo-immune (e.g. foods causing histamine release – strawberries, shellfish) • Food poisoning (bacterial infections, endotoxin production) • Food spoilage • Scavenging • Food intolerance etc

tides, glycoproteins and lectins, but also microorganisms have the ability of interacting with the gut wall and to induce reactions and regulatory and counter regulatory processes. The interaction of luminal factors with the gut wall influences digestion (secretion, absorption, motility), immunological mechanisms (exclusion of antigens, regulation of the GI immune system, antigen processing, sensitivity, allergy), and neuro-endocrine processes.

Nutrition has a significant impact on the gastrointestinal tract of puppies and is of special importance for the function of the gut and the associated immune system during the early growth phase and later in adulthood. If animals are sensitized, reducing the exposure to potential allergens seems to be an important prerequisite for clinical improvement.

- ***Dietary management of adverse reactions to food***

Dietary management of adverse reactions to food can be difficult in practice because clinical signs can be slow to respond, and the animal will remain at risk of recurrence if dietary indiscretion occurs. Therefore, good owner compliance is essential if long-term success is to be ensured. Because of the difficulties in deciding whether the underlying reason is a dietary allergy or unspecified dietary intolerance without allergic etiology, dietary protocols should follow a standard model. In this regard, the diet should have a balanced nutrient composition, high digestibility in the small intestine and a restricted number of ingredients. Such a diet will support the patient because it facilitates the digestion and absorption of essential nutrients and helps to reduce the amount of potential antigens in the GIT. These goals can be achieved by using:
- home prepared diets;
- commercial diets with single or a limited number of protein sources; or
- hydrolyzed protein diets.

Even in those cases where the dietary intolerance is not linked to a specific protein or ingredient, a dietary change can be helpful because the new diet may have a beneficial impact on the intestinal digestive processes and it may also influence the intestinal microflora. Such a change may limit growth of potentially harmful microorganisms, and reduce the concentration of microbial metabolites in the gut. Although it has not yet been proven that microbial metabolites can have negative impact on the health of dogs with dietary intolerance, this concept seems to work in practice.

In all cases of dietary intolerance, veterinarians should obtain a complete overview of the dietary history of the patient. In this regard, the clinician should ask detailed questions on the dietary history, including information on the usual diet(s) fed and on all treats or table scraps that are fed. In some cases it is possible to identify problematic food components which can then help when formulating an elimination diet or selecting adequate diets from a commercial source. When it is not possible to identify the offending compound, the choice of initial elimination diet will depend upon the history of ingredients fed to that individual.

When a diet has been selected, it should be fed as the sole source of nutrition for sufficient time to determine whether a positive response will occur. The ideal duration of such a diet trial has not been determined. Some recommend up to 3 months, especially for dermatological cases. However, GI signs will often resolve more quickly, and owners of patients with diarrhea rarely have that degree of patience. Therefore a trial length of ~3-4 weeks seems appropriate for most GI cases.

If a positive response is documented, food provocation trials can be performed to identify the exact causal protein(s) i.e. single proteins are added sequentially to the diet for 7 days at a time. If no response occurs the ingredient can be deemed safe; however, if signs recur the ingredient should be avoided in the future. However, this is laborious and many owners elect not to pursue provocation if the elimination diet works *(Willard et al, 1994; Zentek et al, 2002; Guilford & Matz, 2003)*.

- ***Diets containing single sources of protein and carbohydrate***

Choice of protein

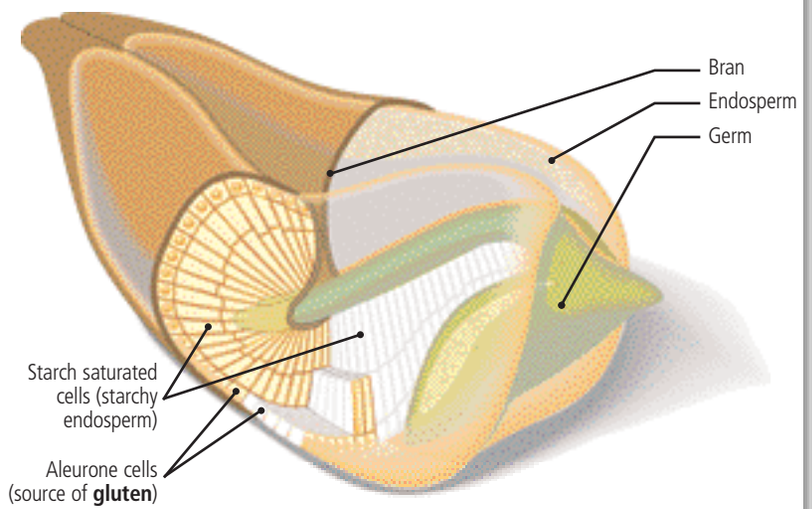
Meat, poultry and fish are usually used as a source of protein in exclusion diets. Suitable foods include chicken, turkey, venison, rabbit, duck or lamb. Although lamb has commonly been used, the widespread use of lamb protein in commercial diets would make this choice less suitable. Fish is an excellent choice because it is an uncommon ingredient in commercial diets. Vegetable protein sources may be used in as long as they are properly processed (e.g. isolated soy protein).

Many foodstuffs that are used as a source of carbohydrates also include significant amounts of protein, and this could complicate the elimination test.

Gluten proteins from cereals (e.g. wheat – **Figure 10** – and barley) have been investigated extensively because they can cause dietary allergy (including celiac disease) in humans, and have the potential to cause similar problems in companion animals. Therefore, this carbohydrate source may be unsuitable for some patients with dietary intolerance. However, given their high digestibility, it may be worth considering their use in patients that are not specifically sensitive to them.

Another problem may result from other ingredients that are commonly used in a complete balanced diet. For instance, fat sources may contain small amounts of proteins, either animal or plant derived. Although oils or fats may contain only traces of proteins, it cannot be excluded that this may affect the result of the feeding trial.

FIGURE 10 - WHEAT GLUTEN



Wheat gluten is a highly concentrated protein source (80-82% protein) with exceptional digestibility. It is used in hydrolyzed form as a milk protein substitute in neonatal food.

Wheat gluten is a complex mix of proteins from two different families: the **prolamines** and **glutenins**.

It is obtained through traditional milling methods: cleaning to eliminate wheat flour and bran, steeping to eliminate the germ, grinding and centrifugation to separate the solid non-soluble part (the gluten) from the starch and other soluble substances. The remaining solid part, without the fiber and starch, is dried to obtain a powder: **gluten**.

Wheat gluten has many nutritional qualities that make it an exceptional source of protein. It is a highly concentrated source of protein (80%-82%), it is free of biogenic amines, has a very low dietary fiber level and excellent ileal digestibility (99%).

Accordingly, using significant quantities of wheat gluten helps reduce the flow of indigestible proteins into the colon by 20% to 40%.

Wheat gluten is also a rich source of glutamine (almost 40%). This amino acid has an important role in maintaining digestive integrity, in conserving muscle mass during intensive activity and in taurine homeostasis in the event of illness or stress. Glutamine is involved in protein synthesis and constitutes a precursor of nucleic acids.

These different qualities rationalize the use of wheat gluten as a dairy protein substitute (over 99% digestible) in neonatal food.

Carbohydrate source

A single source of carbohydrate is also recommended for the elimination diet. Suitable ingredients include corn, potato, rice and tapioca. Cereals are often avoided given the concerns over gluten proteins. However, given that such sources are often highly digestible, such a carbohydrate source may still be suitable for many cases.

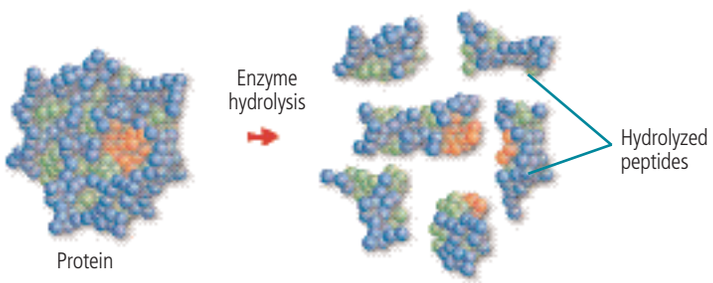
Minerals and Trace elements

Minerals and trace elements have to be added to the main ingredients to make it complete and balanced. However, some sources of mineral salts could contain small amounts of protein, which might itself provoke an adverse reaction. Supplementation of a diet with vitamins can also be problematic, since some of the commonly used vitamins are protected by encapsulation with gelatin (usually derived from beef or pork). Although the production process is rigid and most of the potentially antigenic epitopes are destroyed, traces of proteins or peptides could still be introduced into a diet. These problems are of relevance for home-prepared diets as well as for commercial prescription diets. If this is a significant concern, one option is to use a home-prepared diet that is based on a minimum of dietary ingredients. Adult dogs will tolerate this for a few weeks without developing severe nutrient deficiencies. However, diets need to be balanced and complete if they are fed for longer than a few weeks. Commercially prepared pet foods offer the advantage of being nutritionally balanced from the beginning.

Diets containing single hydrolyzed proteins

In the last few years diets with hydrolyzed protein sources have became available. In these diets the protein is treated enzymatically to alter its structure **(Figure 11)**.

FIGURE 11 - ACQUISITION OF PROTEIN HYDROLYSATE



Given their small size, these peptides are in theory less likely to interact with the immune system, and recent work has demonstrated reduced in vitro antigenicity compared with the native molecule *(Cave & Guilford, 2004)*. Nevertheless, more work is required to confirm that these diets are truly 'hypoallergenic'. Hydrolyzed protein diets have already been used successfully in the production of diets for babies with milk allergy. A hydrolyzed diet is likely to be beneficial in patients with true food allergy (especially type 1), but whether there is any benefit in non-immunological food intolerance, is less clear. Given their high digestibility, these diets are likely to benefit patients with a variety of different gastrointestinal disorders, and recent clinical trials have been encouraging *(Dossin et al, 2002; Mandigers & Biourge, 2004)*. Therefore, hydrolyzed diets offer an alternative for patients when single protein source or restricted antigen diets do not work.

> Gluten-sensitive Enteropathy (GSE)

GSE is a specialized type of food sensitivity caused by an adverse reaction to gluten (wheat protein). It has been described in certain lines of Irish setters, although it is an extremely uncommon diagnosis in clinical practice. The pathogenesis has been better defined in recent years *(Garden et al, 2000)*, although it is unclear whether an aberrant immune response to gluten, a direct toxic effect of the gluten, or both is involved. The clinical condition has similarities with human celiac disease, but the pathogenesis is different. Diagnosis can be made in a similar manner to other dietary sensitivities, and treatment involves feeding a gluten-free diet (i.e. avoid wheat, rye, barley, oats and tritical which is a wheat-rye hybrid). Rice and corn do not contain gluten. Interestingly,

many Irish setters that are affected when young grow out of the condition in adulthood. The extent to which gluten is a potential allergen in other breeds is not known. Given that the frequency of adverse reactions to food are usually related to the frequency with which the protein is fed in commercial diets, there is no reason to suspect that dogs are especially sensitive to wheat proteins. Therefore, the need to avoid gluten in every case with an adverse food reaction is questionable.

Irish Setter with gluten enteropathy.

> Inflammatory Bowel Disease (IBD)

IBD defines a diverse group of intestinal disorders, which are characterized by inflammatory mucosal changes (both architectural abnormalities and cellular infiltrates) without a known inciting cause. Therefore, diagnosis requires that there is histological evidence of inflammation, and that all potential causes for inflammation be excluded e.g. endoparasites, dietary sensitivity, ARD. IBD is usually classified on the basis of the predominant infiltrating cell type; lymphocytes and plasma cells are most commonly seen (lymphocytic-plasmacytic enteritis; LPE), whilst eosinophilic predominance (eosinophilic enteritis; EE) is noted in a few cases. Many cases have a generalized increase in many immune cell subsets and cannot easily be classified into one histological group.

Gluten enteropathy in the Irish Setter

This is not a gluten 'allergy'. Although often used by owners this term is inaccurate.

The disease manifests itself in clinical signs generally associated with chronic small intestinal pathology including diarrhea, wasting and delayed growth. It is a rare hereditary disease that primarily affects certain lines of Irish Setters.

Humans suffering from celiac disease are said to be gluten-intolerant, but in reality they are gliadin-intolerant. This is a chronic disease whose symptoms vary from light, non-specific digestive complaints to severe malabsorption (severe diarrhea).

Celiac disease depends on the exposure of genetically sensitive individuals to one specific gluten protein, gliadin. The cause is a defect in intestinal permeability that allows antigens in the intestinal lumen to traverse the mucosa.

Clinical symptoms:
- Intermittent or chronic diarrhea at an early age, between 4 and 7 months
- Weight loss
- Malabsorption

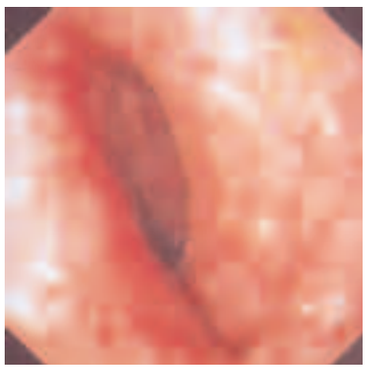
Treatment: a gliadin-free diet (wheat, barley, oats, rye, triticale, which is a wheat-rye hybrid).

Such classification is often arbitrary, and depends upon the opinion of the pathologist concerned. Other types of IBD (e.g. granulomatous enteritis) are rare in dogs. Moderate to severe changes are often associated with protein-losing enteropathy (PLE) **(see below)**.

The underlying etiology of canine IBD is unknown, and comparisons have been made with the human counterparts where a breakdown of immunological tolerance to luminal antigens (bacteria and dietary components) is thought to be critical. Antigens derived from the endogenous microflora and (possibly) dietary antigens are likely to be important in disease pathogenesis, whilst a potential role for diet-related factors is suggested by the clinical benefit of dietary therapy in some cases of canine IBD.

Alterations in immune cell populations in canine LPE have been documented, including increases in lamina propria T cells (especially $CD4^+$ cells), IgG+ plasma cells, macrophages and granulocytes *(German et al, 2001)*. Marked increases in mucosal cytokines have also been documented in canine LPE, with increased expression of Th1 (IL-2, IL-12 and IFNγ), Th2 (IL-5), proinflammatory (TNF-α) and immunoregulatory (TGF-β) cytokines (*German et al, 2000)*. This suggests immune system dysregulation in dogs with IBD, but does not confirm how this has arisen. The pathogenesis of eosinophilic enteritis (EE) has not been studied in detail, but similar mechanisms may exist to those suggested for LPE. EE must be differentiated from other diseases that can cause increases in eosinophil number such as endoparasitism and dietary hypersensitivity.

FIGURE 12 - ENDOSCOPIC LESIONS CLASSICALLY ENCOUNTERED IN CHRONIC INTESTINAL INFLAMMATORY DISEASE



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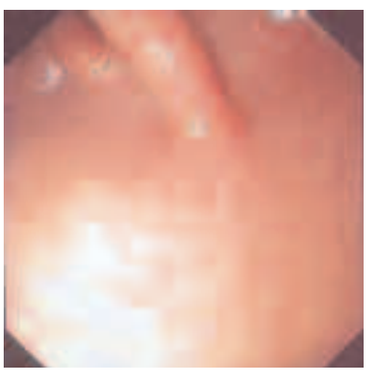
12A - Duodenitis
View from a portion of the proximal duodenum. Note the erythematous coloration and increased granularity.



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***12B -** – Endoscopic appearance of the stomach mucosa illustrating a cobble-stoned appearance due to a parietal infiltration of an inflammatory nature.*

In dogs, the most common clinical sign is chronic small bowel diarrhea, which can be accompanied by weight loss and vomiting. Owners often mention that the gastroenteritis symptomatic periods become more and more frequent, month after month. If PLE is severe, there may be signs of ascites and/or subcutaneous edema (especially if total serum/plasma protein and albumin concentrations are low), whilst other clinical sequelae can occur including systemic immune-mediated disorders and, exceptionally, thromboembolism. Diagnosis is usually made by histopathological assessment of intestinal tissue by endoscopic or exploratory laparotomy, after having eliminated other potential causes with a thorough diagnostic work up **(Table 22) (Figures 12A-B)**.

Given the variability in interpretation of pathological changes in intestinal biopsies between pathologists, a world small animal veterinary association (WSAVA) working party is currently in the process of defining standardized criteria.

Treatment often involves a combination of therapies including dietary modification, antibacterials and immunosuppressive medication. If clinical signs are stable and sequelae not too severe (e.g. PLE), treatment trials should first be instigated with dietary modification and with antibacterials **(See above)**. Immunosuppressive medication should only be used when other treatments fail. In this way cases that are truly idiopathic in nature can be discerned from food-responsive and antibiotic-responsive conditions.

> Alimentary lymphoma

The most common malignancies in dogs are lymphoma, epithelial tumors and smooth muscle tumors. However, other types of neoplasia can occur including fibrosarcoma, haemangiosarcoma and plasma cell tumors.

Lymphoma is characterized by mucosal and submucosal infiltration with neoplastic lymphocytes, which can then lead to clinical sequel. Lymphoma can either present in a diffuse manner, infiltrating large areas of intestinal wall, or can present as a focal mass lesion. Diffuse forms affect digestive and absorptive processes and lead to malabsorption and protein losing enteropathy (PLE). In contrast, focal forms can cause complete or partial obstruction of the intestine. The etiology in dogs is not known. LPE is reported to progress to lymphoma, and lymphoma can also co-exist with LPE within adjacent regions of small intestine. However, given discrepancies in histopathological interpretation, it is not clear whether these theories are genuine or are the result of initial misdiagnosis of lymphoma.

Treatment of lymphoma involves standard combination chemotherapy protocols, based on prednisolone, cyclophosphamide and vincristine. However, the disease is usually rapidly progressive, and the majority of patients respond poorly to therapy. In the minority of cases that do respond dietary management may form a useful adjunct **(See Oncology Chapter 13)**. If gastrointestinal signs are severe, changing to a highly digestible diet may be of benefit. The concurrence of cancer cachexia may require a diet with increased energy density.

> Protein-losing enteropathy and lymphangiectasia

Protein-losing enteropathy (PLE) is the term used to describe an intestinal disease that is accompanied by marked loss of plasma proteins through the gastrointestinal tract. When the hepatic capacity for protein synthesis is exceeded serum protein concentrations (both albumin and globulin) fall. The situation can be confounded by the concurrence of protein malabsorption with many of these conditions. Reductions in circulating protein concentrations (especially albumin) lead to reduced plasma oncotic pressure, and severe reductions (e.g. albumin <1.5 g/dL) lead to clinical consequences (e.g. ascites, subcutaneous edema, intestinal wall edema etc).

Dietary management of Inflammatory Bowel Disease (IBD)

An elimination diet may discriminate adverse food reactions, and benefit IBD cases because these diseases can occasionally be secondary to mucosal inflammation. Thus a dietary change might be beneficial even if there is no proven sensitivity against the current protein ingredients. Changing to a diet that is highly digestible is also beneficial.

Another relevant factor is **fat restriction or modification of the fat source**. The response of dogs to dietary fat cannot be predicted. Some patients may benefit from a low-fat diet because fatty acids can be hydroxylated in the GIT by certain bacteria. Hydroxylated fatty acids can induce secretory diarrhea. Conversely, fat restriction means that the diet contains higher amounts of either proteins or carbohydrates.

When the digestive processes are impaired due to the inflammation of the gut wall, the absorption of amino acids, peptides and carbohydrates can be reduced. Low-fat diets will have reduced energy densities compared to standard products. A study on ten IBD patients demonstrated that a high-fat dry food (20% fat) can help improve fecal consistency, resolve vomiting and improve body condition *(Lecoindre & Biourge, 2005)*. The effectiveness of the nutritional treatment is also explained by the choice of **high-quality highly-digestible proteins** to minimize protein indigestion and consequently reduce the production of toxins by putrefying bacterial flora.

Suitable fat sources include vegetable oils, poultry fat and fish oil. Fish oil offers the advantage of a high percentage of long chain omega-3 fatty acids (EPA-DHA). These fatty acids may have some beneficial effects due to their anti-inflammatory activities.

Probiotics and prebiotics may be used as ingredients or additives in these patients. Many practitioners prescribe live yoghurt and other probiotic supplements, although these have not been fully evaluated in dogs and the clinical benefits in cases with IBD need to be identified. There is some evidence that probiotics and prebiotics can be helpful in managing chronic IBD in humans *(Willard et al, 1994; Zentek et al, 2002; Guilford & Matz, 2003)*.

The causes of PLE are listed in **Table 25**; the three most important conditions are IBD, lymphoma and lymphangiectasia. However, there has also been a recent report of PLE associated with intestinal crypt lesions, without evidence of lymphangiectasia or inflammation in most cases *(Willard et al, 2000)*. The underlying etiology of such lesions is not known. Response to therapy, with antibacterials and immunosuppressive medication is variable. Some dogs deteriorate suddenly and can die from thromboembolic disease. However, malnutrition is the most significant problem.

A very high quality protein source is vital for patients with protein-losing enteropathy (cottage cheese, cooked chicken or turkey meat, boiled eggs). The protein intake should be adjusted to achieve if possible a normalization of the serum protein levels.

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Yorkshire Terriers, soft-coated Wheaten Terriers and Rottweilers are predisposed to lymphangiectasia.

Table 25 - Causes of protein-losing enteropathy

Lymphangiectasia	Primary	intestinal generalized
	Secondary	venous hypertension e.g. right cardiac failure, hepatic cirrhosis
Infectious	Parvovirus, Salmonella	
Structural	Intussusception	
Neoplasia	Lymphoma	
Inflammation	**IBD**	lymphoplasmacytic enteritis, eosinophilic enteritis, granulomatous enteritis
Endoparasitism	Giardia, Ancylostoma	
Gastrointestinal hemorrhage	Hepatic disease, neoplasia, ulceration	

Dietary management for lymphangiectasia

The nutritional treatment of patients with lymphangiectasia is based on the application of foods with a low-fat concentration. Low-fat diets seem to be helpful in counteracting the pathophysiology in lymphangiectasia. However, patients with this type of intestinal disease need to be supplied with adequate amounts of essential fatty acids, e.g. linoleic acid.

Previously, medium-chain triglycerides were recommended since they were though to be absorbed directly into the portal blood circulation, therefore bypassing the lymphatic system. However, recent studies have contradicted this mechanism, and suggested that this lipid group is absorbed via lymphatics. Furthermore, high doses of medium-chain fatty acids can have negative effects in dogs and may induce vomiting and diarrhea. Therefore the use of these nutrients cannot be recommended.

Supplementation with fat-soluble vitamins is advised, and there are anecdotal reports of improvement with glutamine supplementation *(Willard et al, 1994; Zentek et al, 2002; Guilford & Matz, 2003)*.

Intestinal lymphangiectasia is characterized by the abnormal dilatation and dysfunction of lymphatic vessels within the mucosa and submucosa. It may be primary (localized or generalized lymphatic abnormality) or secondary (e.g. to lymphatic obstruction). Such an obstruction can be within the intestine (i.e. neoplastic infiltration, inflammation or fibrosis) or systemic (e.g. right-sided cardiac failure, caval obstruction or hepatic disease). The lacteal dilatation is associated with exudation of protein-rich lymph into the intestine, and severe lipid malabsorption. As a result, severe hypoproteinemia or lymphatic flow disturbances result in ascites, subcutaneous edema and chylothorax.

Treatment for secondary lymphangiectasia involves rectifying (if possible) the underlying cause e.g. right-sided cardiac failure. For primary lymphangiectasia, treatment is usually supportive and symptomatic. This involves decreasing enteric protein loss (see below), resolving associated inflammation and controlling edema or effusions. Glucocorticoid therapy may benefit some cases especially if the disease is secondary to an inflammatory cause e.g. IBD. Adjunctive therapy with metronidazole or tylosin may also be of benefit. Finally, diuretics are indicated in the management of effusions and combinations of diuretics are preferred (e.g. furosemide and spironolactone). Intravenous administration of plasma or colloid may also help if hypoproteinemia is marked. The prognosis is most cases is guarded, and response to therapy is usually poor in most cases.

7 - Specific large intestinal conditions causing diarrhea

Table 26 - Conditions of the large intestine causing chronic diarrhea

Adverse reactions to food - Dietary intolerance - Dietary sensitivity
Stress associated colitis
Fiber-responsive colitis
C. perfringens associated colitis
IBD - Lymphocytic-plasmacytic colitis - Eosinophilic colitis - Granulomatous colitis? - Histiocytic ulcerative colitis
Large intestinal neoplasia - Rectal polyp (adenomatous) - Adenocarcinoma - Smooth muscle tumors
Cecal inversion
etc.

Specific diseases of the large intestine are presented in **Table 26**. Adverse reactions to food and IBD can affect the large intestine, resulting in large intestinal signs i.e. hematochezia, tenesmus, fecal mucus. The pathogenesis and treatment of the condition is similar to that discussed above. However, some clinicians favor the use of the anti-inflammatory medication sulphasalazine, and there is some evidence that modification of dietary fiber content may be of benefit (see below). Other common chronic large intestinal conditions include idiopathic colitis, stress-associated colitis ('irritable colon syndrome'), fiber-responsive colitis and *Clostridium perfringens* associated colitis.

► Stress-associated colitis (irritable colon syndrome, irritable syndrome)

Stress-associated colitis is a condition with similarities to irritable bowel syndrome and presents with signs of intermittent, often mucoid, diarrhea, with urgency, occasional vomiting, tenesmus and hematochezia. In some cases borborygmi, flatulence, 'bloating', and abdominal pain are described. This often occurs in nervous/highly strung dogs e.g. toy breeds and competition dogs. The etiopathogenesis is poorly understood, but a number of hypotheses have been suggested:

- Primary intestinal motility defect
- Heightened sensation of intestinal distension/motility
- Psychological factors
- Undiagnosed organic disease

There are no specific diagnostic tests for stress-associated colitis, and diagnosis is made by consideration of the signalment together with exclusion of all other organic diseases. Treatment involves eliminating stressful events if possible, behavioral modification and (in some cases) drug therapy (anticholinergics, sedatives, and antispasmodics, e.g. hyoscine, diazepam or peppermint oil).

The syndrome of fiber-responsive colitis has recently been reported *(Leib et al, 2000)*. The etiopathogenesis is poorly understood but may well have similarities to stress-associated colitis **(see above)**. As the name implies, therapy involves dietary management with a high-fiber diet (>8% crude fiber or 15% total dietary fiber DMB). It may be interesting to test various sources of soluble and insoluble fiber.

For legal reasons, the fiber content stated on packaging relates to the crude fiber content, which significantly underestimates the actual fiber content of the food, especially if it has not been lignified to any great degree. The total dietary fiber stated in technical documentation or available on request from the manufacturer is a more reliable estimation.

► *Clostridium perfringens* associated colitis

The existence of this condition is controversial, and many gastroenterologists do not agree as to causes and pathogenesis. C. *perfringens* can be a normal inhabitant of the canine large intestine, and its identification at fecal culture is not abnormal. However, sporulation is associated with liberation of endotoxin, which is not necessarily associated with clinical signs. It was previously suggested that the presence of spore-forming organisms on a fecal smear / rectal cytology was diagnostic. However, recent studies have demonstrated spores and detectable endotoxin in both healthy dogs and those with clinical signs *(Marks et al, 1999)*. Whilst small numbers of endospores does not confirm the condition (e.g. up to 8-10 per high power microscope field), the presence of large numbers may be suggestive. Nevertheless, tests for C. *perfringens* enterotoxin A or B (CPA, CPB) are commercially available and are the preferred method of diagnosis.

The condition is more likely to arise as an acute intestinal disorder, especially in dogs housed in a colony environment. Some individuals may be susceptible to the organism and, given its ubiquitous nature, may suffer repeated bouts or persistent clinical signs. Treatment usually involves prescribing antibacterials to which the organism is sensitive e.g. ampicillin, metronidazole, and multiple or long courses may be required. Increasing the fiber content of the diet is also reported to be beneficial. It is possible, that there may be overlap between this condition and the syndrome of fiber-responsive colitis **(see above)**.

Dietary management for large intestinal diseases causing diarrhea

Dietary management of large intestinal diarrhea depends on the underlying disease. Initially, a bland diet fed in multiple small feedings can be used for 2-6 weeks. The diet may either be a commercial diet or a home prepared diet based on low-fat types of meat (chicken or lamb) or fish, low lactose dairy products (low-fat cottage cheese) and carbohydrate sources that are easily digestible and that have low allergenicity (rice, potatoes, tapioca, starch).

Long-term treatment of colonic diseases is based on three principles of dietary treatment, which may be used in different combinations.
The goals are:
- regulating the disturbed motility
- influencing the composition and metabolic activity of the gastrointestinal microflora
- excluding dietary antigens if allergy or sensitivity is involved

Adding dietary fiber, either quantitatively or qualitatively by using soluble and insoluble fiber sources, can modify motility. Fiber sources that may be used include insoluble fibers such as wheat bran, oat bran or cellulose. When tolerated, these fibers may have a regulatory effect on peristalsis and transit time. Soluble fibers may have positive effects on stool quality by their water binding effects. Good sources for soluble fiber include carrots (cooked, ground) or the bulk forming seeds of psyllium (*Plantago psyllium*), or ispaghula (*Plantago ovata*).

Soluble fiber sources can be used to modify the composition and the metabolic activity of the intestinal bacteria. Soluble fibers are fermented by a variety of bacteria in the large intestine and increase the production of short chain organic acids, including lactic, acetic, propionic and butyric acid.

The acid production influences intestinal acidity and impacts the metabolic activity of the microflora. Butyric acid is directly utilized by colonocytes and has anti-inflammatory properties. Many commercial high-fiber diets already contain fermentable dietary fiber, such as the moderately fermentable fiber, beet pulp.

Many patients with chronic colitis respond to hypoallergenic diets, and the underlying mechanisms are similar to those described for dietary allergy **(see above)** *(Willard et al, 1994; Zentek et al, 2002; Guilford & Matz 2003)*.

8 - Chronic diseases of the intestinal tract causing constipation

Constipation is defined as infrequent defecation, of excessively dry or hard feces. It is commonly accompanied by increased straining to defecate. Causes of constipation are listed in **Table 27**.

Table 27 - Conditions of the large intestine causing chronic constipation

- **Dietary and environmental**
  - Diet e.g. low residue diet, bones, foreign material
  - Lack of exercise
  - Change of environment
  - Hospitalization
- **Painful defecation**
  - Ano-rectal disease e.g. anal sacculitis and abscess, perianal fistula, rectal foreign body
  - Trauma e.g. fractured pelvis or limb, dislocated hip (unable to squat)
- **Mechanical obstruction**
  - Extraluminal e.g. healed pelvic fracture, prostatic enlargement, pelvic tumor
  - Intraluminal e.g. rectal tumor, perineal hernia
- **Neuromuscular disease**
  - CNS e.g. paraplegia, cauda equina syndrome
  - Intrinsic dysfunction e.g. idiopathic megacolon, dysautonomia
- **Metabolic and endocrine disease** These diseases can interfer with colonic muscle function. Examples include:
  - Hypothyroidism
  - Diabetes mellitus
  - Hypokalemia
- **Debility** resulting in general muscle weakness and dehydration

Obstipation is defined as an inability to pass feces, and arises when constipation is prolonged resulting in formation of progressively harder and drier feces. Defecation becomes increasingly more difficult, until it is virtually impossible because of secondary degenerative changes in colonic muscle.

Megacolon is a descriptive term for a persistent, generalized enlargement of the diameter of the colon. It may be congenital or acquired, with the acquired cases arising secondary to numerous disorders including fluid/electrolyte imbalances (especially hypokalemia), dietary problems (low residue diet, ingestion of foreign material), painful defecation, neuromuscular disorders and colonic obstruction.

Colonic impaction usually occurs with a mixture of feces and ingested hair, bones etc. Recurrent bouts may lead to secondary megacolon / obstipation. The main clinical sign of constipation is tenesmus, with multiple unsuccessful attempts to defecate. Occasionally animals may pass scanty liquid feces around the impaction and the owner thinks animal has 'diarrhea '. Other signs include vomiting and dyschezia (painful or difficult defecation).

► Diagnosis and treatment

Diagnosis of constipation involves first confirming that the large intestine is the organ involved e.g. by ruling out other possible causes of tenesmus (urogenital tract diseases). The presence of fecal matter within the large intestine can be confirmed on physical examination by abdominal and rectal palpation. This enables the differentiation of constipation from colitis as a cause of tenesmus. Radiography will confirm the diagnosis and enable predisposing factors to be identified e.g. pelvic canal narrowing from previous pelvic fracture. Other diagnostic measures (e.g. laboratory analyses) are required to assess for metabolic diseases as an underlying cause.

Treatment involves first rectifying the underlying cause if possible e.g. perineal hernia repair. Options for medical management are listed in **Table 28**. If megacolon has developed surgical management may be necessary e.g. subtotal colectomy.

Table 28 - Medical management of constipation

Laxatives				Enema	Gentle manual evacuation under GA	Prokinetic drugs?	Prevention of recurrence
Osmotic	**Surfactant**	**Lubrication**	**Stimulant**	Warm (soapy) water		Cisapride?	• Adaptation of the diet
Lactulose	Docusate Sodium citrate	Paraffin paste Liquid paraffin/ mineral oil	Castor oil Glycerol Danthron Poloxamer	Docusate Phosphate		Tegasarod? Ranitidine?	• Fecal bulking & softening agents - Ispaghula, Psyllium, Sterculia, Bran • Avoidance of bones

► Dietary management of colonic diseases including constipation, obstipation and colonic impaction

Dysfunction of the colon can be related to different etiologies. Nutritional treatment includes restriction of dietary antigens, as already described for patients with allergy, and the addition of ingredients that help to modify intestinal motility. Further, diet composition is an important determinant for the water holding capacity of the undigested material reaching the colon.

Some cases of constipation will respond to an increased fiber content of the diet. Fiber sources have to be selected according to their physiological properties.

• Dietary fiber with a low solubility e.g. cellulose, increase the bulk in the intestine and may help to regulate intestinal motility. Besides their effects on motility, insoluble fiber has a certain capacity to bind non-absorbed fluid by physical forces. Therefore, fecal quality of patients with colonic disorders may improve by the addition of small amounts of insoluble fiber. The disadvantage of higher amounts of insoluble fiber is, that these ingredients lower the digestibility of the diet. Therefore, the concentration of insoluble fiber needs to be carefully controlled.

THE COMPOSITION OF THE DIET MUST BE BASED ON THE NATURE OF THE DIGESTIVE COMPLAINT ENCOUNTERED

Swallowing conditions: choose a ration type that is concentrated in energy, high in fats, and adapted to cachexic conditions.

Gastrointestinal conditions: the same type of diet may be used, except in cases of fat intolerance. Focus on a diet containing a moderate lipid level, adapted to hyperlipidemia.

In some cases (increase in intestinal permeability, IBD, intolerance reaction or dietary allergy), a hypoallergenic diet constitutes the best alternative.

Colonic conditions: while many cases of chronic colitis respond well to a hypoallergenic diet, disruptions to digestive transit are sometimes resolved by increasing the fiber content in the ration.

• Other types of fibers are suitable for patients with colonic disorders due to their higher solubility. Typical examples include beet pulp, pectins from carrots or fruits, and gum-like fiber e.g. guar gum or psyllium. These fiber sources have a different structure compared to cellulose, and can, with the exception of psyllium, be fermented by intestinal bacteria. Negative effects of higher amounts of soluble dietary fiber include increased moisture content of the feces which, when in high amounts can negatively impact fecal quality.

• The fermentation processes induced by the ingestion of fermentable fibers have a strong impact on the colonic milieu, because bacteria release organic acids as products of the metabolism that tend to reduce the colonic pH. The short chain fatty acids that are released by bacteria can be partly utilized by the colonic mucosa. Improved supply with butyric acid has beneficial effects in humans suffering from colitis. The organic acids can also have some regulatory effects on motility. Furthermore, the addition of fermentable dietary fiber reduces the concentration of some bacteria that can be considered potentially harmful and increase the concentrations of some bacteria that are regarded as being beneficial.

Although these ideas need further investigation, the addition of moderate amounts of insoluble/non fermentable and soluble/fermentable dietary fiber is common in practice and seems to work in many patients with chronic colonic disorders. It may be necessary to investigate the effects individually and to adjust the amount of fiber according to the tolerance and the clinical effects in the patient. In cases with severe problems due to constipation or fecal impaction the laxative effects of soluble fiber sources are used specifically for treatment. In those patients the application of fermentable carbohydrates, e.g. lactulose or lactose is possible. Again, the dosage needs to be adjusted individually. As a general rule, the dosage should be altered to produce a slight increase in fecal moisture. The fecal pH normally drops from values above 7 to 6.5. In those cases where owners prefer to use common feedstuffs, wheat bran is a good additive that increases the fiber content of a diet and has regulatory effects on the gut motility. Ingredients with laxative properties are liver, milk and milk products *(Willard et al, 1994; Zentek et al, 2002; Guilford &Matz 2003)*.

Frequently asked questions: diet in case of digestive complaints

Q	A
I want to perform an elimination diet trial, should I use a home-prepared diet or a commercially-formulated diet?	Some investigators recommend using a home-prepared diet for such a purpose, because it is easier to keep track of the ingredients and there are no hidden additives. However, such diets are unbalanced and inappropriate for long-term use. They are laborious for the client and the exact composition of the diet may vary from batch to batch. Home-prepared diets are often more expensive than feeding a 'prescription diet'. The advantage of a commercial diet is that the same diet can be used both for diagnosis and treatment.
I want to perform an elimination diet trial, what is the best diet to use, and for how long should I feed it?	No single diet necessarily suits every patient, and the exact choice should be tailored to the individual. The previous diet of the individual should be used to decide upon the most appropriate ingredients. A traditional elimination diet is composed of single protein and carbohydrate source; available choices for protein include chicken, soy, fish, venison, rabbit, and duck; available choices for carbohydrate include rice, corn [maize], tapioca and potato. Foodstuffs based upon fish protein often make suitable choices for dogs because, unlike cats, this protein is uncommonly used in standard canine diets. Hydrolyzed protein diets are also available, and these are based either on chicken or soy protein. The major advantage of using a hydrolyzed protein diet is that such diets are highly digestible, and it is unlikely for a patient to have previously been exposed to hydrolyzed proteins. The optimum duration for an elimination diet trial is unknown, and many cases require 12 weeks to respond. For dogs with gastrointestinal signs, many investigators recommend an elimination diet trial of 3-4 weeks, partly because clinical experience suggests most cases respond rapidly (1-2 weeks), and partly because most owners will not tolerate their pet having continued signs of vomiting and diarrhea.
I want to provide fiber-supplementation for a dog with large intestinal diarrhea, how should I go about this?	There are two possible approaches; first, to feed a commercial 'high-fiber' diet and second, to add a fiber supplement to the existing diet. Both approaches have their merit, but the latter approach can be tried in clinical cases. In this regard, an elimination diet is tried first, since many cases with large intestinal signs have adverse reactions to food. If response is suboptimal a fiber supplement (e.g. psyllium or Metamucil®), can then be added to gage the effect of additional fiber supplementation.
What is a sacrificial protein, and should I contemplate using this approach?	A sacrificial protein is a novel protein incorporated into a diet fed during the initial treatment phase of a dog with inflammatory bowel disease. A second novel protein is then fed once the inflammation has subsided and used for long-term management. The basis of such an approach is that such patients have ongoing mucosal inflammation, and increased permeability. By feeding a novel protein in the face of such inflammation, there is a theoretical concern that normal mucosal tolerance will be abrogated allowing hypersensitivity to the novel protein. If a single novel protein is used, the potential benefit of using a novel protein diet may be lost; using two diets in series means that a novel hypersensitivity does not develop against the diet intended for long-term control. Whilst there may be theoretical merit, there is no real scientific or clinical basis on which to base this approach, and it is seldom if ever necessary to undertake it. Hypoallergenic diets based on protein hydrolysates may make this practice even less useful (*Mandigers & Biourge, 2004*).
How much should I feed a dog with severe IBD that has lost 30% of its body weight?	It is important to remember to feed the patient according to its current body weight. The amount fed can then be gradually increased to take account of the individual status of the patient (e.g. activity level, working dog etc), the effects of malabsorption and to achieve adequate body weight gain. The patient should be weighed regularly and the exact caloric intake tailored to response. If the patient tolerates a moderate fat diet, this may be preferable to a traditional low-fat diet, because the overall volume of diet fed can be reduced.

References

Baillon ML, Marshall-Jones ZV, Butterwick RF - Effect of probiotic Lactobacillus acidophilus strain DSM 13241 in healthy adult dogs. Am J Vet Res 2004; 65 (3).

Benno Y, Nakao H, Uchida K et al - Impact of the advances in age on the gastrointestinal microflora of beagle dogs. J Vet Med Sci 1992a; 54: 703-706.

Benno Y, Nakao H. Uchida K et al - Individual and seasonal variations in the composition of fecal microflora of beagle dogs. Bifidobact Microfl 1992b; 11: 69-76.

Cave NJ, Guilford WG - A method for in vitro evaluation of protein hydrolysates for potential inclusion in veterinary diets. Res Vet Sci 2004; 77: 231-238.

Caywood D, Teague HD, Jackson DA et al - Gastric gas analysis in the canine gastric dilatation voluvulus syndrome. J Am Anim Hosp Assoc 1977; 13: 459-462.

Devitt CM, Seim HB, Bonagura JD - Esophageal feeding tubes. Kirk's Current Veterinary Therapy XIII: Small Animal Practice 2000: 597-599.

Dossin O, Semin MO, Raymond I et al - Soy hydrolysate in the management of canine IBD: a preliminary study. Proceedings of the 12th European Society of Veterinary Internal Medicine Congress 2002; Munich, Germany: 167.

Garden OA, Pidduck H, Lakhani KH et al - Inheritance of gluten-sensitive enteropathy in Irish setters. Am J Vet Res 2000; 61: 462-468.

German AJ, Hall EJ, Day MJ - Immune cell populations within the duodenal mucosa of dogs with enteropathies. J Vet Inter Med 2001; 15: 14-25.

German AJ, Helps CR, Hall EJ et al - Cytokine mRNA expression in mucosal biopsies from German shepherd dogs with small intestinal enteropathies. Dig Dis Sci 2000; 45: 7-17.

Glickman, LT, Glickman NW, Perez CM et al - Analysis of risk factors for gastric dilatation and dilatation-volvulus in dogs. J Am Vet Med Assoc 1994; 204 (9): 1465-1471.

Glickman, LT, Glickman NW, Schellenberg DB et al - Non-dietary risk factors for gastric dilatation-volvulus in large and giant breed dogs. J Am Vet Med Assoc 2000; 217 (10): 1492-1499.

Guilford WG, Matz ME - The nutritional management of gastrointestinal tract disorders in companion animals. NZ Vet J 2003; 51: 284-291.

Lecoindre P, Biourge V - Troubles gastro-intestinaux et matières grasses alimentaires. Prat Méd Chir Anim Comp 2005; 40: 13-16.

Leib MS - Treatment of chronic idiopathic large bowel diarrhea in dogs with a highly digestible diet and soluble fiber: a retrospective review of 37 cases. J Vet Intern Med 2000; 14: 27-32.

Mandigers PJ, Biourge V - Efficacy of a soy hydrolysate based diet in the management of chronic canine gastroenteritis: A controlled study. Proceedings of the 8th Meeting of the ESCVN, Budapest, Hungary, Sept 23-25, 2004, 128-129.

Marks SL, Melli A, Kass PH et al - Evaluation of methods to diagnose Clostridium perfringens-associated diarrhea in dogs. J Am Vet Med Assoc 1999; 214: 357-360.

Marks SL - Enteral and parenteral nutritional support. Textbook of Veterinary Internal Medicine: Diseases of the Dog and Cat; dietary considerations of systemic problems; 5th ed: 2000, Ettinger SJ, Feldman EC (ed): 275-282.

Meyer H, Zentek J - Ernährung des Hundes 2001; 4, Auflage, Berlin.

Mohr AJ, Leisewitz AL, Jacobson LS et al - Effect of early enteral nutrition on intestinal permeability, intestinal protein loss, and outcome in dogs with severe parvoviral enteritis. J Vet Intern Med 2003; 17: 791-798.

Raghavan M, Glickman N, McCabe G et al - Diet related risk factors for gastric dilatation-volvulus in dogs of high-risk breeds. J Am Anim Hosp Assoc 2004; 40: 192-203.

Rogolsky B, Van Kruiningen HJ - Short-chain fatty acids and bacterial fermentation in the normal canine stomach and in acute gastric dilatation. J Am Anim Hosp Assoc 1978; 14: 504-515.

Sanderson S, Bartges JW, Bonagura JD - Management of anorexia. Kirk's Current Veterinary Therapy XIII: Small Animal Practice 2000: 69-74.

Sigalet DL, Winkelaar GB, Smith LJ - Determination of the route of medium-chain and long-chain fatty acid absorption by direct measurement in the rat. J Parent Ent Nutr 21: 275, 1997.

Theyse LF, Van de Brom WE, Van Sluijs FJ - Small size of food particles and age as risk factors for gastric dilatation volvulus in Great Danes. Vet Rec 1998; 143: 48-50.

Van Kruiningen HJ, Gregoire K, Meuten DJ - Acute gastric dilatation: a review of comparative aspects, by species, and a study in dogs and monkeys. J Am Anim Hosp Assoc 1974; 10: 294-324.

Warner NS, Van Kruiningen HJ - The incidence of clostridia in the canine stomach and their relationship to acute gastric dilatation. J Am Anim Hosp Assoc 1978; 14: 618-623.

Willard MD, Helman G, Fradkin JM et al - Intestinal crypt lesions associated with protein-losing enteropathy in the dog. J Vet Intern Med 2000;14(3): 298-307.

Willard MD, Simpson RB, Delles EK et al - Effects of dietary supplementation of fructo-oligosaccharides on small intestinal bacterial overgrowth in dogs. Am J Vet Res 1994; 55: 654-659.

Zentek J, Hall EJ, German A et al - Morphology and immunopathology of the small and large intestine in dogs with nonspecific dietary sensitivity. J Nutr 2002; 132: 1652S-1654S.

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Brachycephalic dog breeds (e.g. Bulldogs) have a higher risk of frequent regurgitation. This problem is facilitated by two anatomical characteristics: the esophagus is slightly convoluted rather than straight, and the cardia is often atonic. Abdominal compressions due to inspiration also facilitate gastro-esophageal reflux.

Key Points
to remember:

Dysphagia

Dysphagia refers to disorders of deglutition. Oral dysphagia is characterized by the inability to take food, to lap liquids or to propel the food bolus to the pharynx. Pharyngeal and esophageal dysphagia are typically characterized by the occurrence of regurgitation and ptyalism.

Regurgitation refers to spontaneous or induced expulsion, without any effort of abdominal contraction, of masticated food coated with saliva. Regurgitation contents rarely contain blood and never contain bile.

Regurgitation commonly occurs shortly after eating, however, it may be delayed in certain esophageal diseases.

In all cases, etiological diagnosis should be established because esophageal disorders can be a manifestation of systemic disease. However, the treatment of these disorders often remains symptomatic, combining specific nutritional and medical approaches.

Nutritional therapy is essential. Sometimes advanced malnutrition will have to be treated. In these cases enteral or parenteral feeding may be necessary.

When oral feeding is possible, it is necessary to use highly digestible foods with a fairly liquid consistency. These diets should be fed from a height to capitalize on gravity to facilitate the transit of food to the stomach.

Key Points
to remember:

Chronic Diarrhea

The scientific definition of **diarrhea** is based on an increase in the liquidity and the volume of fecal matter as well as the frequency of evacuation. This is the most common clinical sign of an intestinal complaint in dogs, although many extra-digestive complaints may accompany diarrhea.

Chronic diarrhea is described somewhat arbitrarily if it does not resolve spontaneously or if it does not respond to symptomatic treatment within 3-4 weeks.

A logical and well reasoned diagnostic procedure will establish a rational foundation for an appropriate therapeutic plan in which nutrition is essential.

Efficacy of a soy hydrolysate-based diet in the management of chronic canine gastroenteritis: a controlled study

The purpose of this study was to compare the response of dogs with chronic gastrointestinal signs suggestive of adverse reaction to food to high digestible diets. One of the test diets was a soy protein isolate hydrolysate based diet.

Materials and methods

Twenty-six dogs with a history of chronic vomiting, diarrhea, and/or weight loss were included in the study. On the basis of clinical signs, a gastroduodenal or a colonic endoscopy was performed to rule out foreign bodies, gastritis, ulcer, neoplasia, hyperacidity, pyloric stenosis, and to obtain biopsies for histopathology. The mean age at presentation was 4.3 ± 3.3 years (range 0.6-11 yrs) and mean body weight was 23 ± 12 kg (4.7-40 kg). The sex ratio, age and body weight were similar between both groups of dogs.

- Eighteen dogs received a soy protein isolate hydrolysate-based diet *(Veterinary Diet Hypoallergenic DR21, Royal Canin)*
- Eight dogs received a highly digestible low residue diet *(Veterinary Diet Intestinal GI30, Royal Canin)*, which served as a control diet

The owners were instructed to exclusively feed the diet that they were given for two months. No medications were allowed. If no or little improvement was observed over the 2 months of dietary therapy, drug therapy was initiated. If improvement was noted after 2 months owners were requested to challenge their dogs with their previous diet.

Composition of diets

Hypoallergenic DR21*		Intestinal GI30*	
Main ingredients	**Analysis**	**Main ingredients**	**Analysis**
Soy hydrolysate	Protein 21.0%	Dehydrated chicken protein	Protein 30.0%
Rice	Fat 19.0%	Rice	Fat 20.0%
Chicken fat	(Omega 6/Omega 3: 5)	Cornmeal	(Omega 6/Omega 3: 5)
Fish oil	Starch 37.6%	Chicken fat	Starch 27.4%
Soybean and borage oil	Fiber 5.5%	Fish oil	Fiber 6.3%
Beet pulp	Minerals 7.0%	Soybean and coco oil	Minerals 7.3%
FOS	Metabolizable energy 4180 kcal/kg	Chicken liver hydrolysate	Metabolizable energy 4270 kcal/kg
		Beet pulp	
		FOS	
		MOS	
		Zeolite	
		Cellulose	

* *Royal Canin, Veterinary Diet, Aimargues (France)*

Results

Gastroduodenoscopy was performed in 23 dogs and colonoscopy in 3 dogs. Biopsies indicated inflammatory (lymphoplasmacytic, lymphocytic, eosinophilic, eosinolymphocytic) infiltrates in 24 of 26 dogs. Clinical signs resolved in 16 of 18 dogs on the soy hydrolysate diet and 7 of 8 dogs on the low residue diet after two months of dietary therapy. The 3 remaining dogs improved but still had occasional episodes of vomiting or diarrhea. The dogs on the hydrolyzed protein diet gained significantly more body weight compared to the dogs on the low residue diet.

When challenged with their previous diet, 11 of 16 dogs on the hydrolysate diet and 4 of 6 dogs on the low residue diet relapsed.

Follow-up examination was performed in 15 of 16 dogs on the hydrolysate diet and 6 of 7 dogs on the low residue diet 8 ± 8 months after the start of the clinical study.

- 13 of 15 dogs on the hydrolysate diet remained free of clinical signs and 2 of 15 showed minor signs.
- Only 2 of 6 dogs on the low residue diet remained free of clinical signs. The remaining four dogs needed drug therapy to alleviate their clinical signs.

Gastrointestinal biopsies performed in 5 hydrolysate and 4 low residue diet dogs did not reveal any change in histopathology.

Conclusion

Although in the short term, soy hydrolysate and low residue diets appear satisfactory in the management of chronic diarrhea and vomiting associated with adverse reaction to food, the soy hydrolysate based diet induced better weight gain and was better tolerated in the long term.

Reference

Mandigers PJJ, Biourge V - Efficacy of a soy hydrolysate based diet in the management of chronic canine gastroenteritis: A controlled study. Proceedings of the 8th Meeting of the ESCVN, Budapest, Hungary, Sept 23-25, 2004, 128-129.

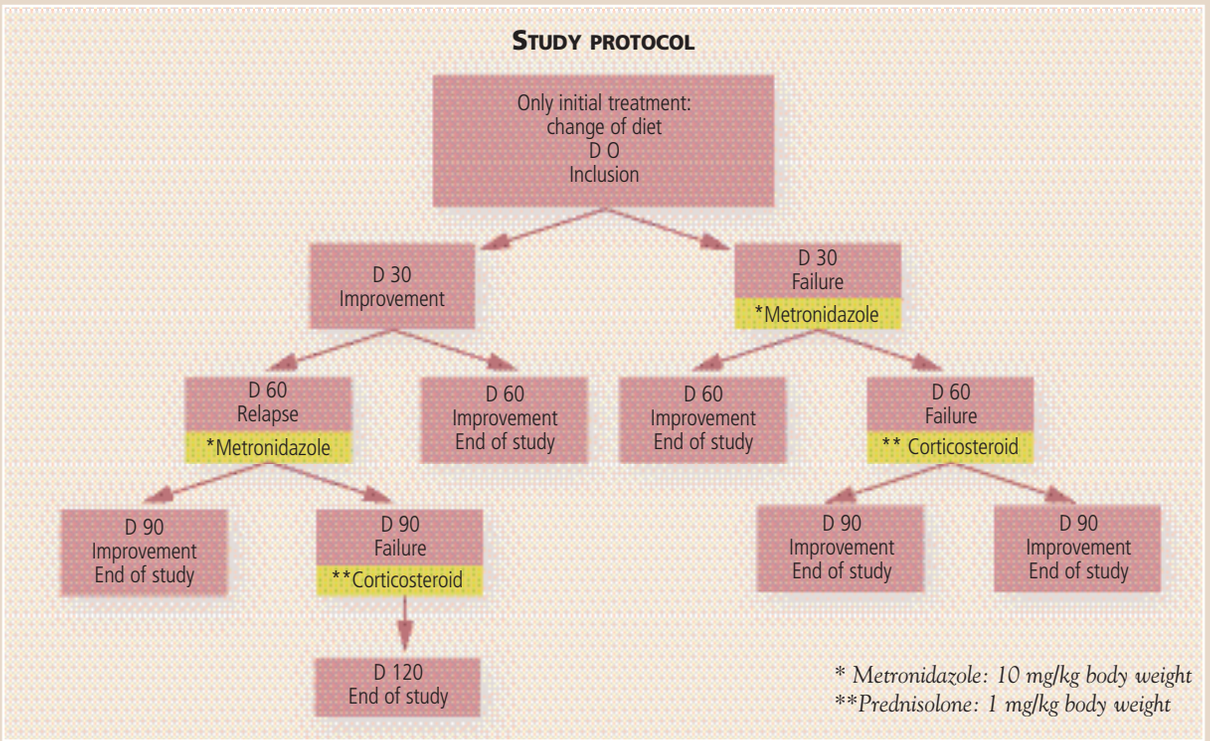
A soy protein hydrolysate-based diet for the nutritional management of canine IBD: a preliminary study

Dietary hypersensitivity is proposed as one possible cause of IBD. The purpose of this study was to assess, in field conditions, the effect of a hypoallergenic diet formulated with soy protein isolate hydrolysate *(Royal Canin, hypoallergenic DR 21)* for the treatment of IBD.

Materials and methods

Eight dogs were included in the study, seven of which were in normal body condition at the start of the study. The inclusion criterion for the study was IBD confirmed by histological evaluation of intestinal biopsies associated with at least one clinical sign (diarrhea, vomiting or weight loss).

Initially the diet was given as the only treatment. If the diet alone did not improve the clinical signs after 4 weeks of therapy, metronidazole followed by prednisolone therapy was used. Clinical and fecal assessments were performed every 2 weeks.



Endoscopic and histological assessments of the intestinal mucosa were performed before and at least 8 weeks after inclusion in the study.

Results

Mean fecal score dramatically improved with dietary therapy (1.5 ± 0.53 vs 3.62 ± 0.52, p< 0.01, Student's t-test). In 6 of 8 dogs which initially had abnormal bowel movements, the mean number of bowel movements improved from 4.12 ± 1.73 /day to 2.5 ± 0.53/day (p<0.05, Student's t-test). Recovery was observed in all dogs between 4 and 16 weeks following introduction of the diet but 3 of 8 dogs required additional treatment.

During endoscopic examination, no obvious improvement of the intestinal mucosa was noted except in the colon of 1 dog. General histological scores were not different before (3.8 ± 0.9) and after treatment (3.4 ± 0.5) but for 2 of 8 dogs the infiltrate in the intestinal mucosa was reduced.

Conclusion

These preliminary results suggest that a soy isolate hydrolysate diet could be useful in the clinical management of IBD, even in severe cases, and might be a good alternative to the use of corticosteroids.

Reference

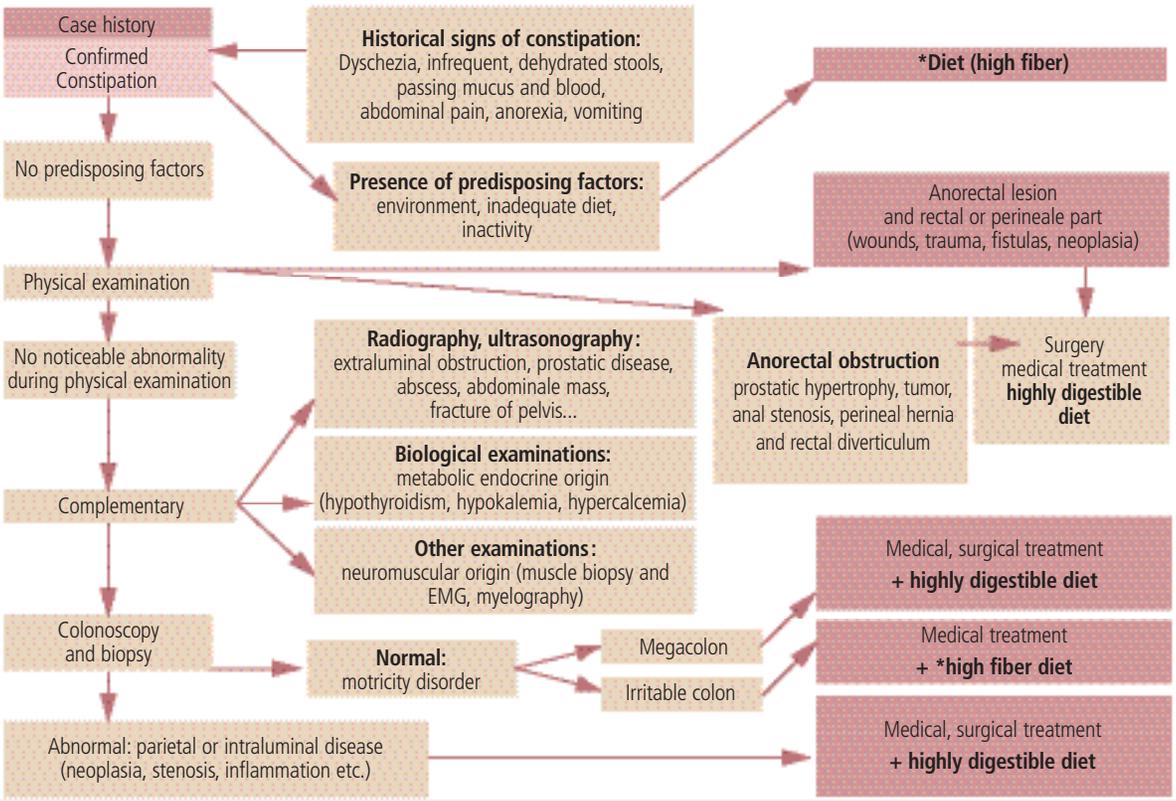
Dossin O, Semin MO, Raymond I et al - Soy hydrolysate in the management of canine IBD: a preliminary study. Proceedings of the 12th European Society of Veterinary Internal Medicine Congress 2002; Munich, Germany: 167.

Key points
to remember:

Constipation

Constipation is characterized by increased fecal transit time. Clinically, this leads to less frequent, sometimes painful defecation and the passing of dehydrated, abnormally hard and dry stools. This syndrome, quite frequent in veterinary medicine, is often considered as a disorder of intestinal transit. However the possible reasons for constipation are numerous and some of these may result in an occlusive syndrome and irreversible lesions in the large intestine.

Diagnostic evaluations should be chosen in a logical way and according to clinical observations. Nutritional therapy is essential in patients with recurrent constipation and those with already severe lesions in the large intestine (megacolon). Finally the nutritional approach should take into account the etiology of constipation.



* *The proportion of dietary fiber in dry foods varies quite considerably. It appears that dietary fiber intake of approximately 5-7% guarantees regular transit in most dogs. In animals with a tendency to constipation, this intake may be increased to 10-15%. Diets containing more than 15% fiber may paradoxically induce constipation.*

Important remark

For legal reasons, the fiber content stated on dog food packaging relates to the crude fiber content, which significantly underestimates the actual fiber content of the food, especially if it has not been lignified to any great degree. The total dietary fiber stated in technical documentation or available on request from the manufacturer is a more reliable estimation.

Focus on:

Psyllium

The various species of psyllium (Plantago ovata, Plantago ispaghula) *are plants that originated in India.*

Psyllium is a plant traditionally used to treat digestive complaints in many countries. It takes its name from the Greek *psyllia*, which means flea. The seeds, black or golden depending on the species, resemble tiny aphids called psyllids or jumping plant lice. Psyllium seeds are odorless and almost flavorless.

The effect of psyllium is related to the great capacity of the fiber, which makes up the testa, to retain water. Due to this fiber, which is 65% mucilage, the seeds are able to bind up to ten times their own weight in water. When only psyllium testae are used the swelling index is between 70 and 85!

Psyllium is well known for its laxative properties. The psyllium fiber is only partially fermented by the colonic microflora. The mucilages work as a sponge by swelling as they bind the water to create a viscous gel. By this mechanism, psyllium has an antidiarrheic effect by increasing the viscosity of the intestinal chyme.

Lubrication induced by the psyllium gel stimulates peristalsis (thus limiting the risks associated with the presence of any toxins), facilitating the propulsion of the contents of the colon and fecal elimination.

Psyllium acts at all levels:

- It slows down gastric emptying *(Xiahong et al, 2005)*, which assists the proper digestion of proteins:
- It combats diarrhea by regulating the progression of chyme in the small intestine and fecal matter in the colon *(Bliss et al, 2001)*. Psyllium is widely used in food for sled dogs to prevent stress diarrhea:
- It reduces constipation by facilitating the elimination of stools *(Voderholzer, 1998)*.

Compared with other sources of fiber, the addition of psyllium produces larger, moister stools. However, being minimally fermentable, psyllium fiber does not alter the digestive tolerance.

The thick, outer-coat of the psyllium seed (testa) represents an interesting source of mucilages, which is soluble fiber that is able to bind up to ten times its weight in water.

References

Bliss DZ, Jung HJ, Savik K et al - Supplementation with dietary fiber improves fecal incontinence. Nurs Res 2001; 50(4): 203-13.

Voderholzer WA, Schatke W, Muhldorfer BE et al - Clinical response to dietary fiber treatment of chronic constipation. Gastroenterol 1997; 92: 95-98.

Xu X, Brining D, Rafiq A et al - Effects of enhanced viscosity on canine gastric and intestinal motility. J Gastroenterol Hepatol 2005; 20(3): 387-94.

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Nutrition of dogs with liver disease

1 - Diagnosis of liver diseases 143
2 - Epidemiology 145
3 - Physiopathology 147
4 - Adaptation of nutritional intakes 151
5 - Nutritional management adapted to the type of liver disease 157

Frequently asked questions - Nutrition of dogs with liver disease 162
References 164
Examples of home-prepared diets adapted to the treatment for liver diseases 166
Royal Canin Nutritional Information 168

Nutrition of dogs with liver disease

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Carolien graduated from Utrecht State University and completed an internship at the University of Pennsylvania and a residency and Masters degree at Ohio State University. In between she worked in referral small animal practice. She joined the University of Liverpool in 1985 as a Lecturer in Small Animal Medicine and moved in 1990 to the Royal Veterinary College, where she later became a Senior Lecturer. She is now an independent consultant. Carolien has published more than 100 scientific papers and book chapters, and has lectured widely in the UK and abroad. Her major research interests are in gastroenterology and liver disease. She is a Diplomate of the American College of Veterinary Internal Medicine (ACVIM), a Foundation Diplomate of the European College of Veterinary Internal Medicine - Companion Animals (ECVIM-CA), and a RCVS Diplomate in Small Animal Medicine. Carolien has been a foundation Board member of the ECVIM-CA and a member of the RCVS Small Animal Medicine and Surgery Board, and a Diploma examiner for both.

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Vincent Biourge graduated from the Faculty of Veterinary Medicine of the University of Liège (Belgium) in 1985. He stayed as an assistant in the nutrition department for 2 more years before moving to the Veterinary Hospital of University of Pennsylvania (Philadelphia, USA) and to the Veterinary Medical Teaching Hospital of the University of California (Davis, USA) as a PhD/resident in Clinical nutrition. In 1993, he was awarded his PhD in Nutrition from the University of California and became a Diplomate of the American College of Veterinary Nutrition (ACVN). In 1994, he joined the Research Center of Royal Canin in Aimargues (France) as head of scientific communication and nutritionist. Since 1999, he is in charge of managing the nutritional research program of Royal Canin. Dr. Biourge has published more than 30 papers, and regularly present scientific papers as well as guest lectures at International Veterinary Medicine and Nutrition meetings. He is also a Diplomate of the European College of Veterinary Comparative Nutrition (ECVN).

The liver has many complex functions which is reflected in the multitude of pathophysiological derangements that can occur in liver disease. The liver has however a huge reserve capacity and great potential to regenerate, and clinical signs occur only when this reserve is exhausted by progressive disease.

The liver is essential for the digestion, absorption, metabolism and storage of most nutrients **(Table 1)**. Malnutrition is therefore common in liver disease, and the lack of nutrients can also aggravate it *(Center, 1999b; Laflamme, 1999)*. Nutritional support is the keystone in the management of dogs with liver disease. It is therefore imperative to maintain nutrition status.

In acute liver disease, treatment is mainly aimed at supporting the patient during this process of hepatic regeneration, and patients may fully recover provided there has only been a single sublethal insult to the liver.

In chronic liver disease, the emphasis is on supporting the limited remaining metabolic capabilities of the liver, to minimize complications and to prevent progression of liver disease, e.g. by curtailing oxidative reactions. Early nutritional intervention in the management of malnutrition, ascites, and hepatic encephalopathy (HE) is especially important and can reduce morbidity and mortality.

TABLE 1 - MAJOR HEPATOBILIARY FUNCTIONS

Protein metabolism	Synthesis of albumin, acute phase proteins, coagulation factors Regulation of amino acid metabolism Detoxification of ammonia and synthesis of urea
Carbohydrate metabolism	Glycogen metabolism and storage Glucose homeostasis Gluconeogenesis
Lipid metabolism	Synthesis of triglycerides, phospholipids, cholesterol Lipid oxidation and ketone production Lipoprotein synthesis Excretion of cholesterol and bile acids
Vitamin metabolism	Storage and activation of vitamins B, K Activation of vitamin D Vitamin C synthesis
Hormone metabolism	Degradation of polypeptides and steroid hormones
Storage functions	Vitamins, lipids, glycogen, copper, iron, zinc
Digestive functions	Bile acid synthesis and enterohepatic circulation Digestion and absorption of lipids Absorption of vitamins A, D, E, K
Detoxification and excretion	Ammonia, drugs and toxins

1 - Diagnosis of liver diseases

► History and clinical signs

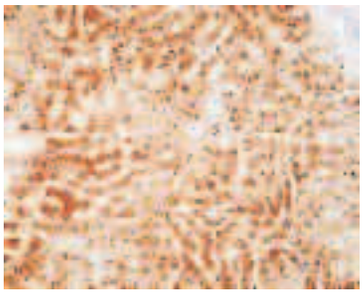
Historical findings in dogs with liver disease are often vague and non-specific, and rarely evident until liver disease is advanced. The onset of clinical signs may be acute, even though this may be the end result of liver disease that has been progressing for many weeks or months.

Physical examination findings are often variable and non-specific. Jaundice, abnormal liver size and ascites are the findings most suggestive of liver disease, but these may also be seen in other diseases not related to the liver. The only sign specific for liver disease is acholic (grey) feces, which may be found in complete extrahepatic bile duct obstruction **(Table 2)**.

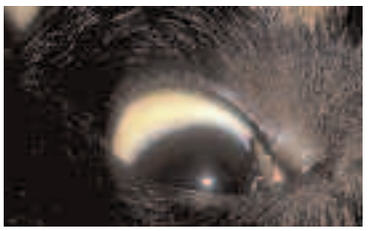
TABLE 2 - CLINICAL FINDINGS IN LIVER DISEASE

Early signs	Anorexia Weight loss Lethargy Vomiting Diarrhea Polydipsia/polyuria
Severe hepatic insufficiency	Jaundice Ascites Hepatic encephalopathy Coagulopathy (excessive bleeding upon blood sampling or liver biopsy, melena)
Major bile duct obstruction	Acholic (pale) feces*

** specific for liver disease, but rarely observed*



Liver biopsy
from a Bedlington Terrier with chronic hepatitis showing extensive copper accumulation (rhodanine stain; the copper grains show up as black).



Jaundice in a Doberman Pinscher with advanced chronic hepatitis.

► Differential diagnosis

> Jaundice

This is not a common sign of liver disease, and signifies severe disease. It may however also be due to hemolysis or post-hepatic causes (such as compression of the common bile duct, commonly seen in acute pancreatitis, or obstruction, due to neoplasia or cholelithiasis) *(Leveille-Webster, 2000)*.

> Altered liver size

In dogs, most chronic liver diseases result in reduced liver size, and even acute diseases may cause little change in size. Hepatomegaly is uncommon but may be seen in hepatic neoplasia and congestion, and with secondary involvement in metabolic disease (e.g. hyperadrenocorticism).

> Ascites

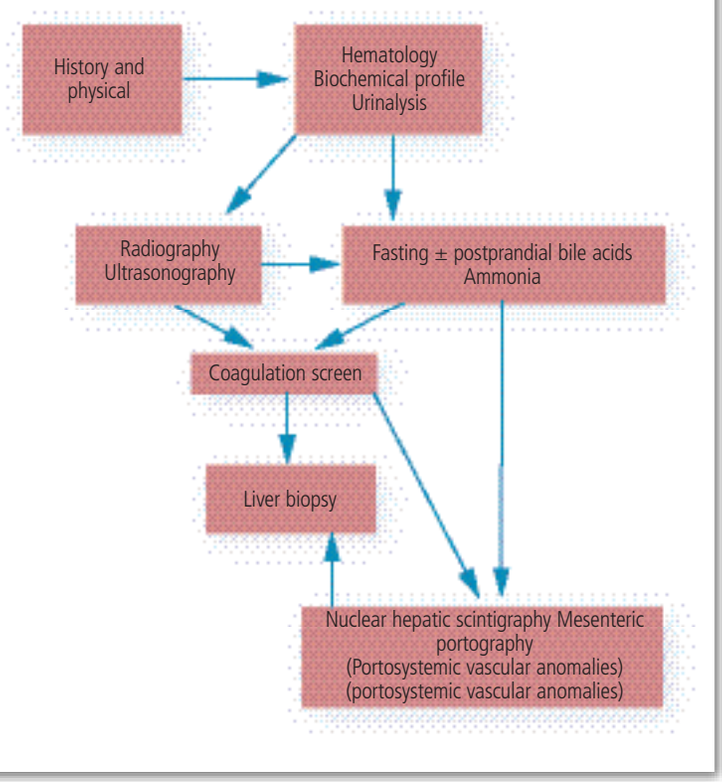
This is a common occurrence in dogs with severe chronic liver disease, and is mostly caused by portal hypertension. It is a modified transudate, as also seen in congestive heart failure and neoplasia. It has to be distinguished from transudate, which may occur in protein-losing enteropathy and nephropathy, and from exudates, as in peritonitis, hemorrhage, and ruptured biliary or urinary tract.

► Laboratory testing

Laboratory assessment is essential to identify hepatic disease, assess severity and monitor progression; however, laboratory tests will not identify specific diseases and may be influenced by non-hepatic disease. Baseline tests (hematology, serum biochemistries and urinalysis) are useful in initial screening to look for evidence of hepatic disease as well as other abnormalities **(Figure 1)**.

Serum bile acid analysis is a sensitive and specific indicator of hepatic function, useful for the diagnosis of subclinical liver diseases and portosystemic shunts. Measurement of fasting serum ammonia can document the presence of HE. Coagulation tests are indicated in animals with a bleeding tendency and prior to biopsy (blind, ultrasound-guided or surgical) or a mesenteric portography if a portosystemic shunt is suspected.

FIGURE 1 - DIAGNOSIS OF LIVER DISEASE



► Diagnostic imaging

Survey abdominal radiographs provide an idea about liver size and shape, but ultrasonography gives more specific information about liver parenchyma, bile ducts and blood vessels. Operative mesenteric portography can visualize vascular anomalies; nuclear hepatic scintigraphy is non-invasive but requires specialized equipment and the use of radioactive tracers.

► Biopsy

Histologic examination of liver tissue is often essential to clarify the cause of abnormal liver tests and/or size, to define whether it is a primary or secondary problem, and determine hepatic copper levels. It may also be used to monitor progression or response to treatment when non-invasive testing is inadequate.

2 - Epidemiology

► Causes

> Non-infectious inflammatory liver diseases

These represent one of the most common manifestations of liver disease in the dog **(Table 3)** *(Center, 1996a; Watson, 2004)*. The liver has a very active reticuloendothelial system and plays an important role in blocking substances from the gastrointestinal tract that have been transported by the portal vein. The liver is also sensitive to endogenous and exogenous toxins, and drugs. Immune-mediated mechanisms may furthermore lead to the perpetuation of inflammation following hepatic damage caused by any agent *(Center, 1999b)*. Primary autoimmune hepatitis, which is an important disease in humans, has however not been conclusively demonstrated to exist in dogs.

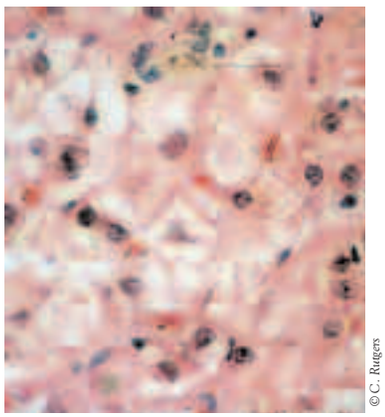
> Infectious inflammatory liver diseases

Viral causes are not important in dogs, in contrast to man. However, infections with 'atypical' leptospires (i.e. those not covered in routine vaccinations) may be a more significant cause of chronic hepatitis than previously assumed *(Adamus et al, 1997; Bishop et al, 1979)*.

> Non-inflammatory liver diseases

Vacuolar hepatopathies are a vague term used to describe a non-inflammatory liver disease that occurs in conjunction with cytoplasmic vacuoles in hepatocytes *(Cullen, 2001)*. Generally, vacuole formation is a nonspecific response to hepatic injury, with glucocorticoid excess (either endogenous or exogenous) the main cause in dogs.

Clinically more important are liver diseases related to vascular anomalies, such as congenital portosystemic shunts and portal hypoplasia (e.g. microvascular dysplasia and juvenile fibrosing liver disease). Neoplasia, commonly secondary, is less frequent.



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Steroid hepatopathy.

TABLE 3 - HEPATOBILIARY DISEASES IN THE DOG

Inflammatory liver disease	Non-inflammatory liver disease	Biliary disease
Non-infectious Chronic hepatitis* Cirrhosis/fibrosis* Toxic and drug-induced*	**Vacuolar hepatopathies** Degenerative/storage Glucocorticoid therapy* Diabetes mellitus Hepatocutaneous syndrome Chronic illnesses*	**Congenital cystic disease** **Cholestasis** - **Intrahepatic** (secondary to hepatocellular disease)* - **Extrahepatic** (bile duct obstruction due to cholelithiasis, neoplasia or compression by pancreatic disease*) **Cholangitis/cholecystitis**
Infectious Bacterial (leptospirosis, abscess, cholangiohepatitis) Viral (ICH Infectious canine hepatitis)	**Portal vascular anomalies** Congenital portosystemic shunts* Portal vein hypoplasia (incl. microvascular dysplasia and juvenile fibrosing liver disease)* Lobular dissecting hepatitis Intrahepatic arteriovenous fistula	
	Neoplasia (primary or metastatic*)	

** Common diseases in the dog*

TABLE 4 -BREED PREDISPOSITION IN LIVER DISEASE

Copper associated liver disease
Bedlington Terrier*
West Highland White Terrier
Sky Terrier
Dalmatian
Doberman Pinscher
Chronic hepatitis
Cocker Spaniel
Doberman Pinscher
Labrador Retriever
Standard Poodle
Congenital portosystemic shunts
Irish Wolfhound*
Cairn Terrier*
Yorkshire Terrier*
Maltese Terrier

* *Inheritance proven.*

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Chronic hepatitis in Doberman Pinschers is associated with increased liver levels of copper and iron, which is a consequence of reduced biliary copper excretion that has a different genetic basis than the disease in Bedlington terriers (Spee et al, 2005).

► Predisposition and risk factors

> Chronic hepatitis

The cause of chronic hepatitis in dogs is usually unknown. Some breeds are however more likely to suffer from chronic hepatitis than others **(Table 4)**. A familial predisposition has been described in Bedlington Terriers, West Highland White Terriers, Skye Terriers, Doberman Pinschers, Cocker Spaniels and Labrador Retrievers *(Johnson, 2000)*. The increased incidence of chronic hepatitis in certain breeds suggests a possible genetic basis.

So far, the genetic defect has only been demonstrated in copper storage hepatopathy in the Bedlington *(Johnson et al, 1980)*. In this breed, copper storage hepatopathy is autosomal recessive.

Copper accumulates in the liver due to an inherited metabolic defect in biliary copper excretion; the increased hepatic copper content then causes hepatocellular injury, chronic hepatitis and cirrhosis *(Twedt et al, 1979)*. The genetic defect was initially demonstrated via a DNA microsatellite marker *(Yusbasiyan-Gurkan et al, 1997; Holmes et al, 1998; Rothuizen et al, 1999)*, but recently the locus of the abnormal copper toxicosis gene has been identified *(van De Sluijs et al, 2002)*. Biopsy and determination of hepatic copper content are still essential for the diagnosis, although a DNA microsatellite marker test is now available to detect both affected and carrier Bedlington Terriers. This test is not 100% accurate (due to recombination), but offers a simple procedure that can be used by breeders to reduce the incidence of this disease.

It is sometimes difficult to establish whether copper accumulation in the hepatocytes is a cause of hepatic disease or a consequence of reduced biliary excretion of copper *(Rolfe & Twedt, 1995; Thornburg, 2000)*. Copper accumulation in association with liver disease has been especially demonstrated in Doberman Pinschers, Dalmatians, West Highland White Terriers and Skye Terriers *(Rolfe & Twedt, 1995)*. The mode of inheritance in these breeds is as yet unknown *(Rolfe & Twedt, 1995; Webb et al, 2002)*. Chronic hepatitis in Cocker Spaniels is often associated with copper accumulation *(Johnson, 2000)*. The copper-storage hepatopathy that was described in young Dalmatians may share some similarities with the disease in Bedlington Terriers, but this needs further investigation *(Webb et al, 2002)*.

> Portovascular anomalies

Congenital intrahepatic portosystemic shunts are more common in large breed dogs. They have been shown to be autosomal recessive inherited in Irish Wolfhounds *(Rothuizen et al, 2001)*. In contrast, most congenital extrahepatic shunts occur in small dogs. They are inherited via a polygenic trait in Cairn Terriers *(Rothuizen et al, 2001)*, and are likely to be inherited in Yorkshire Terriers *(Tobias, 2003; Tobias & Rohrbach, 2003)*.

Portal vein hypoplasia (microvascular dysplasia) occurs more commonly in small breed dogs *(Van den Ingh et al, 1995)*. Yorkshire and Cairn Terriers are both predisposed to congenital portosystemic shunts as well as microvascular dysplasia.

> Drugs

Certain therapeutic agents may provide a risk factor for development of acute or chronic liver disease. Chronic hepatitis has been most commonly associated with anticonvulsant drugs (primidone, phenobarbital, phenytoin), and diethylcarbamazine oxibendazole. Acute toxic injury has been described with several drugs, including carprofen, mebendazole and potentiated sulfonamides (trimethoprim-sulfadiazine) *(Hooser, 2000; Trepanier et al, 2003)*. In addition, excess glucocorticosteroids, either exogenous or endogenous as in hyperadrenocorticism, frequently cause a typical vacuolar hepatopathy (steroid hepatopathy).

3 - Physiopathology

Hepatocellular dysfunction can cause multiple metabolic disturbances, which are compounded by malnutrition.

Hepatocellular dysfunction is associated with a number of metabolic disturbances that alter the utilization of nutrients **(Table 5)**. Alterations in protein, carbohydrate and fat metabolism reflect the influence of neuroendocrine mediators and are particularly prominent in the fasting state. Serum concentrations of glucagon and insulin are increased due to reduced hepatic degradation, with the effects of hyperglucagonemia predominating. This causes a more rapid depletion of hepatic glycogen stores, which results in premature protein catabolism to supply amino acids for gluconeogenesis. Fasting hypoglycemia is in many cases prevented by a compensatory decrease in peripheral glucose oxidation and increase in gluconeogenesis. Peripheral lipolysis is also enhanced, generating fatty acids for energy production *(Marks et al, 1994)*. Prolonged inadequate food intake in dogs with chronic liver disease will therefore result in progressive loss of fat and muscle, which contributes to the malnutrition found commonly in liver disease **(Figure 2)**.

TABLE 5 - NUTRITIONAL CONSEQUENCES OF LIVER DISEASE

Substrate	Clinical effect
Carbohydrate metabolism	
Decreased hepatic glycogen storage	Hypoglycemia (acute liver disease)
Increased gluconeogenesis	Muscle wasting, malnutrition
Glucose intolerance and insulin resistance	Hyperglycemia (end-stage liver disease)
Fat metabolism	
Increased lipolysis	Malnutrition
Decreased excretion of bile acids	Malabsorption of fats and fat-soluble vitamins
	Steatorrhea
	Coagulopathy
Protein metabolism	
Increased catabolism	Malnutrition, HE*
Enhanced peripheral utilization of BCAA	Contributory to HE**
Impaired urea cycle	HE*
Decreased albumin synthesis	Hypoalbuminemia
Decreased synthesis of coagulation factors	Coagulopathy
Vitamin metabolism	
Decreased storage	Oxidant damage (vitamin E)
Decreased absorption of vit. A, D, E, K (cholestasis)	Coagulopathy (vitamin K)
Minerals and trace elements	
Increased hepatic copper content (copper hepatotoxicosis)	Oxidative damage, hepatitis
	Decreased zinc levels
	Decreased antioxidant protection
Detoxification and excretion	
Decreased excretion of bilirubin	Jaundice
Decreased detoxification (drugs, ammonia)	HE*

* *HE: hepatic encephalopathy*

Figure 2 - Etiology of malnutrition in liver disease

Decreased intake
Anorexia, nausea, vomiting
Unpalatable diet

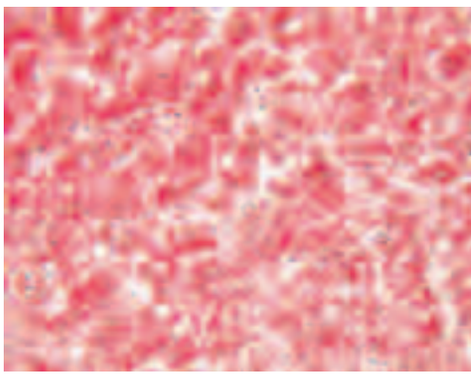
Malabsorption
Cholestasis
Enteropathy (portal hypertension)

Increased requirements
Hypermetabolism
Increased protein breakdown

The liver has a large functional reserve and is able to preserve homeostasis and minimize catabolism for a long time, despite extensive damage. The appearance of metabolic alterations and clinical signs of liver dysfunction usually signify advanced disease.

► Carbohydrate, fat and protein metabolism

Carbohydrate – The liver is responsible for the maintenance of blood glucose levels because it is the primary organ for glucose storage (as glycogen) and provides glucose during fasting (through glycogenolysis). Liver disease results in more rapid depletion of hepatic glycogen stores, and glucose needs are then supplied through catabolism of muscle proteins to amino acids. This causes muscle wasting and increases the nitrogen load, which may potentiate hyperammonemia and hepatic encephalopathy *(Bauer, 1996)*. Fasting hypoglycemia may occur in severe acute liver disease and portosystemic shunts due to inadequate glycogen storage and gluconeogenesis. In contrast, a mild hyperglycemia can occur in cirrhosis due to reduced hepatic clearance of glucocorticosteroids.



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Microscopic view of hepatic glycogen reserves (PSA X 40).

Lipid – The liver has an important function in the synthesis, oxidation and transport of lipids. Liver disease causes an increase in peripheral lipolysis in order to generate fatty acids for energy production, resulting in fat depletion, while the rate of hepatic fatty acid oxidation increases *(Bauer, 1996)*.

Through its synthesis of bile acids and secretion of bile, the liver plays an important role in the digestion and absorption of lipids and fat-soluble vitamins (A, D, E, K). Fat malabsorption is nevertheless not common in liver disorders, since some dietary tri glycerides still can be absorbed in the complete absence of bile acids *(Gallagher et al, 1965)*.

In severe cholestatic liver disease, the reduced availability of enteric bile acids can cause malabsorption of fats, fat-soluble vitamins and some minerals. The liver is the only site of cholesterol synthesis. Hypocholesterolemia may occur in acute liver failure and portosystemic shunts, whereas hypercholesterolemia is seen in obstructive jaundice.

Protein – The liver has an essential role in protein synthesis and degradation. It controls serum concentrations of most amino acids, with the exception of branched chain amino acids (BCAA), which are regulated by skeletal muscle. The liver synthesizes the majority of circulating plasma proteins and is the only site of albumin synthesis.

Albumin has a relative priority for synthesis; hypoalbuminemia does not occur until the disease is chronic, and is compounded by malnutrition.

The liver furthermore synthesizes the majority of coagulation factors. Lack of synthesis in liver failure may lead to prolonged coagulation times (↑ PT, ↑ PTT) but only when factors are reduced to less than 30% of normal. Disseminated intravascular coagulation (DIC) is however the most common coagulopathy associated with liver disease, and is most likely to cause spontaneous hemorrhage *(Center, 1999b)*. Decreased absorption of vitamin K in chronic biliary obstruction may also lead to prolonged clotting times, but these can be corrected by parenteral administration of vitamin K1.

In acute disease, functional proteins in skeletal muscle and other tissues are catabolized to meet the demands for synthesis of host defense proteins. In chronic liver disease, the etiology of the catabolic state is multifactorial *(Mizock, 1999)*. Plasma concentrations of aromatic amino acids (AAA) increase in liver disease due to increased peripheral release and decreased hepatic clearance, but BCAA levels decrease because of enhanced utilization as an energy source by muscle. This imbalance between AAA and BCAA has been implicated in the pathogenesis of HE, although its significance is now being questioned *(Mizock, 1999)*.

L-carnitine is an essential cofactor for transport of long-chain fatty acids from the cytoplasm into mitochondria **(Figure 3)**. The liver is a central organ for whole body L-carnitine homeostasis, and its metabolism can be impaired in multiple ways in chronic liver disease. L-carnitine deficiency in liver disease may occur due to insufficient intake of carnitine or its precursors, reduced hepatic synthesis, or increased turnover *(Krahenbuhl & Reichen, 1997)*. L-carnitine supplementation has a protective influence against the development of ammonia-induced HE in experimental animals *(Therrien et al, 1997)* and may be protective against the development of hepatic lipidosis in cats *(Twedt, 2004)*, but its usefulness in dogs is still undetermined.

THE LIVER CONTROLS MANY METABOLIC FUNCTIONS. MOST IMPORTANTLY, IT:

- maintains homeostasis of blood levels of glucose, amino acids and trace elements
- synthesizes albumin and coagulation factors
- detoxifies and excretes endogenous and exogenous waste products (i.e. NH_3, drugs and toxins
- regulates immune function
- regulates hormone balance.

Protein catabolism is increased in all liver diseases. Protein breakdown is augmented in patients with infections or gastrointestinal hemorrhage, which can precipitate hepatic encephalopathy due to increased ammonia production.

► Micronutrient metabolism

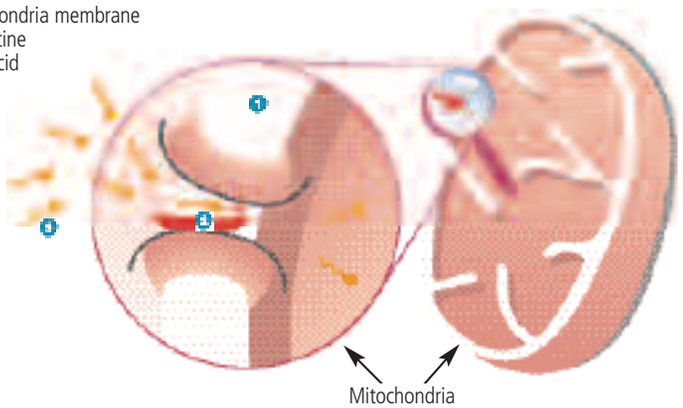
> Vitamins

The liver stores many vitamins and converts them to metabolically active forms. Liver disease can therefore result in deficiency of vitamins stored in the liver, such as B-complex vitamins. Vitamin deficiencies are augmented by increased demands for hepatocyte regeneration, reduced metabolic activation and increased urinary losses. B-complex deficiencies are common in people with liver disease and probably also occur in dogs.

Vitamin C can be synthesized in dogs but is not stored. Its synthesis may be affected by liver disease *(Center, 1996a)*.

FIGURE 3 - MODE OF ACTION OF L-CARNITINE

1 - Mitochondria membrane
2 - L-carnitine
3 - Fatty acid



L-carnitine is incorporated into the enzyme chain needed to convey long-chain fatty acids though the mitochondrial membrane.

This permits the transfer of fatty acids to the interior of the mitochondria. In case of deficiency, the transport system is disturbed and the production of energy is compromised.

Deficiencies of the fat-soluble vitamins A, D, E and K can occur in any condition that impairs the enterohepatic circulation of bile acids or fat absorption. Deficiencies of vitamins E and K are most significant. Vitamin E is an important antioxidant that protects lipoproteins and cell membranes from lipid peroxidation. In addition, Vitamin E deficiency, common in chronic liver disease *(Sokol, 1994)*, causes an increased susceptibility to oxidative stress, which perpetuates ongoing liver injury. Vitamin K deficiency is best recognized in dogs, since it develops rapidly and is readily detectable by measurement of coagulation times *(Leveille-Webster, 2000)*.

> Minerals and trace elements

Iron, zinc and copper are the main trace elements stored in the liver. Both iron and copper can be hepatotoxic in high levels, but only copper appears to be a potential hepatotoxin in the dog.

Zinc deficiency is common in chronic liver disease, due to poor dietary intake, reduced intestinal absorption and increased urinary loss. Deficiency results in low resistance to oxidative stress and reduces ammonia detoxification in the urea cycle, thus promoting hepatic encephalopathy.

The liver is central to the maintenance of copper homeostasis, since it takes up most of the absorbed copper and regulates the amount retained by controlling excretion through the biliary tract. Copper may accumulate in the liver as a result of a primary metabolic defect in copper metabolism, or secondary to decreased hepatic copper excretion associated with longstanding cholestasis *(Thornburg, 2000)*. In dogs with primary copper storage disease, copper accumulates in the liver before the development of hepatic damage or cholestasis. Excessive hepatic copper accumulation in Bedlington Terriers has been shown to result in mitochondrial injury, generation of reactive oxygen species and free radicals, and hepatocellular damage *(Sokol et al, 1994)*.

Zinc is an essential cofactor in many biological processes. It has an antioxidant role, anti-fibrotic properties, and enhances ureagenesis *(Dhawan & Goel, 1995; Marchesini et al, 1996)*.

Manganese is another trace element with antioxidant properties that can become deficient in cirrhosis.

> Antioxidants

There is mounting evidence that free radicals play important roles in many liver diseases. They damage cellular macromolecules via lipid peroxidation and other mechanisms, and can initiate and perpetuate liver injury. Their production is increased in inflammation, cholestasis, immunological events, and exposure to heavy metals and toxins *(Sokol et al, 1994; Feher et al, 1998)*. There is a wide range of both dietary and endogenous enzymatic antioxidant defense systems that hold the generation of free radicals in check. A disruption in this natural defense system results in oxidant stress **(Figure 4)**.

This type of disruption may occur during liver disease **(Table 6)**.

► Detoxification and excretion

The liver is the primary site of detoxification of both endogenous by-products of the intermediary metabolism (e.g. ammonia) and exogenous substances absorbed from the gastrointestinal tract. All of these may play a role in the etiology of HE. The precise pathogenesis is likely to be multifactorial, and may be based on inter-related changes in reduced hepatic clearance of gut-derived substances such as ammonia, altered amino acid neurotransmission and endogenous benzodiazepines *(Maddison, 2000)*. Ammonia is the substance most commonly linked with HE, although serum ammonia levels correlate poorly with the degree of HE **(Figure 5)**.

TABLE 6 - ANTIOXIDANT DEFENSES

Dietary antioxidants	Endogenous enzyme systems
Vitamin E Vitamin C Taurine Carotenoids	Superoxide dismutase Glutathione peroxidase Catalase

FIGURE 4 - ETIOLOGY OF OXIDANT STRESS IN LIVER DISEASE

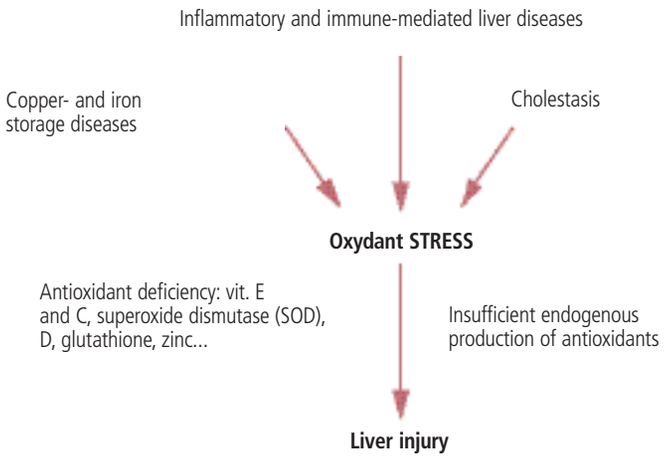
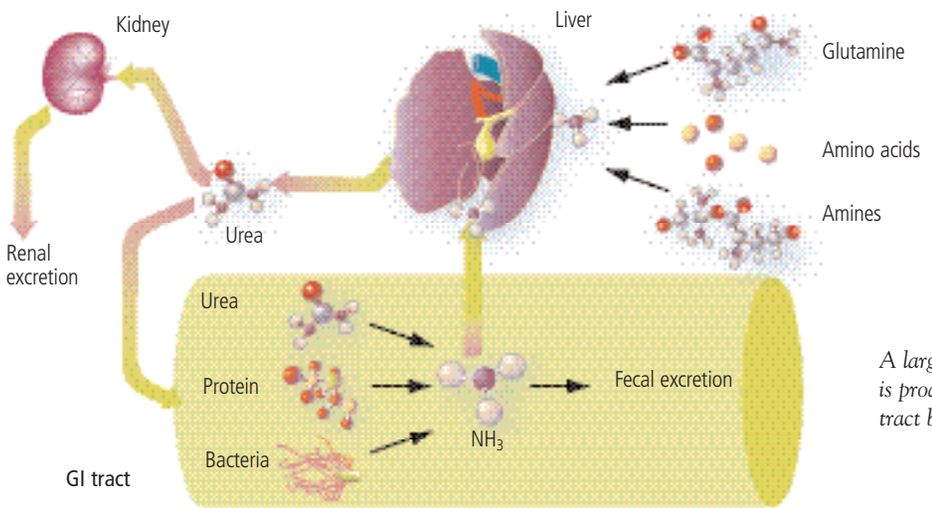


FIGURE 5 - AMMONIA METABOLISM



A large part of ammonia is produced in the gastrointestinal tract by urease-producing bacteria.

4 - Adaptation of nutritional intakes

Diets for animals with liver disease are best formulated on an individual basis, with consideration given to the type and origin of the liver disease and the extent of liver dysfunction *(Laflamme, 1999)*. Care must be taken to avoid overwhelming the remaining metabolic capacities of the diseased liver. The diet must be highly palatable and provide adequate energy, protein, fat, and all essential micronutrients. It is furthermore becoming increasingly evident that it is possible to modulate metabolic and pathological processes through the use of specific nutrients and metabolites.

THE AIMS OF DIETARY MANAGEMENT OF LIVER DISEASE ARE:

(1) to supply adequate energy and nutrients to fulfill basic requirements and prevent malnutrition
(2) to limit further liver damage by preventing accumulation of copper and free radicals
(3) to support hepatocellular regeneration
(4) to prevent or minimize metabolic complications, such as hepatic encephalopathy and ascites

Dogs with liver disease are usually catabolic and have increased energy requirements.

Provision of adequate high-quality proteins as well as calories is essential to ensure a positive protein balance and enable hepatic regeneration.

Protein levels are often inappropriately restricted in dogs with liver disease in order to manage possible hyperammonemia. In fact, protein requirements are at least normal or even increased, and many dogs with liver disease do not have hyperammonemia.

Correction and prevention of malnutrition are essential in the management of dogs with liver disease. Impaired dietary intake, malabsorption associated with severe cholestasis or portal hypertension, and catabolism all contribute to protein-calorie malnutrition, resulting in loss of muscle mass and hypoalbuminemia. Negative protein and energy balance promote HE, reduce immune response and increase mortality *(Center, 1998)*. Providing several small meals daily as well as a bedtime snack will improve nitrogen balance and carbohydrate availability. Tube feeding via a nasogastric, esophagostomy or gastrostomy tube may be required in dogs that are anorexic for more than 3-5 days.

► Energy

An adequate supply of both energy and protein is essential to prevent weight loss. The use of non-protein calories is important to prevent the use of amino acids for energy and reduce the need for gluconeogenesis. The diet should have a high energy density, since dogs with liver disease usually have reduced appetites. Normal daily maintenance needs in the dog are 110-130 kcal ME/kg$^{0.75}$ **(Table 7)** *(Bauer, 1996)*.

Normally, energy is best supplied in the form of fat since it is a highly palatable and concentrated source of energy. The diet's caloric density is proportional to its fat content. Dogs with liver disease can tolerate larger quantities of fat in the diet (30-50% of calories) than previously assumed *(Biourge, 1997)*.

TABLE 7 - INDICATIVE RANGE OF THE MAINTENANCE ENERGY REQUIREMENT OF DOGS BASED ON WEIGHT

Dog's weight (kg)	MER (kcal) = 110 kcal/kg BW$^{0.75}$	MER (kcal) = 130 kcal/kg BW$^{0.75}$
1	110	130
5	368	435
10	619	731
15	838	991
20	1040	1229
25	1230	1453
30	1410	1666
35	1583	1871
40	1750	2068
45	1911	2259
50	2068	2444
55	2222	2626
60	2371	2803
65	2518	2976
70	2662	3146
75	2803	3313
80	2942	3477

Fat restriction should only be considered in the few cases with severe cholestatic liver disease and suspected fat malabsorption, although adequate essential fatty acids must be provided.

Altered carbohydrate metabolism in dogs with liver disease can induce either hyper- or hypoglycemia. Hypoglycemia may be seen in acute fulminant liver disease, whereas hyperglycemia is infrequently seen in dogs with cirrhosis. Carbohydrates should not represent more than 45% of dietary calories, especially in dogs with cirrhosis, which may be glucose intolerant. Boiled white rice, and to a lesser degree pasta, are useful because of their high digestibility. Soluble fibers are useful in dogs with cirrhosis and a tendency to hyperglycemia, because they smoothen the postprandial glycemic response and prolong glucose delivery to the liver *(Center, 1998)*.

► Protein

> Dietary protein level

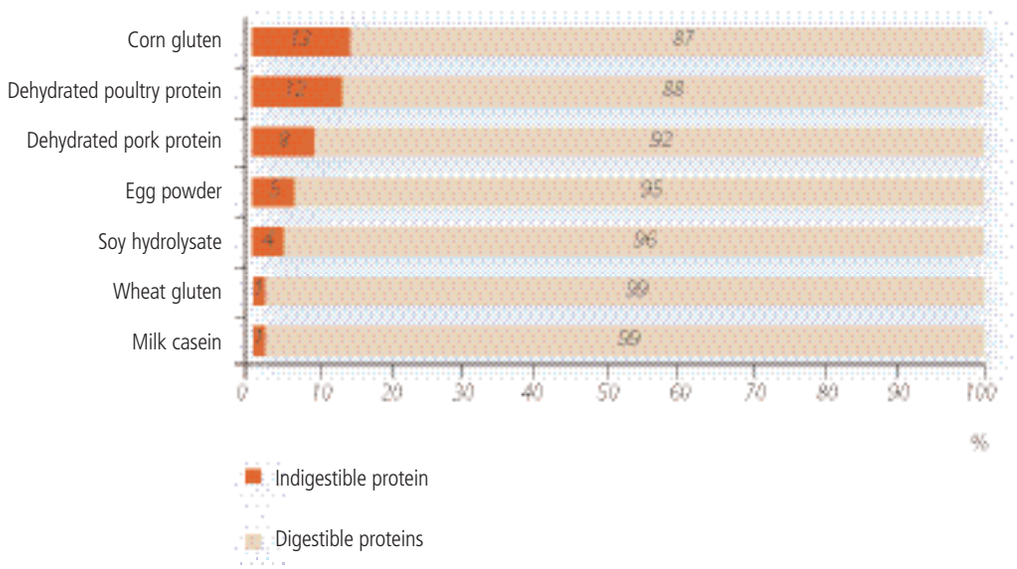
Incorrect protein restriction in dogs with liver disease causes catabolism of endogenous proteins and loss of muscle mass, both of which increase the potential for HE. Feeding of excessive and/or poor quality protein should also be avoided since this may aggravate signs of HE. In dogs, protein should represent as a minimum 10 to 14% of dietary calories, preferably at least 20%, and most dogs can tolerate higher quantities *(Biourge, 1997; Laflamme, 1999)*. The aim is to gradually increase the amount of protein in the diet, keeping the protein intake as close to normal as can be tolerated without precipitating signs of HE *(Michel, 1995)*.

> Protein type

The quality and source of the protein are important. High-quality proteins are better digested **(Figure 6)** and have an amino acid content close to the animal's requirements. Proteins of animal origin used to be considered as having a higher quality than proteins of plant origin, but soy isolates, wheat gluten and dairy products are better tolerated than meat proteins in people with HE, and this is probably also the case in dogs *(Strombeck et al, 1983)*. The potential benefit of vegetable proteins is attributed to their high fiber content, which causes a decrease in transit time and promotes incorporation and excretion of nitrogen in fecal bacteria, whereas the effect of dairy products is likely due to the influence of lactose on intestinal transit and pH *(Center, 1998)*. The

FIGURE 6 - COMPARABLE QUANTITIES OF INDIGESTIBLE PROTEIN IN DIFFERENT SOURCES OF PROTEIN USED IN DOG FOOD

(Source: Royal Canin)



benefit of soy and dairy proteins cannot be attributed to their amino acid composition, since this is similar to that of meat and fish proteins. Exclusive use of soybean or lactose-containing dairy protein diets is generally not advocated in dogs, since they have low palatability and can cause diarrhea, although this is less significant when purified proteins are used.

> The role of branched chain amino acids

BCAA supplementation has been used to improve protein and energy utilization and HE in people with advanced liver disease, since a decreased plasma ratio of BCAA to AAA has been considered an important pathogenetic factor in HE. Results however have been mixed *(Als-Nielsen et al, 2003; Marchesini et al, 2003)*, and it is now thought that any beneficial effect of BCAA supplementation is mostly related to improvement of the nutritional status, likely due to a stimulating effect on hepatocyte growth factor, favoring liver regeneration *(Bianchi et a, 2005)*. A study in dogs showed no efficacy on HE from a diet high in BCAA and low in AAA, and it was concluded that the total protein intake was more important than dietary amino acid profile *(Meyer et al, 1999)*. At present, BCAA supplements are unlikely to be of benefit in the management of canine liver disease, in view of their expense and questionable efficacy.

► Fiber

Moderate quantities of dietary fiber can have several beneficial effects in liver disease. Soluble fiber is of particular benefit in managing HE. Colonic fermentation of soluble fibers such as fructo-oligosaccharides, beet pulp and gums lowers the intraluminal pH and thus reduces the production and absorption of ammonia, the effect of which is similar to that of lactulose. Colonic fermentation also favors the growth of acidophilic bacteria that produce less ammonia and promote incorporation and excretion of ammonia in fecal bacteria (e.g. *Lactobacillus spp)*. Fiber (both soluble and insoluble) binds bile acids in the intestinal lumen and promotes their excretion. Insoluble fibers (lignin, cellulose, hemicellulose) act by normalizing transit time, whereas they can also prevent constipation and bind toxins. Diets containing soluble fiber and some insoluble fiber should therefore be useful in the long-term dietary management of dogs with HE *(Marks et al, 1994; Center, 1998)*.

► Minerals

> Potassium

Hypokalemia is a common precipitating cause of HE in dogs with liver disease *(Center, 1998)*. It occurs due to a combination of anorexia, vomiting or diarrhea, or excessive use of diuretics in the management of ascites. Diets for dogs with liver disease should therefore be potassium replete. Anorectic dogs may need supplementation by either intravenous administration of potassium chloride (10-40 mEq/500 ml fluids, depending on serum potassium) or oral potassium gluconate (0.5 mEq/kg once or twice daily). Potassium citrate should be avoided because of its alkanizing properties, since alkalosis can aggravate HE.

> Sodium

Abnormalities in sodium balance are less frequent, but moderate restriction of dietary sodium (less than 0.5 g/1000 kcal) is recommended in dogs with ascites and/or portal hypertension.

► Trace elements

> Zinc

Zinc is an essential trace metal involved in many metabolic and enzymatic functions of the body. Zinc benefits the urea cycle and central nervous system neurotransmission, has clear hepatoprotective effects against a variety of hepatotoxic agents, and has antioxidant functions *(Marchesini et al, 1996)*. Diets high in zinc (>43 mg/1000 kcal) are therefore useful for all patients with liver disease. Additional zinc supplementation may furthermore be useful to prevent hepatic copper

accumulation in copper hepatotoxicosis, since dietary zinc induces an increase in the intestinal metal-binding protein metallothionein. Dietary copper then binds to the metallothionein with a high affinity that prevents its transfer from the intestine into the blood. When the intestinal cells die and are sloughed, the metallothionein bound copper passes out through the stool, thus blocking copper absorption *(Sokol, 1996)*.

Dietary supplementation with zinc in patients with severe liver disease is done empirically with doses similar to those used in dogs with copper hepatopathies. Zinc is available as zinc acetate (2-4 mg/kg per day), sulfate, gluconate (3 mg/kg per day) and methionine. It is administered divided into two or three daily doses, and can be used as a dietary supplement *(Brewer et al, 1992)*. Zinc should be given on an empty stomach and should not be given in combination with copper chelators. Toxicity other than occasional vomiting is minimal and the acetate salt may cause fewer GI signs.

Many liver diseases result in increased generation of free radicals and oxidant stress. **Supplementation with antioxidants** will therefore help to reduce oxidative liver injury.

Zinc supplementation may reduce lipid peroxidation, has antifibrotic properties, prevents hepatic copper accumulation, and can reduce the severity of hepatic encephalopathy.

> Copper

Diets low in copper are recommended for dog breeds known to be prone to hepatic copper accumulation, especially Bedlington Terriers, and for dogs with documented increased hepatic copper **(Table 8)**. Restriction of dietary copper in itself does little to lower increased hepatic copper levels, but it is an additional adjunct to decoppering therapy such as d-penicillamine and zinc.

► Vitamins

> B Vitamins

B Vitamins are often empirically supplemented at double maintenance dose, based upon recommendations for people with liver disease.

> Vitamin C

The diet should contain adequate levels of vitamin C in order to compensate for failing hepatic synthesis and to take advantage of the antioxidant properties of vitamin C. Most commercial pet foods contain adequate amounts, and additional supplementation should only be necessary in case of severe fat malabsorption *(Laflamme, 1999)*. Mega doses of vitamin C should be avoided in dogs with copper storage hepatotoxicity, since it can function as a pro-oxidant in the presence of high concentrations of heavy metals *(Sokol, 1996)*.

TABLE 8 - FOOD CLASSIFICATION ACCORDING TO COPPER CONTENT

	Food stuffs rich in copper	Food stuffs moderately rich in copper	Food stuffs containing little copper
Animal protein sources	Lamb, pork, duck, organ meats, salmon, shellfish	Turkey Chicken All other fish	Beef Cheese Eggs
Starch sources	Dried beans, dried peas, lentils, soybeans, barley, wheat germ, bran	Whole wheat bread Potatoes	-
Vegetables	Mushrooms, broccoli	Beet, spinach, bean sprout	Fresh tomatoes

> Vitamin E

Vitamin E is an important endogenous free radical scavenger that protects against oxidative injury. There is evidence that oxidative damage from free radical formation plays an important role in the pathogenesis of liver disease. In particular, abnormal concentrations of bile acids, accumulation of heavy metals such as copper and iron, and inflammation can cause free radical generation and oxidant stress in the liver. Supplementation with vitamin E (400-600 IU/day) is especially indicated in cholestatic and copper-associated liver disease, but is likely also important in other forms of chronic liver disease. In severe cholestatic disease parenteral administration or an oral water-soluble form is preferred, since a certain level of enteric bile acids are required for its absorption.

Vitamin E supplementation can reduce free radical or oxidant injury in many types of liver disease and may prevent progression of disease.

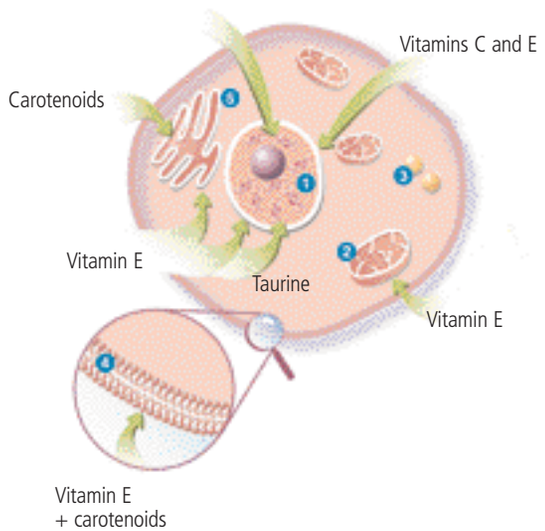
> Vitamin K

Vitamin K deficiency is mostly relevant in cholestatic disorders, although it may also become depleted in severe chronic liver disease. Vitamin deficiency is documented by demonstration of prolonged coagulation times and normalization after parenteral administration of vitamin K1. Coagulopathies secondary to vitamin K deficiency should be treated with two or three doses of vitamin K1 (0.5-1.0 mg/kg subcutaneously every 12 hours) *(Laflamme, 1999)*. The same dose can be given biweekly or monthly in chronic disorders in which continued repletion of vitamin K is required.

4E - Antioxidants

Chronic hepatitis and fibrosis, cholestatic liver disease and heavy metal hepatotoxicity are all known to be associated with increased generation of free radicals, and this is likely also the case in other types of liver disease *(Britton & Bacon, 1994; Feher et al, 1998)*. Adequate dietary levels of antioxidants such as vitamins E and C, as well as taurine, are essential to minimize oxidative injury. A combination of dietary antioxidants is better than a single one, since they appear to act synergistically **(Figure 7)**. A good balanced diet should also contain nutrients such as zinc, manganese and selenium, which are normally incorporated in enzymatic antioxidant systems *(Sokol, 1996)*.

FIGURE 7 - CELLULAR FREE RADICAL SCAVENGERS



The intake of highly diverse antioxidants acting in synergy helps improve the protection of the cell's various sensitive points and optimize protection against oxidation.

S-Adenosylmethionine (SAMe) may also be helpful in reducing oxidative injury *(Davidson, 2002)*. It is a precursor of glutathione, an important hepatic antioxidant enzyme that is often reduced in dogs with liver disease. Oral administration helps to replenish hepatic glutathione stores and may thus improve antioxidant function. In addition, SAMe has anti-inflammatory properties *(Center et al, 2002)*.

Phosphatidylcholine (PC) is a phospholipid that is one of the components of bile required for normal bile acid transport and a building block for cell membranes. Its hepatoprotective actions are thought to be by improvement of membrane integrity and function *(Twedt, 2004)*. Based on its multiple mechanisms of action, this nutrient may be beneficial for chronic liver disease associated with oxidative stress, but it has not yet been validated for use in dogs.

Silymarin is the active component of milk thistle, and is thought to have antioxidant and free radical scavenging properties for various types of liver disease, as well as a protective agent against various hepatotoxicities *(Saller et al, 2001)*. There are currently limited clinical studies evaluating its efficacy in dogs with liver disease. Suggested doses range from 50 to 250 mg/day *(Twedt, 2004)*.

5 - Nutritional management adapted to the type of liver disease

► Acute liver diseases

Acute liver disease is most commonly caused by toxic injury, and less frequently by infection (e.g. infectious canine hepatitis, sepsis), trauma, heat stroke, or vascular compromise *(Center, 1996b)*. The spectrum of disease can range widely, and signs vary from mild to fulminant hepatic failure. Vomiting and diarrhea are common, whereas HE, melena, hematochezia, and DIC may occur in acute liver failure.

Stabilization - Fluid therapy with a balanced electrolyte solution is necessary for initial stabilization. Potassium and glucose should be supplemented as appropriate, and correction may reduce the severity of HE. Vomiting may be controlled by anti-emetics (metoclopramide, 0.2-0.5 mg/kg q 6-8h IV, IM, PO), whereas gastroprotectants (ranitidine 2 mg/kg q 8-12h IV, PO) are indicated in dogs with bloody vomiting and/or diarrhea. Treatment of HE may be needed as outlined below, using lactulose and oral antibiotics.

Dogs with acute liver disease are typically hypercatabolic and need prompt nutritional intervention in order to prevent debilitating malnutrition. The liver has tremendous regenerative capacities, but this is dependent on the availability of sufficient nutrients.

> Enteral nutrition

Enteral nutrition via tube feeding of frequent meals (3-6 hrs) should be instituted when the dog remains anorexic after 48 to 72 hours *(Michel, 1995)*, provided there is no intractable vomiting. Tube feeding is usually first started using a naso-esophageal tube; esophagostomy or gastrostomy tubes may have to be used at a later stage when the dog remains anorexic **(see chapter 14)**.

> Dietary management

Oral feeding should be started gradually with small frequent meals in order not to overload the liver's metabolic capacity. Half of the daily requirements should be fed initially, and this should be increased by 10% every day dependent upon the dog's response. The diet should contain normal amounts of protein (20%) if at all possible, since a positive nitrogen balance is essential for hepatic regeneration. Protein tolerance can be augmented by increasing caloric content (for instance by mixing a hepatic support diet with a convalescence diet) and/or using drugs to counteract hepatic encephalopathy (e.g. lactulose, oral antibiotics). Moderate protein restriction may be necessary in patients with persistent HE. However, in acute liver disease it is especially important not to over-restrict dietary protein, since this could result in endogenous ammonia production from protein catabolism as well as a reduction in the availability of protein for hepatocellular repair. The source of protein is also important, with milk and soy protein being better tolerated than animal protein.

The diet should also include free radical scavengers and antioxidants, such as vitamin E, vitamin C and SAMe. Ursodesoxycholic acid (10-15 mg/kg PO q24h) can be given as a hepatoprotectant in the subacute stage when serum bile acids remain high.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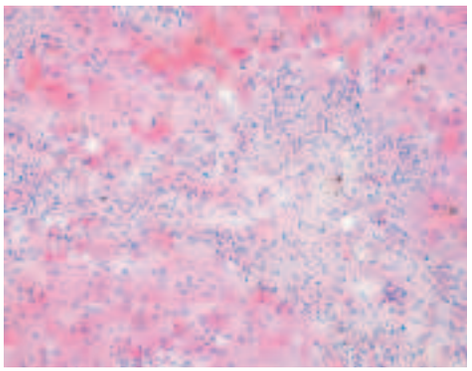
In case of acute liver failure, oral feeding must be reintroduced gradually, with frequent small meals so as not to overload the liver's metabolic capacity.

► Chronic liver disease

Chronic hepatitis includes a diverse group of disorders characterized by mixed inflammatory cell infiltrates, in which lymphocytes and plasma cells predominate *(Center, 1996b; Johnson, 2000)*. The etiology is often never determined. Documented causes include abnormal hepatic copper accumulation and drug- or toxin-induced hepatic injury (anticonvulsants). The presence of lymphocytic-plasmacytic infiltrates may be suggestive of an immune-mediated mechanism, but this is difficult to distinguish from immunological disease that occurs secondary to hepatocellular injury, due to release of liver antigens and subsequent antibody formation. The use of immunosuppressive therapy remains therefore limited to the few cases with clear lymphocytic-plasmacytic inflammation of unknown etiology *(Center, 1996a,b)*, especially since immunosuppressents may have detrimental effects on liver function.

Remember that glucocorticoids can have side-effects that may impact dietary needs, e.g. by aggravating HE, ascites, glucose intolerance and/or gastric ulceration *(Laflamme, 1999)*. This disease is usually in an advanced stage when recognized, and prognosis is guarded.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Liver biopsy of a dog suffering from chronic hepatitis, showing periportal inflammation with mononuclear inflammatory cells (H&E).

Dietary management – Nutritional therapy is particularly important in chronic liver disease. The amount fed should at first be based on an estimation of the patient's energy requirements **(Table 7).**

> Energy

Every effort should be made to get the dog to eat voluntarily. Food should be palatable, at room temperature and be fed in small portions 3 to 6 times daily. Dogs that refuse to eat or consume insufficient amounts to meet minimum requirements may require tube feeding, usually initially via a nasogastric tube, in order to halt the vicious cycle of excessive muscle catabolism and worsening signs of liver dysfunction. If the dog remains anorexic, esophagostomy or gastrostomy tubes may have to be inserted in order to ensure continuing nutritional adequacy **(see chapter 14)**.

> Protein

Dietary protein should ideally represent 17-20% of metabolic energy, be highly digestible and of high biological value. Protein restriction should only be instituted when there are signs of HE. Protein tolerance can be increased by administering lactulose (0.5 ml/kg orally three times daily), which may be combined with oral antibiotics (metronidazole 7.5 mg/kg q 12hr, or ampicillin 20 mg/kg q 8hr). Increasing dietary levels of vegetable, soy or dairy protein may also help to reduce the likelihood of HE.

REVERSIBILITY OF PROBLEMS

Dietary management of dogs with chronic liver disease aims to maintain adequate body condition in order to support hepatic regeneration and reduce signs of hepatic encephalopathy.

Assessment of the protein-calorie adequacy of the diet is generally based upon weekly monitoring of body weight and serum albumin concentrations. Progressive hypoalbuminemia (in absence of proteinuria) is indicative of protein malnutrition and/or progressive liver disease.

> Fiber

The diet should contain both soluble fiber, in order to promote an acidic colonic pH and decrease NH_4^+ absorption, and insoluble fiber, which helps to normalize transit time, prevent constipation and bind toxins. Foods low in fiber can be supplemented with psyllium (1 tsp per 5 to 10 kg bodyweight per meal).

> Minerals and vitamins

It is essential that the diet contains increased zinc levels and a mixture of antioxidants including vitamins E and C. Additional oral zinc supplementation (zinc acetate 2 mg/kg daily) may be helpful because it is an antioxidant that also has antifibrotic properties and can reduce the severity of HE.

Bedlington Terriers suffering from copper intoxication syndrome may present toxic liver copper concentrations from age 2 to 4 years (Twedt et al, 1979).

► Copper toxicosis

Bedlington Terriers affected with primary copper toxicosis develop progressive liver disease and die within a few years. This disease in Bedlington Terriers has similarities to Wilson's disease in man but differs clinically and genetically *(Brewer, 1998; Muller et al, 2003)*; the treatment is however similar. The role of copper in other breeds is less clear, although it is thought that in some breeds copper accumulation may contribute to the development of liver disease (e.g. West Highland White Terriers, Doberman Pinschers and Dalmatians) *(Rolfe & Twedt, 1995; Webb et al, 2002; Spee et al, 2005)*. Quantitative determination of liver copper levels as well as histopathologic assessment is important in differentiating primary copper storage disease from secondary copper retention due to cholestasis. Dogs with secondary copper accumulates tend to have lower concentrations in the liver, rarely exceeding 2000 ppm, and a different localization of copper within the lobule *(Center, 1996b; Rolfe & Twedt, 1995)*.

Dietary management – Diets for dogs with copper hepatotoxicosis should be low in copper while high in zinc, contain increased vitamin B levels and adequate levels of high quality proteins. Many canine diets contain copper well above the minimum required amount, and it is important to choose a diet with levels as low as possible. Feeding copper-restricted diets slows hepatic copper accumulation but does little to lower liver copper levels in already diseased dogs with large amounts of hepatic copper accumulation.

Dogs with severely increased liver copper levels (> 2000 ppm; normal less than 400 ppm) should be partially decoppered for 2-4 months using a copper chelator such as D-penicillamine (10-15 mg/kg orally q 12hr). Subsequently, treatment with oral zinc, which blocks intestinal copper absorption by induction of copper-binding metallothionein, is continued lifelong *(Brewer et al, 1992)*. Treatment of dogs with secondary copper retention involves addressing the primary cause, as well as measures to reduce the accumulated copper.

Prevention – Diets low in copper are essential in breeds known to accumulate copper or that have increased concentrations on biopsy. Bedlington Terriers that have been genetically assessed as being at risk of developing copper hepatotoxicosis should be fed a low-copper diet from a young age since copper accumulation happens early in life. Other foodstuffs (e.g. shellfish, liver), mineral supplements or water with a high copper concentration should also be avoided **(Table 8)**. DNA testing may help to identify affected and/or carrier Bedlingtons.

► Hepatic encephalopathy (HE)

HE is a metabolic disorder affecting the central nervous system, which develops secondary to hepatic disease *(Maddison, 2000)*. It is usually a result of congenital portovascular anomalies (congenital portosystemic shunts, microvascular dysplasia) and less commonly due to severe hepatocellular disease. Acquired shunts may occur in response to portal hypertension caused by severe chronic hepatitis, cirrhosis and fibrosis, and will also predispose to development of HE. Rarely, HE is due to urea cycle deficiencies as reported in Irish Wolfhounds *(Rothuizen et al, 2001)*. Signs are typically intermittent, may be precipitated by a high-protein meal, and vary from anorexia, vomiting, diarrhea and polyuria/polydipsia to disorientation, apparent blindness and seizures. Stunted growth or failure to gain weight may occur in young dogs with congenital portovascular shunts. A high index of clinical suspicion is important, since appropriate management of HE will greatly improve the patient's demeanor and may restore appetite.

> Dietary modification

- ***Protein quantity***

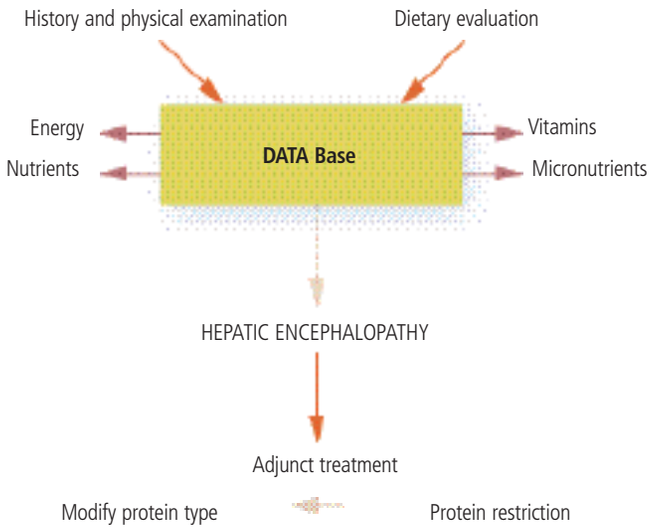
Dogs with HE are initially offered a highly digestible, protein-restricted diet (around 15 % ME), in combination with medication aimed at reducing ammonia production and colonic absorption (lactulose; oral antibiotics such as metronidazole or ampicillin) **(Figure 8)**. High diet digestibility as well as the addition of moderate amounts of fermentable fibers is of added benefit in regulating the intestinal microflora. Frequent, small meals should be fed in order to limit the time between meals, which improves nutritional status and reduces catabolism *(Laflamme, 1999)*. If the patient becomes neurologically asymptomatic, protein quantity is gradually and cautiously increased at weekly or biweekly intervals. Normal or near-normal maintenance protein requirements should be fed unless the animal again becomes encephalopathic, and in that case the medical treatment ought to be reinstituted and/or intensified. Serum proteins should be monitored to prevent hypoalbuminemia, in which case dietary protein content is increased in association with more aggressive adjunctive treatment. In dogs with refractory HE, protein quality may be modified by replacing animal proteins with vegetable (soy) and/or dairy proteins.

Maintenance of muscle mass and a positive nitrogen balance is essential in reducing the risk of hepatic encephalopathy (HE). Dietary protein should be restricted only as needed to prevent HE. Correction of enteric bleeding, constipation, infection, alkalosis, hypokalemia and azotemia is also important in reducing the risk of HE.

- ***Protein quality***

In addition to a protein-restricted diet and adjunct medication, it can be helpful to replace meat proteins with highly digestible vegetable (e.g. soy isolate) and/or milk proteins (e.g. casein, cottage cheese) *(Strombeck et al, 1983; Center, 1998)*.

FIGURE 8 - OVERVIEW OF NUTRITIONAL MANAGEMENT OF LIVER DISEASE



- ***Soluble fiber***

Addition of soluble fiber can be of benefit by acidifying colonic contents and minimizing ammonia absorption. Psyllium (1-3 tsp per 5-10 kg of weight mixed with food daily) also contains some insoluble fiber, which adds bulk to the stool and prevents constipation.

- ***Drug therapy***

Adjunct medical therapy can increase protein tolerance. Lactulose is a synthetic disaccharide that is fermented in the colon, resulting in colonic acidification and reduced ammonia absorption. The starting dose is 0.25-0.5 ml/kg two to three times daily, which is titrated to produce two soft stools daily.
Oral antibiotics (e.g. metronidazole 7.5 mg/kg q 8-12 hr or ampicillin 20 mg/kg q 8hr) are given during severe encephalopathic episodes in order to modify the enteric microbial flora that is responsible for the generation of ammonia and other toxins.

► Homemade versus commercial diets

Commercial diets are preferred above homemade ones because they are nutritionally complete. Veterinary diets formulated for dogs with hepatic insufficiency are now available and meet the specific nutritional requirements of the liver patient. It is difficult to create homemade diets that are balanced enough to be used for prolonged periods *(Laflamme, 1999)*.

In general, diets for dogs with liver disease should be highly digestible with a high energy density provided by fat and carbohydrates **(Table 9)**. Moderate protein restriction may be necessary in dogs with clinically evident HE, but protein quality should be very high. In addition, the diet should contain high normal to increased levels of water-soluble vitamins, enhanced zinc (>43 mg/1000kcal), restricted copper, restricted sodium (<0.5 g Na/1000 kcal) in case of ascites, and a moderate amount of mostly soluble fiber. Protein restriction should be avoided as much as possible, especially in dogs with acute inflammatory hepatic disease or necrosis.

Table 9 - Dietary recommendations for management of liver disease in dogs

Provide adequate energy

Supply sufficient energy (110-130 kcal ME/kg $BW^{0.75}$)
Provide energy as protein as well as non-protein calories
High diet palatability and energy density
Small meals fed frequently
- increases total food intake
- maintains energy and nutrient supply
- prevents overwhelming hepatic metabolic capacity

Fat:
- 30-50 % of dietary calories
- avoid high fat diets in: severe cholestasis, hyperlipidemia or vacuolar hepatopathies

Carbohydrates:
- maximal 45% of dietary calories

in glucose intolerance: avoid simple sugars, increase complex carbohydrates

Provide adequate protein

Protein should be of high quality and digestibility
Avoid inappropriate protein restriction (>14% of dietary calories, preferably >20%)
Feed protein at level of body condition and serum albumin
Restrict protein only as necessary in HE, and even then protein tolerance can be increased by augmenting caloric content (e.g. soy hydrolyzate) and adjunctive medical management

Fiber

Moderate amounts, predominantly soluble fiber

Provide adequate vitamins and minerals

Double maintenance level of vitamin B
Increased vitamin E
Moderate dietary restriction of sodium
Potassium replete
Restricted copper

Include additional antioxidants

Increased zinc (>43 mg/1000 kcal)
Increased vitamin E (10-100 IU/kg)
Increased vitamin C
Taurine

Management of complications

a) Hepatic encephalopathy:
- correct precipitating factors (e.g. hypokalemia, infection, GI bleeding)
- restrict dietary protein (12 to 16%, with a minimum of 2.1 g/kg per day)
- increase dietary protein tolerance with adjunctive treatment:
  - increasing caloric content
  - lactulose 0.25-0.5 mL/kg q 8h po
  - metronidazole 7.5 mg/kp q 12h po
  - ampicillin 20 mg/kg q 8h po
  - soluble fiber
- modify protein quality: vegetable and/or dairy proteins

b) Ascites
- dietary sodium restriction (<0.5 g Na/1000 kcal)
- diuretics (spironolactone 1-2 mg/kg q 12h, furosemide 2-4 mg/kg q8-12h PO)

Frequently asked questions - Nutrition of dogs with liver disease

Q	A
Dogs with liver disease often have a decreased appetite or are anorexic. How can they be stimulated to eat?	The diet must be highly palatable and high in energy, and provide adequate protein, fat, and all essential micronutrients. Feeding small amounts frequently and slightly warming canned food can increase palatability. Tube feeding, initially via a nasogastric tube, may be required in dogs that are anorexic for more than 3-5 days, since correction and prevention of malnutrition are essential to halt the vicious cycle of excessive muscle catabolism and worsening signs of liver dysfunction.
The liver biopsy of a seven-year-old Golden Retriever showed chronic hepatitis and copper accumulation. Is this copper important?	Golden Retrievers are not known to have primary copper hepatotoxicosis, and copper accumulation is probably a consequence of cholestatic liver disease resulting in decreased biliary excretion of copper. Typically, these copper levels are not high enough to result in hepatocellular damage. However, zinc treatment together with measures for chronic liver disease will help to prevent further copper accumulation.
Are antioxidants important in managing liver disease?	**Yes.** There is mounting evidence that free radical production is increased in many liver diseases and it can play an important role in initiating and perpetuating liver injury. Furthermore, endogenous antioxidant systems become depleted during liver disease, which aggravates the problem. Supplementation with antioxidants such as vitamins E, C, and S-adenosylmethionine (SAMe) helps to minimize oxidative injury. A combination of dietary antioxidants is better than a single one, since they appear to act synergistically.
Should dogs with liver disease be fed a protein-restricted diet?	**Not necessarily.** Protein levels are often inappropriately restricted in order to manage possible hyperammonemia. In fact, protein requirements are at least normal or even increased, and many dogs with liver disease do not have hyperammonemia. Provision of adequate high-quality proteins as well as calories is essential to ensure a positive protein balance and enable hepatic regeneration. The aim is to keep the protein intake as close to normal as can be tolerated without precipitating signs of hepatic encephalopathy (HE). Protein restriction should only be instituted when there are signs of HE, and additional treatments such as lactulose and oral antibiotics can help to avoid excessive restriction of dietary protein.
How should I feed a dog with acute liver disease?	A dog with acute liver disease needs an ample supply of energy and protein to allow for hepatic regeneration. Protein should never be restricted; protein tolerance can be enhanced if necessary by increasing caloric content and/or using drugs (lactulose, oral antibiotics). The dog should be fed small frequent meals in order not to overload the liver's metabolic capacity. Tube feeding should be considered if the dog remains anorexic for more than 72 hours.

Q	A
What are the dietary recommendations for dogs with chronic hepatitis?	The diet should have high palatability and energy density, contain normal levels of fat (which provides energy as well as palatability), adequate levels of high quality protein (>14% of dietary calories, preferably >20%), be restricted in copper and sodium, and contain some fermentable fiber. In addition, the diet should have increased vitamin B and zinc levels, and a mixture of antioxidants (e.g. vitamin E, C and S-adenosylmethionine). Zinc supplementation is useful because it is an antioxidant, reduces copper accumulation in the liver, can reduce the severity of HE and has antifibrotic properties.
What are the dietary recommendations for a Bedlington Terrier with copper hepatotoxicosis?	The diet should be low in copper while high in zinc, and contain adequate levels of high quality proteins. Many canine diets contain copper well above the minimum required amount, and it is important to choose a diet with levels as low as possible. Feeding copper-restricted diets slows hepatic copper accumulation but does little to lower liver copper levels in already diseased dogs with large amounts of hepatic copper. Additional treatment with a copper chelator (D-penicillamine) will be needed, followed by life-long zinc therapy to prevent further copper accumulation.
How do I manage a dog with hepatic encephalopathy?	Firstly, determine the cause – congenital portosystemic shunt or severe liver disease. Dietary management should focus on providing adequate energy and adequate protein to support hepatic regeneration while preventing worsening of HE. Patients with signs of HE are initially offered a protein-restricted diet in combination with medication aimed at reducing colonic absorption of ammonia (lactulose, oral antibiotics). Protein quantity is gradually increased at weekly or biweekly intervals when the dog becomes neurologically asymptomatic. Serum proteins should be monitored to prevent hypoalbuminemia, in which case dietary protein content should be increased in association with more aggressive adjunct treatment. When HE persists despite a protein-restricted diet and adjunct medication, it may be helpful to replace meat proteins with highly digestible vegetable and/or milk proteins. Addition of soluble fiber (psyllium 1-3 tsp mixed with food daily) can also help by acidifying colonic contents and minimizing ammonia absorption.

References

Adamus C, Buggin-Daubie M, Izembart A et al - Chronic hepatitis associated with leptospiral infection in vaccinated beagles. J Comp Path 1997;117; 311-328.

Als-Nielsen B, Koretz RL, Kjaergard LL et al - Branched-chain amino acids for hepatic encephalopathy. Cochrane Database Syst Rev 2003; 2: CD001939.

Bauer JE - Hepatic disease, nutritional therapy, and the metabolic environment. J Am Vet Med Assoc 1996; 209: 1850-1853.

Bianchi G, Marzocchi R, Agostini F et al - Update on branched-chain amino acid supplementation in liver diseases. Curr Opin Gastroenterol 2005; 21: 197-200.

Biourge V - Nutrition and liver disease. Semin Vet Med Surg 1997;12: 34-44.

Bishop L, Strandberg JD, Adams RJ et al - Chronic active hepatitis in dogs associated with leptospires. Am J Vet Res 1979;40: 839-844.

Brewer GJ, Dick RD, Schall W et al - Use of zinc acetate to treat copper toxicosis in dogs. J Am Vet Med Assoc 1992; 201:564-568.

Brewer GJ - Wilson disease and canine copper toxicosis. Am J Clin Nutr 1998; 67: 1087S-1090S.

Britton RS, Bacon BR - Role of free radicals in liver diseases and hepatic fibrosis. Hepatogastroenterology 1994; 1:343-348.

Center SA - Nutritional support for dogs and cats with hepatobiliary disease. J Nutr 1998; 128: 2733S-2746S.

Center SA - Balanced therapy for chronic liver disease. Eur J Com Gastroent 1999a; 4: 25-36.

Center SA - Chronic liver disease: current concepts of disease mechanisms. J Sm Anim Pr 1999b; 40: 106-114.

Center SA - Pathophysiology of liver disease: Normal and abnormal function. In: Strombeck's Small animal gastroenterology. 3rd ed, 1996a; W. Grant Guilford et al, WB Saunders Co, Philadelphia: 553-632.

Center SA - Chronic liver disease. In: Guilford WG, Center SA, Strombeck DR et al (eds). Strombeck's Small Animal Gastroenterology. 3rd edition. WB Saunders, Philadelphia, 1996b: 705- 765.

Center SA, Warner KL, Erb HN - Liver glutathione concentrations in dogs and cats with naturally occurring liver disease. Am J Vet Res 2002; 63: 1187-1197.

Cullen JM - Vacuolar hepatopathies.In Proceedings 19th Annual Vet Forum Am College Vet Intern Med Denver 2001;769-771.

Davidson G - S-Adenosylmethionine. Com Cont Educ 2002; 24: 600-603.

Dhawan D, Goel A - Further evidence for zinc as a hepatoprotective agent in rat liver toxicity. Exp Mol Pathol 1995; 63:110-117.

Feher J, Lengyel G, Blazovics A -Oxidative stress in the liver and biliary tract diseases. Scand J Gastroenterol Suppl 1998: 38-46.

Gallagher N, Webb J, Dawson AM - The absorption of 14C oleic acids and 14Ctriolein in bile fistula rats. Clin Sci 1965; 29: 73-80.

Hooser SB - Hepatotoxins. In Bonagura JD (ed). Kirk's Current Veterinary Therapy XIII. Philadelphia: WB Saunders Co, 2000: 217-219.

Holmes NG, Herrtage ME, Ryder EJ et al - DNA marker CO4107 for copper toxicosis in a population of Bedlington terriers in the United Kingdom. Vet Rec 1998; 142: 351-352.

Johnson J, Sternlieb I, Twedt DC et al - Inheritance of copper toxicosis in Bedlington terriers. Am J Vet Res 1980; 41: 1865-1866.

Johnson SE - Chronic hepatic disorders. In Ettinger SJ, Feldman EC (eds). Textbook of Veterinary Internal Medicine Diseases of the Dog and Cat. 5th edition. Philadelphia: WB Saunders Co, 2000: 1298-1325.

Krahenbuhl S, Reichen J - Carnitine metabolism in patients with chronic liver disease. Hepatology 1997; 25: 148-153.

Laflamme DP - Nutritional management of liver disease. In: Kirk's Current Veterinary Therapy XIII, Bonagura JW (ed). Philadelphia: WB Saunders Co, 1999: 693-697.

Leveille-Webster CR - Laboratory diagnosis of hepatobiliary disease. In: Ettinger SJ, Feldman E (eds). Textbook of Veterinary Internal Medicine Diseases of the Dog and Cat. 5th edition. Philadelphia: WB Saunders Co, 2000: 277-293.

Maddison JE - Newest insights into hepatic encephalopathy. Eur J Comp Gastroent 2000; 5: 17-21.

Marchesini G, Bianchi G, Merli M et al - Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. Gastroenterology 2003; 124: 1792-801.

Marchesini G, Fabbri A, Bianchi G et al - Zinc-supplementation and amino-acid-nitrogen metabolism in patients with advanced cirrhosis. Hepatology 1996; 23: 1084-1092.

Marks SL, Rogers QR, Strombeck DR - Nutritional support in hepatic disease. Part I. Metabolic alterations and nutritional considerations in dogs and cats. Comp Cont Educ Pract Vet (Small Anim) 1994: 971-978.

Meyer HP, Chamuleau RA, Legemate DA et al - Effects of a branched-chain amino acid-enriched diet on chronic hepatic encephalopathy in dogs. Metab Brain Dis 1999; 14: 103-105.

Michel KE - Nutritional management of liver disease. Vet Clin North Am Small Anim Pract 1995; 25: 485-501.

Mizock BA - Nutritional support in hepatic encephalopathy. Nutrition 1999; 15: 220-228.

Muller T, Van de Sluis B, Zhernakova A et al - The canine copper toxicosis gene MURR1 does not cause non-Wilsonian hepatic copper toxicosis. J Hepatol 2003; 38: 164-168.

Rolfe DS, Twedt DC - Copper-associated hepatopathies in dogs. Vet Clin North Am Small Anim Pract 1995; 25: 399-417.

Rothuizen J, Ubbink GJ, Meyer HP et al - Inherited liver diseases: New findings in portosystemic shunts, hyperammonaemia syndromes, and copper toxicosis in Bedlington terriers. In Proceedings 19th Annu Vet Forum Am Coll Vet Int Med 2001; Denver: 637-639.

Rothuizen J, Ubbink GJ, Van Zon P et al - Diagnostic value of a microsatellite DNA marker for copper toxicosis in West European Bedlington terriers and incidence of the disease. Anim Genet 1999; 30: 190-194.

Saller R, Meier R, Brignol R - The use of sylmarin in the treatment of liver disease. Drugs 2001; 61: 2035-2063.

Sokol RJ, Twedt DJ, McKim J et al - Oxidant injury to hepatic mitochondria in patients with Wilson's disease and Bedlington terriers with copper toxicosis. Gastroenterology 1994; 107: 1788-1798.

Sokol RJ - Antioxidant defenses in metal induced liver damage. Semin Liver Dis 1996; 16: 39-46.

Sokol RJ - Fat-soluble vitamins and their importance in patients with cholestatic liver disease. Pediatr Gastroenterol 1994; 23: 673-705.

Spee B, Mandigers PJ, Arends B et al - Differential expression of copper-associated and oxidative stress related proteins in a new variant of copper toxicosis in Doberman pinschers. Comp Hepatol 2005: 24; 4: 3.

Strombeck DR, Schaeffer ME, Rogers QR - Dietary therapy for dogs with chronic hepatic insufficiency. In: Kirk's Current Veterinary Therapy VIII, Kirk RW (ed). WB Saunders, Philadelphia, 1983: 817-821.

Therrien G, Ross C, Butterworth J et al - Protective effect of L-Carnitine in ammonia-precipitated encephalopathy in the portocaval shunted rat. Hepatology 1997; 25: 551-556.

Thornburg LP - A perspective on copper and liver disease in the dog. J Vet Diagn Invest 2000; 12: 101-110.

Tobias KM, Rohrbach BW - Association of breed with the diagnosis of congenital portosystemic shunts in dogs: 2,400 cases (1980-2002). J Am Vet Med Assoc 2003; 223: 1636-1639.

Tobias KM - Determination of inheritance of single congenital portosystemic shunts in Yorkshire terriers. J Am Anim Hosp Assoc 2003; 39: 385-389.

Trepanier LA, Danhoff R, Toll J et al - Clinical findings in 40 dogs with hypersensitivity associated with administration of potentiated sulfonamides. J Vet Int Med 2003; 17: 647-652.

Twedt DC, Sternlieb I, Gilbertson SR - Clinical, morphologic and chemical studies on copper toxicosis of Bedlington terriers. J Am Vet Med Assoc 1979; 175: 269-275.

Twedt DC - Nutraceuticals in liver disease. Proceed 22nd ACVIM Forum, Minneapolis 2004; 678-680.

Van den Ingh TS, Rothuizen J, Meyer HP - Portal hypertension associated with primary hypoplasia of the hepatic portal vein in dogs. Vet Rec 1995; 137: 424-427.

Van De Sluijs B, Rothuizen J, Pearson PL et al - Identification of a new copper metabolism gene by positional cloning in purebred dogs. Hum Mol Genet 2002; 11: 165-173.

Watson PJ - Chronic hepatitis in dogs: a review of current understanding of the aetiology, progression and treatment. Vet J 2004; 167: 228-241.

Webb CB, Twedt DC, Meyer DJ - Copper-associated liver disease in Dalmatians: a review of 10 dogs (1998-2001). J Vet Intern Med 2002; 16: 665-668.

Yuzbasiyan-Gurkan V, Halloran Blanton S, Cao Y et al - Linkage of a microsatellite marker to the canine copper toxicosis locus in Bedlington terriers. Am J Vet Res 1997; 58: 23-27.

EXAMPLES OF HOME-PREPARED
THE TREATMENT FOR

Example 1

COMPOSITION
(1000 g diet)

Chicken, breast with skin . . . . . 220 g
Rice, cooked . . . . . 680 g
Carrots (boiled, drained) . . . . . 60 g
Wheat bran . . . . . 20 g
Rapeseed oil . . . . . 20 g

Add a low-sodium and low-copper mineral and vitamin supplement.

ANALYSIS		
The diet prepared in this way contains 31% dry matter and 69% water		
	% dry matter	**g/1000 kcal**
Protein	22	50
Fat	12	27
Available carbohydrate	60	136
Fiber	4	10

Key Points

- **Reduce the copper content** to limit the risk of copper accumulation in the liver
- **Reduce the sodium content** to reduce portal hypertension and limit the loss of fluid through the extra-luminal space
- **Increase the energy level** to prevent the risk of excessive protein catabolism and combat hepatic encephalopathy

INDICATIVE RATIONING			
Energy value (metabolizable energy) 1355 kcal/1000 g of diet prepared (2380 kcal/1000 g DM)			
Dog's weight (kg)*	Daily amount (g)**	Dog's weight (kg)*	Daily amount (g)**
2	160	45	1670
4	270	50	1800
6	370	55	1940
10	540	60	2070
15	730	65	2200
20	910	70	2320
25	1070	75	2450
30	1230	80	2570
35	1380	85	2690
40	1530	90	2800

**The rationing is offered in accordance with the dog's healthy weight. In case of obesity, the rationing must be prescribed in accordance with the ideal weight and not the real weight of the dog.*
***The fractioning of the daily amount over two or three meals is recommended to limit the postprandial hepatic load.*

DIETS ADAPTED TO LIVER DISEASES

Example 2

COMPOSITION
(1000 g diet)

Beef, minced meat, 15% fat . . . . . 100 g
Tofu . . . . . 400 g
Rice, cooked . . . . . 440 g
Carrots (boiled, drained) . . . . . 30 g
Wheat bran . . . . . 10 g
Rapeseed oil . . . . . 20 g

Add a low-sodium and low-copper mineral and vitamin supplement.

INDICATIVE RATIONING

Energy value (metabolizable energy) 1265 kcal/1000 g of diet prepared (1900 kcal/1000 g DM)

Dog's weight (kg)*	Daily amount (g)**	Dog's weight (kg)*	Daily amount (g)**
2	170	45	1790
4	290	50	1930
6	390	55	2080
10	580	60	2220
15	780	65	2350
20	970	70	2490
25	1150	75	2620
30	1320	80	2750
35	1480	85	2880
40	1630	90	3000

ANALYSIS

The diet prepared in this way contains 26% dry matter and 74% water

	% dry matter	g/1000 kcal
Protein	25	51
Fat	21	43
Available carbohydrate	49	100
Fiber	3	6

Contra-indications

Gestation
Lactation
Growth

Examples of home-made diets are proposed by Pr Patrick Nguyen
(Nutrition and Endocrinology Unit; Biology and Pathology Department, National veterinary School of Nantes)

It is important to serve several smaller meals over the day while respecting the daily ration in order to limit the postprandial hepatic load.

Key points
to remember:

Nutrition in the treatment and prevention of liver diseases

The four objectives of nutritional support for liver diseases in dogs are:

- **Treating the malnutrition** by responding to the energy requirements in terms of essential nutrients
- **Favoring the regeneration of hepatocytes** by ensuring the limited intake of nutrients, particularly proteins
- **Limiting hepatic lesions** by preventing the accumulation of copper and capturing free radicals
- **Preventing or minimizing complications**, such as hepatic encephalopathy, portal hypertension and ascites

Anorexia is a frequent consequence of hepatopathies.

Tube feeding can be utilized to ensure an appropriate intake of energy and nutrients.

Highly digestible vegetable or dairy proteins are better tolerated than animal proteins in animals suffering from hepatic encephalopathy.

Nutritional support must be adapted to the case, based on the type of hepatopathy, the degree of hepatic dysfunction, the tolerance to dietary proteins and the animal's nutritional condition.

The length of the nutritional treatment is dependent on the cause of the disease and the regeneration capacity of the liver tissue. A lifelong prescription may prove necessary in case of a chronic disease.

Focus on:

COPPER

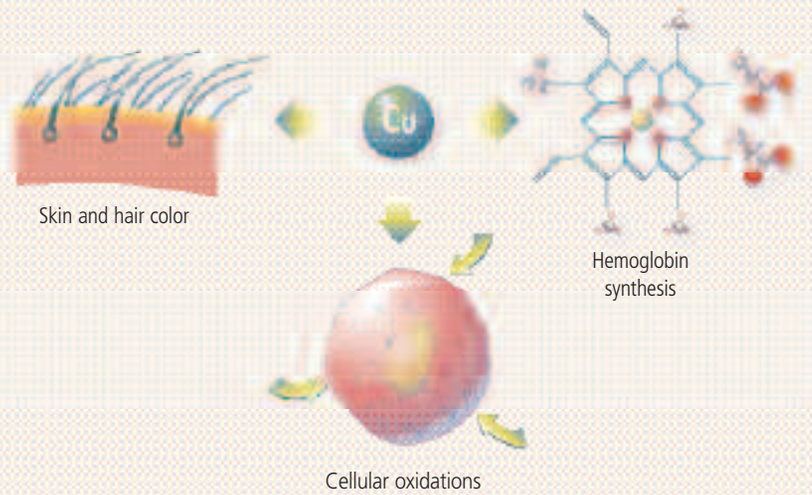
Although it is present in the organism in very low quantities (< 10 mg /kg of body weight), copper plays the role of coenzyme in a great many metabolic reactions.

- Copper is one of the anti-anemic factors that also include folates, vitamin B12 and iron. Copper facilitates the incorporation of iron in hemoglobin.
- Copper helps the synthesis of collagen and myelin.
- Copper also plays a role in the synthesis of melanin, due to its tyrosinase coenzyme function.
- As a cofactor of superoxide dismutase (SOD), copper is an integrative part of the oxidative stress defense mechanisms.

Copper is absorbed and stored by bonding with liver proteins: most of the organism's copper is stored in the liver. This storage capacity is limited and excess copper is eliminated by the bile. Copper may be toxic when accumulation is excessive, as in some predisposed breeds.

The intestinal absorption of copper, zinc and iron is interdependent. An excessive iron or zinc level may reduce the availability of copper. In the enterocytes zinc induces the synthesis of metallothioneine, a metalloprotein that forms a strong bond with copper in the epithelial cells of the intestine and prevents its absorption. Food high in zinc (> 40 mg /1000 kcal) is therefore recommended for dogs with liver failure.

EXAMPLES OF MAJOR FUNCTIONS IN WHICH COPPER PLAYS A ROLE



With pathological accumulation, copper levels in the liver will reach concentrations of several thousand mg/g of dry liver tissue, or ten times that of a healthy liver.

DOG BREEDS PRESENTING INCREASED COPPER IN THE LIVER DURING HEPATOPATHY

(From Johnson, 2000)

Airedale Terrier
Bedlington Terrier*
Bobtail
Boxer
Bull Terrier
Bulldog
Cocker Spaniel
Collie
Dachshund
Dalmatian
Doberman Pinscher
German Shepherd
Golden Retriever
Keeshond
Kerry Blue Terrier
Pekingese
Poodle
Samoyed
Schnauzer
Skye Terrier*
West Highland White Terrier*
Wirehaired Fox Terrier

** accumulation of copper in the liver related to a hereditary mechanism*

References

Biourge V - Nutritional support, a key factor in the management of liver disease. Waltham Focus 2004; 14(2): 22-27.

Johnson SE - Chronic hepatic disorders. In: Ettinger SJ, Feldman EC, eds. Textbook of Veterinary Internal Medicine. Philadephia: Saunders 2000: 1298-1325.

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The role of nutrition in the pathogenesis and the management of exocrine pancreatic disorders

1 - Exocrine pancreatic insufficiency 173

Frequently asked questions: exocrine pancreatic insufficiency 183
References 184

2 - Acute pancreatitis 186

Frequently asked questions: pancreatitis 196
References 197
Royal Canin Nutritional Information 198

The role of nutrition in the pathogenesis and the management of exocrine pancreatic disorders

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Dr. Simpson graduated from the University of Edinburgh (BVM&S) in 1984. His PhD (University of Leicester, 1988) focused on pancreatic and intestinal function in dogs, and was followed by clinical training at the University of Pennsylvania, and the Ohio State University. He is presently an Associate Professor of Medicine at Cornell University with clinical and research interests in internal medicine and gastroenterology.

The exocrine pancreas has an essential role in the digestion and absorption of nutrients. Pancreatic acini synthesize and secrete enzymes such as lipase, trypsin and amylase that digest fats, proteins and carbohydrates. Pancreatic duct cells secrete bicarbonate that maintains an optimal pH for digestive and absorptive processes, and intrinsic factor that enables the absorption of cobalamin (Vitamin B12). The exocrine pancreas also produces bacteriostatic peptides and defensins that regulate the upper GI flora, and has a role in maintenance of the intestinal mucosa and glucose homeostasis.

Dysfunction of the exocrine pancreas is broadly characterized by the loss of functional pancreatic mass (exocrine pancreatic insufficiency), or inflammation (pancreatitis), with consequent diarrhea and weight loss, or abdominal pain and vomiting respectively. This chapter will outline the role of nutrition in the pathogenesis and management of exocrine pancreatic disease in the dog.

1 - Exocrine pancreatic insufficiency

► Diagnosis

> Overview

A diagnosis of exocrine pancreatic insufficiency (EPI) is made on the basis of compatible historical and clinical findings **(Table 1)**, and by ruling out infectious, parasitic, metabolic, and anatomic causes of small bowel diarrhea and weight loss. The diagnosis is confirmed by demonstrating a subnormal serum concentration of trypsin-like immunoreactivity (TLI), recently reviewed by Westermarck & Wiberg *(2003)*.

TABLE 1 - MOST COMMON SIGNS OBSERVED IN 109 GERMAN SHERPHERD DOGS WITH EPI* *VS* 186 NORMAL GERMAN SHERPHERD DOGS

Grey or Yellowish feces	99%
Large amounts of feces	95%
Defecation > 3x /day	90%
Lean body or cachexia	90%
Frequent flatulence	88%
Diarrhea several times per week	77%
Coprophagia	61%
Polydipsia	51%
Vomiting	38%
Skin problems	14% (not different from control group)

(from Raiha & Westermack, 1989)
** Exocrine pancreatic insufficiency*

> Signs

Dogs with EPI usually present for investigation of chronic diarrhea (feces of large volume and cowpat consistency, often yellow to grey in color) **(Figure 1)** and weight loss (mild to extreme), which is often associated with a ravenous appetite. Pica and coprophagia are also common. A poor haircoat (hair loss, eczema, dryness, scurf) polydipsia and marked muscle loss are observed in some dogs.

Polyuria and polydipsia may be present when exocrine pancreatic insufficiency caused by chronic pancreatitis is complicated by diabetes mellitus. Acute abdomen due to mesenteric torsion has also been associated with EPI.

© M. Weber

Figure 1 - *The feces of canine pancreatic insufficiency patients are often of large volume and cowpat consistency, and are discolored and highly pungent.*

> Supplementary tests

- ***Clinicopathological tests***

Routine hematology and biochemistry are fairly unremarkable in dogs with EPI. Modest increases in alanine amino-transferase (ALT) and a decrease in cholesterol are observed in some dogs. Panhypoproteinemia is not a feature of EPI, and its presence suggests that primary small intestinal disease is causing the diarrhea and weight loss, rather than EPI.

The presence of hyperglycemia and glucosuria in dogs with signs of EPI should prompt consideration of diabetes mellitus secondary to chronic pancreatitis, or pancreatic hypoplasia.

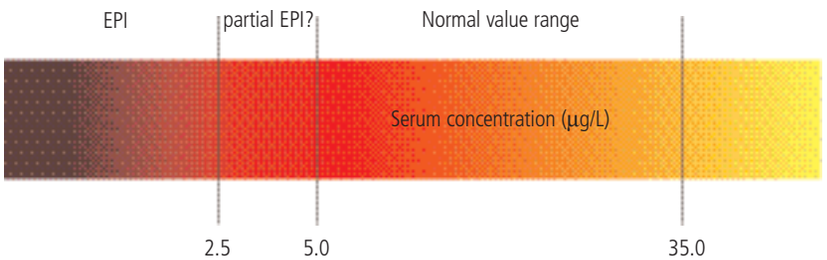
Serum concentrations of cobalamin (Vitamin B12) and Vitamins A and E can also be markedly reduced in dogs with EPI. In contrast, serum folate concentration is often increased. Serum concentrations of zinc and copper are decreased in dogs with experimental pancreatic insufficiency, whereas serum iron and transferrin saturation are increased.

- ***Specific diagnosis***

The specific diagnosis of EPI is made by demonstrating a subnormal concentration of trypsin-like immunoreactivity (TLI) in a fasted serum sample *(Williams & Batt, 1988)*. Serum TLI is considered to originate solely from the pancreas and is an indicator of pancreatic mass and inflammation *(Simpson et al, 1991)*.

In dogs with EPI caused by atrophy or chronic inflammation the amount of TLI leaking from the pancreas into the circulation is reduced, and a subnormal TLI concentration can be demonstrated **(Figure 2)**.

FIGURE 2 - INTERPRETATION OF TYROSIN-LIKE IMMUNOREACTIVITY (TLI) VALUES IN FASTING DOGS



Healthy dogs usually have a fasting (overnight fast) TLI concentration greater than 5.0 µg/L (normal range = 5-35 µg/L) whereas dogs with EPI caused by reduced pancreatic mass have fasting concentrations < 2.5 µg/L. Where the TLI concentration is between 2.5-5.0 µg/L the patient may be normal or have partial EPI and the test should be repeated after ensuring an adequate fast.

DIAGNOSTIC PITFALLS

EPI must be distinguished from primary intestinal disease.
The combination of diarrhea, weight loss, ravenous appetite, and relatively normal laboratory findings, often in a breed that is predisposed (e.g. German Shepherd) **(Figures 3 & 4)**, strongly suggests EPI is a likely cause.

The presence of large bowel diarrhea, frequent vomiting, pallor, jaundice, edema or ascites should prompt consideration of other more likely diagnoses. Hypoproteinemia is not a feature of uncomplicated EPI and usually indicates a protein losing enteropathy.

Do not rely solely on the TLI test result without other supportive evidence of exocrine pancreatic disease.

Patients with persistently intermediate TLI concentrations are likely to have partial EPI that may progress to complete EPI *(Wiberg et al, 1999a; Wiberg & Westermarck, 2002)*.

The TLI test is a simple and reliable way of confirming a diagnosis of EPI. However, if the TLI test result does not fit the patient's clinical signs it is prudent to re-run the test after ensuring an overnight fast to rule out sampling/handling/technician error. The TLI test will not detect conditions that may cause the intra-luminal destruction of pancreatic enzymes e.g. hyperacidic states such as gastrinoma and mast cell tumor, but these conditions have other diagnostic features such as hematemesis and esophagitis to distinguish then from primary EPI.

> Decision tree

The differential diagnosis of EPI includes other causes of small bowel diarrhea and weight loss **(Table 2)**.

Table 2 - Differential diagnosis of chronic small bowell diarrhea		
Infectious	Giardia, Histoplasmosis, pathogenic bacteria (Salmonella, Campylobacter), Phycomycoses, Mycobacteria	
Metabolic	Hypoadrenocorticism, liver disease, kidney disease	
Dietary	Intolerance / Allergy	
Exocrine pancreatic insufficiency	Primary or secondary	
Small intestinal disease	Structural	Partial obstruction : intussusception, foreign object, neoplasia, lymphangiectasia, congenital anomalies
	Inflammatory	Eosinophilic, lymphoplasmacytic, granulomatous
	Neoplastic	Lymphosarcoma, adenocarcinoma, leiomyoma, fibrosarcoma
	Bacterial overgrowth	Secondary, idiopathic
	Functional	Motility disorders, idiopathic

Figure 3 - Frequency distribution of age at diagnosis of canine exocrine pancreatic insufficiency in 199 German Shepherd dogs and 102 dogs of other breeds

(Results are expressed in the percentage of the cases in either group)
(From: Hall et al, 1991)

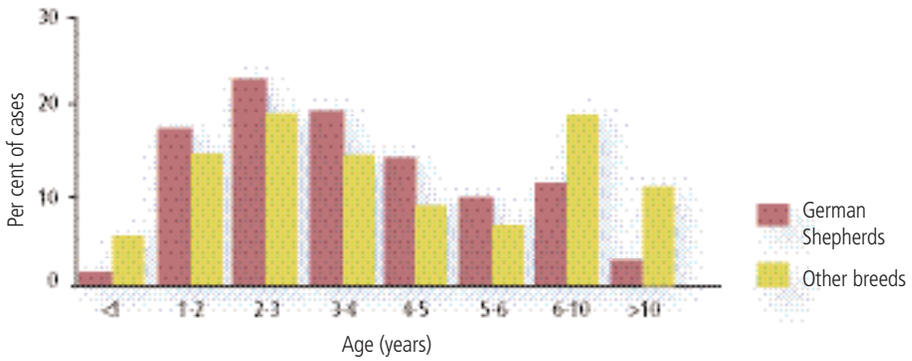
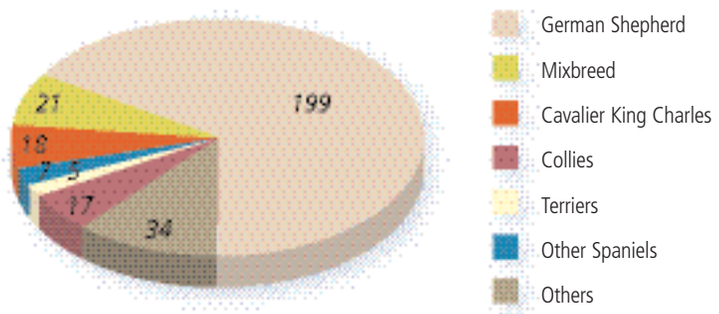


Figure 4 - Frequency distribution of breeds for 301 cases of canine pancreatic insufficiency

(Results are expressed as number of dogs per breed)
(From Hall et al, 1991)



Pancreatic atrophy in German Shepherds and shorthair Collies is preceded by lymphocytic infiltration (Westermarck et al, 1993a; Wilberg et al, 1999b).

► Epidemiology

> Risk factors

Pancreatic acinar atrophy (PAA) is probably the most common cause of exocrine pancreatic insufficiency (EPI) in the dog **(Figure 3)**. Dogs under five years of age diagnosed with EPI are usually suspected of having pancreatic acinar atrophy, whereas older dogs likely have a higher incidence of pancreatitis induced degeneration *(Hall et al, 1991)*. Dogs with chronic relapsing pancreatitis are considered at increased risk of developing EPI.

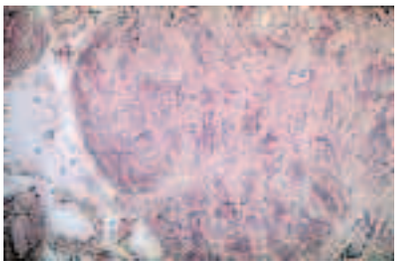
> Breed predispositions

Many different breeds have been diagnosed with EPI **(Figure 4)**.

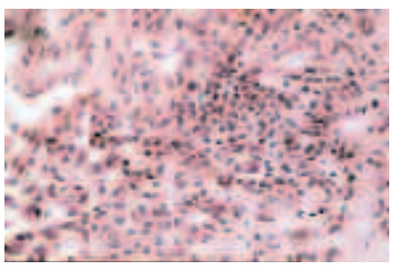
A familial predisposition to pancreatic acinar atrophy has been reported in German Shepherd Dogs, Collies and English Setters *(Westermarck,1980; Boari et al, 1994; Moeller et al, 2002; Wiberg, 2004)*. As it is impossible to determine the cause of atrophy in an end stage pancreas, prospective studies of the development of canine PAA have been conducted. These longitudinal studies have identified German Shepherd dogs and Rough Coated Collies with sub-clinical exocrine pancreatic insufficiency, detected by assay of circulating TLI, in whom pancreatic atrophy is preceded by a marked lymphocytic infiltration *(Westermarck et al, 1993a; Wiberg et al, 1999b, 2000)*. This strongly suggests an autoimmune basis for PAA. There is no evidence that a lack of trophic factors e.g. CCK, or anti-pancreatic antibodies play a role in the genesis of PAA.

Breeds such as Miniature Schnauzers appear to be overrepresented with relapsing pancreatitis and may be predisposed to EPI.

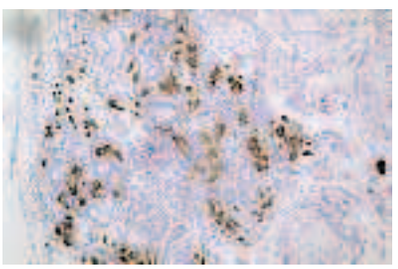
FIGURE 5 - PHOTOGRAPHS OF EPI DUE TO PANCRATIC ACINAR AND CHRONIC ATROPHY AND CHRONIC PANCREATITIS



5A - *Chronic pancreatitis. Fibrosis and atrophy are evident in this section from the pancreas of a dog with EPI secondary to pancreatitis (x10; H&E coloration).*



5B - *Lymphocytic inflammation precedes the development of EPI in dogs with familial acinar atrophy (x40; H&E coloration).*



5C - *Islet cells, stained for insulin (brown), and surrounded by a sea of atrophied exocrine tissue are relatively normal in dogs with EPI. (Glucose tolerance is abnormal but responds to enzyme supplementation- see text for details) (x20; immunocoloration for insulin).*

► Pathophysiological mechanisms of EPI

Exocrine pancreatic insufficiency (EPI) in the dog is most often a consequence of a severe reduction of pancreatic mass caused by pancreatic acinar atrophy, or chronic pancreatitis **(Figure 5)**.

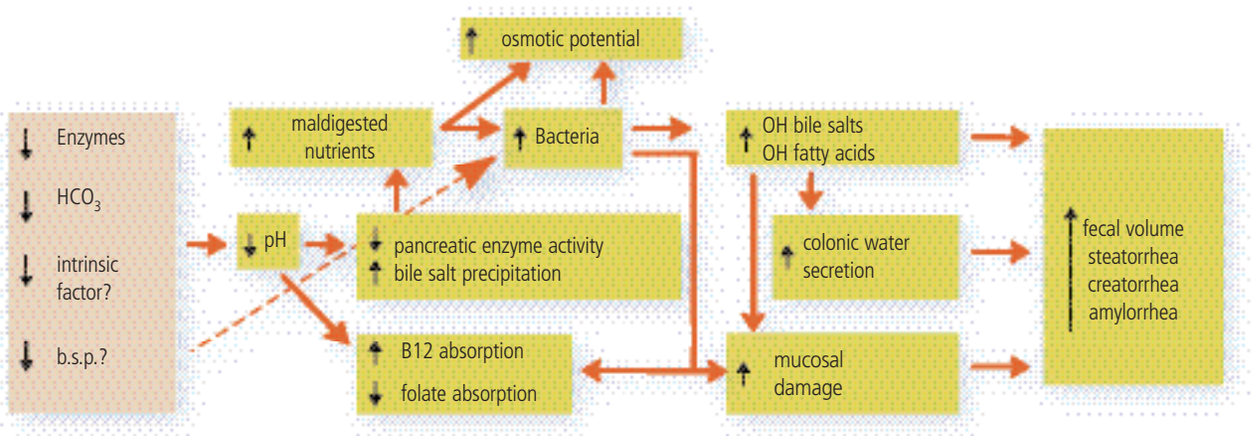
Pancreatic hypoplasia with concomitant EPI and diabetes mellitus has been rarely documented. In theory, EPI can also occur secondary to:
- the increased destruction, or decreased activity, of pancreatic enzymes in patients with acid hypersecretion
- decreased synthesis and secretion of enzymes in the presence of severe malnutrition.

Extensive loss of exocrine pancreatic mass (approx. 90%), whether by atrophy or chronic inflammation is required before signs of EPI are evident *(Simpson et al, 1992)*. The predominant clinical signs of EPI, diarrhea, weight loss and a ravenous appetite can be directly attributed to decreased intra-duodenal concentrations of pancreatic enzymes, bicarbonate, and various other factors with resultant malassimilation of fats, carbohydrates and proteins **(Figure 6)**.

Malabsorption of fat soluble vitamins and cobalamin, and changes in the number and composition of the small intestinal bacterial flora have also been documented in dogs with EPI and may contribute to their clinical condition *(Williams et al, 1987; Westermarck et al, 1993b; Adamama-Moraitou et al, 2002)*. Subnormal serum concentrations of cobalamin are frequently documented (approximately 75% of cases) in dogs with EPI and are likely a consequence of intrinsic factor deficiency, disrupted binding of cobalamin to IF (by intestinal pH, lack of proteases) and bacterial consumption of cobalamin **(Figure 7)** *(Batt et al, 1989; Simpson et al, 1989a; Simpson et al, 1993)*.

Other abnormalities encountered in dogs with EPI include alterations in:
- glucose homeostasis (subclinical glucose intolerance) *(Rogers et al, 1983)*
- pancreatic and gastrointestinal regulatory peptides (e.g. vasoactive intestinal polypeptide, gastric inhibitory polypeptide, somatostatin, pancreatic polypeptide) *(Hellmann et al, 1991)*

FIGURE 6 - SUMMARY OF THE LUMINAL AND INTRALUMINAL CHANGES OCCURING IN EXOCRINE PANCREATIC INSUFFICIENCY



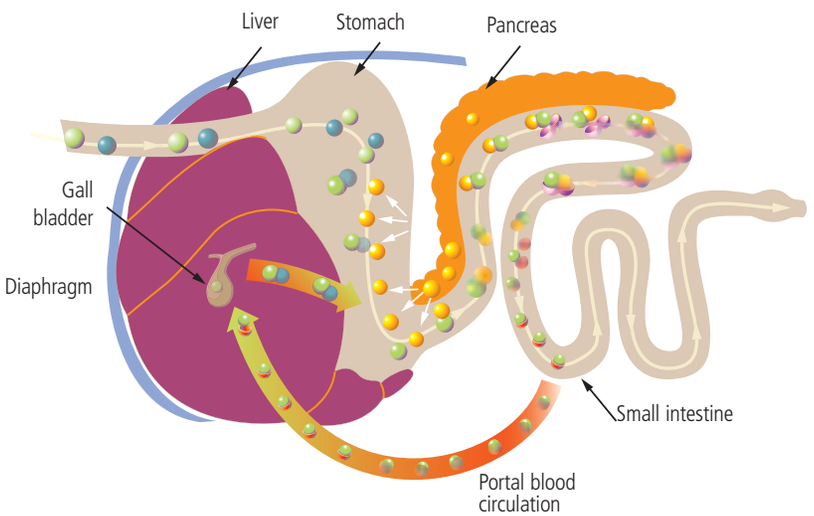
Summary of the luminal and intraluminal changes occurring in exocrine pancreatic insufficiency.

FIGURE 7 - COBALAMIN ABSORPTION IN THE DOG

Following ingestion, cobalamin is released from food in the stomach. It is then bound to a non-specific cobalamin-binding protein of salivary and gastric origin called haptocorrin. Intrinsic factor (IF), a cobalamin binding protein that promotes cobalamin absorption in the ileum, is produced by the stomach and pancreas in dogs. The affinity of cobalamin for haptocorrin is higher at acid pH than for IF, so most is bound to haptocorrin in the stomach.

Upon entering the duodenum haptocorrin is degraded by pancreatic proteases, and cobalamin is transferred from haptocorrin to IF, a process facilitated by the high affinity of IF for cobalamin at neutral pH. Cobalamin-IF complexes traverse the intestine until they bind to specific receptors (previously called IFCR, but recently dubbed cubilin) located in the microvillus pits of the apical brush-border membrane of ileal enterocytes.

Cobalamin is then transcytosed to the portal bloodstream and binds to a protein called transcobalamin 2(TC II), which mediates cobalamin absorption by target cells. A portion of cobalamin taken up by hepatocytes is rapidly (within an hour in the dog) re-excreted in bile bound to haptocorrin.



Cobalamin of hepatobiliary origin, in common with dietary derived cobalamin, undergoes transfer to IF and receptor mediated absorption, thus establishing enterohepatic recirculation of the vitamin.

Low serum cobalamin concentrations in dogs have been associated with exocrine pancreatic insufficiency (EPI), severe intestinal disease, IF-Cbl receptor abnormalities, and conditions associated with the proliferation of enteric abacteria e.g stagnant loops.

Figure 8 - EPI ase study - Neutered female Boxer age 7 years

History and clinical examination

- Weight loss (6 months), chronic diarrhea (>6 times per day for 3 months), ravenous appetite
- Emaciated (1/5 body score), 3mm cutaneous nodules x 2 on left neck and right flank
- Referral veterinarian treated with fluoroquinolone (enrofloxacin), prednisone (10 days) and metronidazole: no signs of improvement

Stat blood tests

Packed cell volume	39%
Total Protein	7.5 g/dL
Blood urea nitrogen	30-40 mg/dL
Glucose	86 mg/dL

Complete blood count

PCV (%)	44	(42-57)
MCV (fl)	74	(63-74)
WBC (thou/µL)	8.1	(6.2-14.4)
Neutrophilis (thou/µL)	6.6	(3.4-9.7)
Lymphocytes (thou/µL)	1.4	(1.3-4.7)
Platelets (thou/µL)	475	(179-483)

Profile

Albumin (g/dL)	3.9	(3.1-4.1)
Globulin (g/dL)	3.0	(1.9-3.6)
ALP (IU/L)	1130	(12-122)
ALT (IU/L)	357	(25-106)
GGT (IU/L)	33	(0-10)
Cholesterol (mg/dL)	106	(124-335)

Urinalysis

USG	1.041
pH	6.5
protein	++ (meaningless because of the urine specific gravity)

Fecal

Giardia ELISA negative, zinc sulphate negative Many *Clostridium perfringens*-like organisms on a smear

TLI	5.58 µg/L (5-25)
Cobalamin	184 pg/mL (175-550)
Folate	27 ng/mL (4-13)

Ultrasound: questionable diffuse hyperechoic liver

Thoracic radiographs: normal

Cutaneous aspirates: blood

Coagulation tests: normal (OSPT, APTT)

Interpretation

Chronic diarrhea, weight loss and polyphagia suggestive of maldigestion or malabsorption. Elevated liver enzymes suggest a primary or secondary hepatopathy in response to exogenous corticoteroids or GI disease. Low cholesterol suggests small intestinal disease, EPI or liver disease. Lack of other evidence of hepatic synthetic failure (normal protein, BUN) suggests low cholesterol may be due to GI disease or EPI.

Normal TLI test lowers the likelihood of EPI suggesting that high folate and low normal cobalamin are due to intestinal disease. Due to the degree of weight loss and lack of a definitive diagnosis an exploratory laparotomy was performed to biopsy the gastrointestinal tract, liver and mesenteric lymph nodes.

At surgery a 10 cm tangled cloth in the stomach and a 6cm cloth in the jejunum were found. These were considered incidental as they were not causing obstruction and likely secondary to the polyphagia. A thickened gastric wall and severe atrophy of the pancreas were observed.

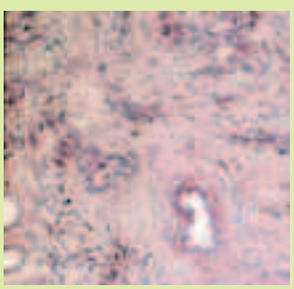
Working diagnosis after surgery

Exocrine pancreatic insufficiency, possible Helicobacter related gastritis, reactive lymphadenopathy presumed secondary to gastrointestinal disease.
Over the next two months the dog gained 10lbs (42# to 52#), fecal consistency normalized and the energy level of the dog increased.

Commentary

The history of marked weight loss, diarrhea and polyphagia coupled with normal serum protein but low cholesterol are typical for EPI. The increases in liver enzymes, particularly ALP are higher than might be anticipated in EPI, but the prior steroid treatment and intestinal foreign bodies may have contributed to these changes. The changes in cobalamin and folate are suggestive of EPI or a blind loop syndrome.

Histopathology



Pancreas: atrophy with lymphoplasmacytic inflammation, still residual acinar tissue fibrosis
Liver: vacuolar hepatopathy - multifocal, clusters
Stomach: moderate lymphoplasmocytic infiltrate lymphoid nodules in deep lamina propria; +++*helicobacter* organisms
Duodenum/jejunum/ileum: Peyers patches sampled
Mesenteric lymph node: hyperplasia

No obstruction was visualized by ultrasound or at surgery, so the changes in cobalamin and folate are likely a consequence of EPI. However the TLI test result at 5.28 argued strongly against EPI. Usually dogs with signs of EPI have TLI < 2.5. In this case histology confirmed atrophy secondary to lymphocytic infiltration. Perhaps the small amount of inflammation in the residual pancreatic tissue was enough to keep the TLI in the normal range while exocrine secretion was severely impaired. Unfortunately the owner declined further TLI tests to further investigate the normal TLI.

- the regulation of small intestinal mucosal growth, enzyme synthesis and enzyme degradation *(Batt et al, 1979; Sorensen et al, 1988; Simpson et al, 1989b)*.

Trace element status in EPI has received relatively little study. One report of German Shepherd dogs with EPI indicates normal serum concentrations of copper and zinc. However, it has been recently demonstrated that serum copper and zinc decline, and serum iron and transferrin saturation increase, after pancreatic duct ligation *(Adamama-Moraitou et al, 2001)*.

The clinical significance of these abnormalities is unclear. The severe malassimilation of nutrients in EPI can lead to protein calorie malnutrition **(Figure 8)** that may further compromise residual pancreatic function, intestinal absorption and metabolic homeostasis.

Dermatological abnormalities are variably present in German Shepherd dogs with EPI and their presence may be related to protein calorie malnutrition, deficiencies in trace elements and minerals and potentially adverse reactions to food.

► Treatment

> Enzyme supplement

A non-enteric enzyme preparation must be given at mealtimes in situations of insufficient enzyme secretion by the exocrine pancreas. Only powder enzyme preparations coated to resist the gastric acid should be administered. The alternative is feeding fresh pancreas.

Use only non-enteric coated powdered supplements that are in date and stored appropriately (dog: 0.25-0.4 g/kg body weight/meal or 2 tsp/20 kg body wt/meal) *(Westermarck et al, 1987; Wiberg et al, 1998)*. The enzyme supplement should be mixed into the food. Pre-incubation does not significantly impact outcome *(Pidgeon & Strombeck, 1982)*. A new batch, change of preparation or increased amounts may produce a response. If cessation of diarrhea and weight gain are observed over a two week period the animal is maintained on this regimen and an attempt is made to decrease the enzyme supplement to the lowest effective dose.

If the therapy fails, the lot or the mode of presentation may be changed, or the enzyme quantities increased. If a response is not being achieved with a dose of 0.4 g/kg of non-enteric coated powdered extract or 3g/kg body weight/meal whole pancreas, inadequate enzyme replacement is an unlikely reason for treatment failure.

> Micronutrients

Fat soluble vitamins are likely candidates for malabsorption, and low levels of Vitamins A and E have been reported in German Shepherd dogs with EPI. Vitamin E can be given orally (400-500 IU SID q 1 month). It seems prudent to examine the vitamin K status of dogs with EPI who have laboratory evidence of a coagulopathy.

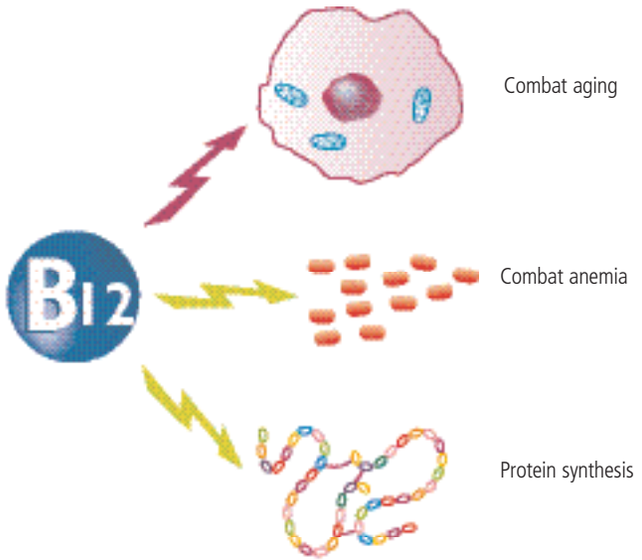
Cobalamin deficiency can have a myriad of effects on the body and the provision of supplementary parenteral cobalamin (cyanocobalamin, Vitamin B12) is recommended because pancreatic enzyme supplementation does not reverse the deficiency. Studies in dogs indicate that the parenteral administration of a single dose of cyanocobalamin (250-500 µg SQ once per month) is enough to prevent recurrence of metabolic abnormalities for up to one month. The cobalamin malabsorption does not resolve after enzyme supplementation and lifelong therapy is recommended.

A 50% reduction of the initial dose is possible in the majority of the dogs *(Simpson et al, 1994)*. This adaptation of the dose is important, because the cost of pancreatic enzymes is an obstacle to treatment for many owners, who prefer to euthanize their dogs.

► Feeding dogs with EPI

The pivotal role of the exocrine pancreas in the digestion and assimilation of nutrients would suggest that EPI is a disease that would be particularly amenable to nutritional intervention. In theory a highly digestible, fat restricted diet (fat is considered the most difficult nutrient to assimilate and lipase

FIGURE 9 - ROLE OF VITAMIN B12 IN THE ORGANISM



Vitamin B12 plays a fundamental role in protein synthesis and red blood cell production and has an enzyme function in many essential biochemical reactions.

activity is the limiting step in its digestion) that is low in fiber (fiber is indigestible, lowers energy density and hinders pancreatic enzyme activity) would seem justified in dogs with EPI. However, analysis of the outcome (survival) of 116 dogs with EPI indicates that dogs that received a modified diet (n=73, 30% dead) did not outlive those receiving a standard diet (n=43, 35% dead) *(Hall et al, 1991)*.

> Potential advantages of a high fat content

In complete contrast to the paradigm of fat restriction in EPI, diets with 43% calories from fat have been shown to promote better protein, fat and carbohydrate digestibility compared to diets containing 18 and 27% calories from fat in dogs with experimental EPI *(Suzuki et al, 1999)*. Improved preservation of exogenous pancreatic enzymes, especially lipase, could explain this observation. It is of note that studies in dogs with experimental exocrine pancreatic insufficiency demonstrated that fecal fat output is more dependant on the digestibility of the fat, rather than the amount fed *(Pidgeon, 1982; Pidgeon & Strombeck, 1982)*.

A case report of 3 German Shepherd dogs with EPI and poor haircoat demonstrated that a 19% fat DM (40.8 % of calories from fat), soy protein isolate hydrolysate and rice diet was well tolerated and improved fecal quality, haircoat and weight gain (2-10 kg) compared with the dogs previous diets. The dogs recovered optimal body condition within a 2-month period *(Biourge & Fontaine, 2004)*.

These observations suggest that high fat, highly digestible diets are not contra-indicated in the management of EPI. Traditionally, dietary supplementation with medium chain triglyceride oil (2-4 mL/meal) has been considered a beneficial way of providing calories to severely malnourished patients fed a highly digestible fat restricted diet but supportive data are lacking. However feeding a higher fat and thus more energy dense diet could promote a rapid restoration of optimal body weight without recourse to medium chain triglyceride oil.

As the importance of nutritional modification in the management of EPI is far from clear, and the costs associated with special diets are a common reason for euthanasia this author recommends initially feeding a good quality maintenance dog food (i.e. high digestibility) with an appropriate exogenous enzyme supplement mixed into it. If the response to treatment is poor then dietary modification is an option (see treatment failure- below).

Benefits of dietary modification in dogs (n=14) fed a "moderate fat, highly digestible low fiber diet" for four weeks versus a maintenance diet were restricted to a tendency (8/14 dogs) to reduced borborygmi, flatulence and fecal volume *(Westermarck et al, 1990)*. A study in 21 EPI dogs, evaluating the benefit of feeding a low fat (13% of calories), low fiber diet compared to the usual commercial or home cooked diet failed to show any significant benefit of severe fat restriction *(Westermarck et al, 1995)*.

Finally, feeding a low fat (13% of calories) diet in combination with exogenous enzymes (2.5 g/300 g food) to dogs (n=20) has been shown to promote a 24% average weight gain over a four month period, and a good response in 17/20 dogs *(Simpson et al, 1994)*. However, the role of the diet in this study is unclear as 11/20 dogs were subsequently successfully maintained on a variety of diets after the trial period.

> Treatment failures

• *Inadequate enzyme supplementation*

This is probably the number one cause of treatment failure. Some dogs develop an aversion to the enzyme supplement and raw pancreas may have to be used, if attempts to disguise the powder are unsuccessful. Stomatitis has been reported as a side effect of exogenous enzyme supplementation and may be remedied by decreasing the supplement by 50% *(Rutz et al, 2002)*. Decreasing the enzyme supplement may also be considered in the majority of dogs with EPI.

• *Bacterial overgrowth/intolerance*

EPI may impact the quantity and composition of the small intestinal flora and compromise the host response to a normal or abnormal flora. These alterations are usually addressed by treatment with an enzyme supplement. However, in some patients, diarrhea cannot be eliminated until antibiotics are administered. In these patients treatment failure may reflect decreased synthesis of intestinal mucosal enzymes associated with EPI. The presence of an abnormal flora cannot be predicted accurately by measuring serum concentrations of cobalamin and folate, so a trial with an antibiotic such as oxytetracycline (20 mg/kg PO TID 28d), or tylosin (10mg/kg PO TID) can be undertaken.

• *Small intestinal disease*

Routine hematology and biochemistry are almost always normal in uncomplicated EPI, so abnormalities such as hypoproteinemia (which may indicate a protein losing enteropathy) should be pursued.

• *Dietary modifications*

Once these common reasons for treatment failure (inadequate enzyme supplementation, the presence of bacterial overgrowth or intolerance, and concomitant small intestinal disease) have been addressed, nutritional modification must be considered.

Dietary management of small intestinal disease is typically based on feeding a highly digestible, usually a rice based diet that is restricted in fat. If dietary sensitivity is suspected an antigen restricted or protein hydrolysate diet may be employed. Hydrolysates are produced by enzymatic proteolysis of native proteins which results in an array of peptides that are small enough so that they may not be recognized by, nor trigger a reaction by the immune system *(Guilford, 1996)*. These peptides are also highly digestible, therefore reducing their retention time in the lumen of the intestine. Soy hydrolysates have been used extensively in the prevention of food sensitivity in babies and in calves *(Lallès et al, 1995; Terracciano et al, 2002)*. If gastrointestinal signs resolve after the dietary trial (usually one to two weeks) it is necessary to rechallenge the individual with the original diet to confirm a diagnosis of dietary intolerance. The addition of specific antigens such as beef, soy, chicken to the diet that induced remission is required to document hypersensitivity.

It is of interest that the use of a soy hydrolysate diet with relatively high fat content was effective in facilitating weight gain, decreasing diarrhea and improving haircoat in three dogs with EPI that had failed to respond to diet and pancreatic extracts *(Biourge & Fontaine, 2004)* **(Figure 10)**.

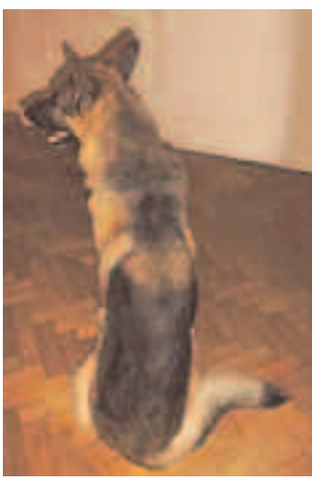
If response to treatment is still poor then acid suppression to protect pancreatic enzymes and empirical dietary modifications can be made, while carefully reviewing the diagnosis of EPI and considering other underlying disorders.

Dogs with confirmed EPI that respond poorly to appropriate enzyme supplementation and antimicrobial therapy usually require investigation of the small intestine.

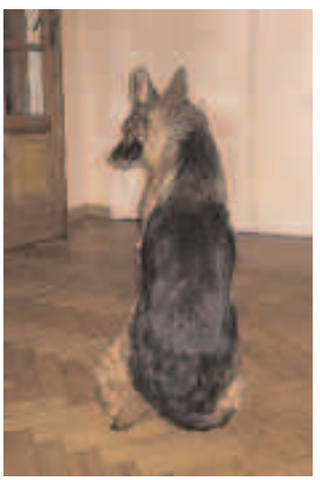
► Conclusion/prognosis

In a majority of dogs suffering from EPI a high quality maintenance diet supplemented with powdered pancreatic enzymes resolves most of the abnormalities associated with the disease. The relatively high cost of enzyme supplementation and special diets can significantly impact the outcome, precipitating euthanasia. If pancreatitis or diabetes is associated, prognosis is more reserved.

FIGURE 10 - GERMAN SHERPHERD SUFFERING FROM EXOCRINE PANCREATIC INSUFFICIENCY



(A) Pre-treatment



(B) Post-treatment

Pre (A) and post (B) dietetic treatment with a rice and soy protein isolate hydrolysate based food.

Frequently asked questions: exocrine pancreatic insufficiency

Q	A
The expense of pancreatic enzymes makes it hard for me to justify treating my dog. Is there any way around this?	Enzyme costs can be reduced by feeding cow or pig pancreas (where available), this can be stored frozen in individual portions. A powdered pancreatic extract is usually recommended and the dose of this may decrease with time, reducing cost.
Do I have to pre-incubate the food with the pancreatic enzymes?	No. Sprinkle on the powder and mix it thoroughly. Pre-incubation is unnecessary.
Will my dog have to be on pancreatic enzyme supplementation for life?	Usually this is the case. However, the amount of enzymes is often able to be reduced with time and some reports suggest that occasional dogs may eventually be maintained enzyme free.
Can I breed my dog that has been diagnosed with exocrine pancreatic insufficiency?	Pancreatic acinar atrophy is a heritable condition in breeds such as German Shepherds and Rough Coated Collies. It is therefore recommended not to breed dogs that have EPI, or come from lines associated with EPI.

References

Adamama-Moraitou K, Rallis T, Papasteriadis A et al - Iron, zinc, and copper concentration in serum, various organs, and hair of dogs with experimentally induced exocrine pancreatic insufficiency. Dig Dis Sci 2001; 46(7): 1444-57.

Adamama-Moraitou KK, Rallis TS, Prassinos NN et al - Serum vitamin A concentration in dogs with experimentally induced exocrine pancreatic insufficiency. Int J Vitam Nutr Res 2002; 72(3): 177-82.

Batt RM, Bush BM, Peters TJ - Biochemical changes in the jejunal mucosa of dogs with naturally occurring exocrine pancreatic insufficiency. Gut 1979; 20(8): 709-15.

Batt RM, Horadagoda NU, McLean L et al - Identification and characterization of a pancreatic intrinsic factor in the dog. Am J Physiol 1989; 256(3 Pt 1): G517-23.

Biourge V, Fontaine J - Exocrine Pancreatic Insufficiency and Adverse Reaction to Food in Dogs: a Positive Response to a High-Fat, Soy Isolate Hydrolysate-Based diet. J of Nutrition 2004; 134: 2166S-2168S.

Boari A, Williams DA, Famigli-Bergamini P - Observations on exocrine pancreatic insufficiency in a family of English setter dogs. J Small Anim Pract 1994; 35: 247-251.

Guilford WG - Adverse reactions to food and Nutritional management of gastrointestinal diseases. In: Strombeck's small animal gastroenterology 1996; Guilford WG, Center SA, Strombeck DR, Williams DA & Meyer DJ eds, 436-450 & 889-910. WB Saunders Company, Philadelphia, A.

Hall EJ, Bond PM, Butt RM et al - A survey of the diagnosis and treatment of canine exocrine pancreatic insufficiency. J Small Anim Pract 1991; 32: 613-619.

Hellmann J, Loppnow H - Hyperplasia of somatostatin and pancreatic polypeptide immunoreactive cells in dogs with idiopathic atrophy of the exocrine pancreas. Zentralbl Veterinarmed A 1991; 38(2): 80-9.

Lallès, JP, Toullec R, Branco Pardal P et al. Hydrolyzed soy protein isolate sustains high nutritional performance in veal calves. J Dairy Sci 1995; 78: 194-204.

Moeller EM, Steiner JM, Clark LA et al - Inheritance of pancreatic acinar atrophy in German Shepherd Dogs. Am J Vet Res 2002; 63(10): 1429-34.

Pidgeon G - Effect of diet on exocrine pancreatic insufficiency in dogs. J Am Vet Med Assoc 1982; 181(3): 232-5.

Pidgeon G, Strombeck DR - Evaluation of treatment for pancreatic exocrine insufficiency in dogs with ligated pancreatic ducts. Am J Vet Res 1982; 43(3): 461-4.

Raiha M, Westermack E - The signs of pancreatic degenerative atrophy in dogs and the role of external factors in the etiology of the disease. Acta Vet Scand. 1989; 30(4): 447-52.

Rogers WA, O'Dorisio TM, Johnson SE et al - Postprandial release of gastric inhibitory polypeptide (GIP) and pancreatic polypeptide in dogs with pancreatic acinar atrophy. Correction of blunted GIP response by addition of pancreatic enzymes to a meal. Dig Dis Sci 1983; 28(4): 345-9.

Rutz GM, Steiner JM, Williams DA - Oral bleeding associated with pancreatic enzyme supplementation in three dogs with exocrine pancreatic insufficiency. J Am Vet Med Assoc 2002; 221(12): 1716-8.

Simpson KW, Alpers DH, De Wille J et al - Cellular localization and hormonal regulation of pancreatic intrinsic factor secretion in dogs. Am J Physiol 1993; 265(1 Pt 1): G178-88.

Simpson KW, Johnstone JMS, Bell PRF et al - Pancreatic function following partial pancreatectomy and anastomosis of the pancreatic duct to the stomach or duodenum in dogs. Res Vet Sci 1992; 52: 97-104.

Simpson JW, Maskell IE, Quigg J et al - Long term management of canine exocrine pancreatic insufficiency. J Small Anim Pract 1994; 35: 133-138.

Simpson KW, Morton DB, Batt RM - Effect of exocrine pancreatic insufficiency on cobalamin absorption in dogs. Am J Vet Res 1989a; 50(8): 1233-6.

Simpson KW, Morton DB, Sorensen SH et al - Biochemical changes in the jejunal mucosa of dogs with exocrine pancreatic insufficiency following pancreatic duct ligation. Res Vet Sci 1989b; 47(3): 338-45.

Simpson KW, Simpson JW, Lake S et al - Effect of pancreatectomy on plasma activities of amylase, isoamylase, lipase and trypsin-like immunoreactivity in dogs. Res Vet Sci 1991; 51: 78-82.

Sorensen SH, Riley JE, Lobley RW et al - Investigation of the physical properties of dog intestinal microvillar membrane proteins by polyacrylamide gel electrophoresis: a comparison between normal dogs and dogs with exocrine pancreatic insufficiency. Biochim Biophys Acta 1988; 955(3): 275-82.

Suzuki A, Mizumoto A, Rerknimitr R et al - Effect of bacterial or porcine lipase with low- or high fat diets on nutrient absorption in pancreatic-insufficient dogs. Gastroenterology 1999; 116: 431-437.

Terracciano L, Isoardi P, Arrigoni S et al - Use of hydrolysates in the treatment of cow's milk allergy. Ann Allergy Asthma Immunol 2002; 89 (6 Suppl 1): 86-90.

Westermarck E - The hereditary nature of canine pancreatic degenerative atrophy in the German shepherd dog. Acta Vet Scand 1980; 21(3): 389-94.

Westermarck E -Treatment of pancreatic degenerative atrophy with raw pancreas homogenate and various enzyme preparations. Zentralbl Veterinarmed A 1987; 34(10): 728-33.

Westermarck E, Batt RM, Vaillant C et al - Sequential study of pancreatic structure and function during development of pancreatic acinar atrophy in a German shepherd dog. Am J Vet Res 1993a; 54(7): 1088-94.

Westermarck E, Junttila JT, Wiberg ME - Role of low dietary fat in the treatment of dogs with exocrine pancreatic insufficiency. Am J Vet Res 1995; 56: 600-605.

Westermarck E, Myllys V, Aho M - Effect of treatment on the jejunal and colonic bacterial flora of dogs with exocrine pancreatic insufficiency. Pancreas 1993b; 8(5): 559-62.

Westermarck E, Wiberg M - Exocrine pancreatic insufficiency in dogs.Vet Clin North Am Small Anim Pract. 2003; 33(5):1165-79.

Westermarck E, Wiberg M, Junttila J - Role of feeding in the treatment of dogs with pancreatic degenerative atrophy. Acta Vet Scand 1990; 31(3): 325-31

Wiberg ME - Pancreatic acinar atrophy in German shepherd dogs and rough-coated collies. Etiopathogenesis, diagnosis and treatment. A review. Vet Q 2004; 26(2): 61-75.

Wiberg ME, Lautala HM, Westermarck E - Response to long-term enzyme replacement treatment in dogs with exocrine pancreatic insufficiency. J Am Vet Med Assoc 1998; 1; 213(1): 86-90.

Wiberg ME, Nurmi AK, Westermarck E - Serum trypsinlike immunoreactivity measurement for the diagnosis of subclinical exocrine pancreatic insufficiency. J Vet Intern Med 1999a; 13(5): 426-32.

Wiberg ME, Saari SA, Westermarck E - Exocrine pancreatic atrophy in German Shepherd Dogs and Rough-coated Collies: an end result of lymphocytic pancreatitis. Vet Pathol 1999b; 36(6): 530-41.

Wiberg ME, Westermarck E - Subclinical exocrine pancreatic insufficiency in dogs. J Am Vet Med Assoc 2002; 220(8): 1183-7.

Williams DA, Batt RM - Sensitivity and specificity of radioimmunoassay of serum trypsin-like immunoreactivity for the diagnosis of canine exocrine pancreatic insufficiency. J Am Vet Med Assoc 1988; 192: 195-201.

Williams DA, Batt RM, McLean L - Bacterial overgrowth in the duodenum of dogs with exocrine pancreatic insufficiency. J Am Vet Med Assoc 1987; 191: 201-206. 76

2 - Acute pancreatitis

► Diagnostic reminder

A diagnosis of acute pancreatitis is based on a combination of compatible clinical, clinicopathological and imaging findings. Surgical biopsy may be required to confirm a diagnosis, and to distinguish inflammation from neoplasia.

Dog suffering from acute pancreatitis.

> History

The history may reveal a recent episode of dietary indiscretion, toxin ingestion (e.g. chocolate or high-fat food) or drug administration. Common clinical signs include lethargy, anorexia, hunched stance, vomiting (± blood), diarrhea (± blood), increased respiratory rate and enlarged abdomen. Some dogs have a history of icterus preceded by vomiting.

Polyuria and polydipsia may be present in dogs with diabetes mellitus and pancreatitis.

> Physical examination

Physical findings in dogs with acute pancreatitis are very variable, ranging from depression, to mild dehydration with signs of abdominal pain, to acute abdominal crisis, shock (tachycardia, prolonged capillary refill time, tacky mucous membranes, hypothermia), petechiation, icterus and ascites. An abdominal mass is palpated in some dogs.

> Supplementary tests – clinicopathological findings

- ***Hematology***

Extremely variable, ranging from mild neutrophilia and slightly increased hematocrit, through marked leukocytosis with or without a left shift, to thrombocytopenia, anemia and neutropenia with a degenerative left shift. When thrombocytopenia is detected, tests of hemostasis (OSPT, APTT, FDP or D-dimer, fibrinogen, antithrombin III) are performed to determine if the patient has a disseminated intravascular coagulopathy (DIC).

- ***Serum biochemistry***

Serum biochemical abnormalities include azotemia (pre-renal and renal), increased liver enzymes (ALT, AST, AP), hyperbilirubinemia, lipemia, hyperglycemia, hypoproteinemia, hypocalcemia, metabolic acidosis and variable abnormalities (usually decreased) in sodium, potassium and chloride.

- ***Urinalysis***

Urinalysis enables azotemia to be characterized as renal or pre-renal. Proteinuria occurs in some dogs with acute pancreatitis, possibly as a consequence of pancreatic enzyme-mediated glomerular damage, and is usually transient. The presence of glucose or ketonuria should prompt consideration of diabetes mellitus.

- ***Pancreas specific enzymes***

Classically, elevations in serum amylase and lipase activity have been used as indicators of pancreatic inflammation in dogs. However these enzymes can be increased in non-pancreatic disease, and dogs with confirmed pancreatitis may also have normal amylase and lipase activity. For example, in dogs with histologically confirmed pancreatitis, lipase is normal in 28 to 61% of dogs, and amylase is normal in 31 to 47% of dogs (*Strombeck et al, 1981; Hess et al, 1998; Mansfield et al, 2003)*. These limitations have led to the development of assays for enzymes or markers considered pancreatic in origin such as trypsin-like immunoreactivity (TLI), trypsinogen activation peptide (TAP), and pancreatic lipase immunoreactivity (PLI). Experimental studies have documented high concentrations of TLI, TAP and PLI in dogs with experimental acute pancreatitis.

The utility of TLI, TAP and PLI for the diagnosis of spontaneous pancreatitis in dogs has not been thoroughly evaluated.

Normal, subnormal and increased concentrations of TLI have been observed in dogs with confirmed pancreatitis and TLI level does not predict severity *(Ruaux & Atwell, 1999)*.

Elevations of TAP have been observed in the serum and urine of dogs with severe pancreatitis, and TAP may be a better prognostic than diagnostic indicator of pancreatic inflammation *(Mansfield & Jones, 2000; Mansfield et al, 2003)*.

Experience with PLI is even more limited, though it appears more promising than TLI as serum elevations of PLI seem more substantial and prolonged than TLI. Diseases such as renal disease can increase TLI, TAP and PLI.

- ***Radiography***

Radiographic findings in dogs with acute pancreatitis are generally non-specific and include loss of serosal detail, increased opacity in the right cranial quadrant of the abdomen, displacement of the duodenum ventrally and/or to the right, dilated hypomotile duodenum and caudal displacement of the transverse large intestine. Punctate calcification may occasionally be identified in dogs with long-standing pancreatitis. It indicates saponification of mesenteric fat around the pancreas.

Thoracic radiographs may enable the detection of pleural fluid, edema or pneumonia which has been associated with pancreatitis in dogs.

- ***Ultrasonography***

One study of dogs with fatal acute pancreatitis indicated that ultrasound supported a diagnosis of pancreatitis in 23/34 dogs *(Hess et al,1998)*.

Ultrasonographic signs identical to those observed in the case of pancreatitis **(Figure 11)** may exist alongside other disorders such as pancreatic neoplasia, pancreatic edema (associated with hypoproteinemia or portal hypertension) and enlarged peri-pancreatic structures *(Lamb et al, 1995)*. Fine needle aspirates of cavitary lesions may be useful to distinguish abscess from pseudocyst.

- ***Other imaging modalities***

Contrast enhanced computed tomography is the imaging technique of choice in people with pancreatitis and enables the distinction between pancreatic necrosis and mild pancreatitis. It has only undergone preliminary evaluation in dogs *(Jaeger et al, 2003)*.

- ***Abdominal paracentesis***

Examination of peritoneal fluid may aid the detection of various causes of acute abdominal signs such as pancreatitis, gastrointestinal perforation or ruptured bile duct.

- ***Surgery***

Surgical intervention can be undertaken in patients with persistent or recurrent pancreatitis to confirm the diagnosis and to detect neoplasia and complicating factors such as infection. Surgery is also indicated to drain pancreatic abscesses and persistent pseudocysts *(Salisbury et al, 1988)*. The advent of laparascopic techniques may decrease morbidity *(Harmoinen et al, 2002)*. Surgery is also indicated to place enteral feeding tubes (see nutritional management below) and it is prudent to consider feeding tube placement prior to an exploratory surgery in dogs with suspected pancreatitis.

Ultrasonographic findings in a dog

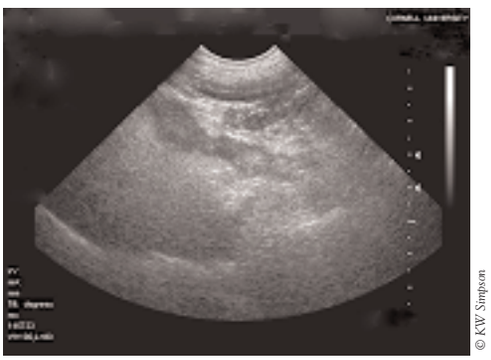


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Figure 11A - *English translation*
The pancreas is diffusely enlarged with irregular margins and mixed echogenicity. The mesenteric fat in the right cranial abdomen is hyperechoic and scatters sound.

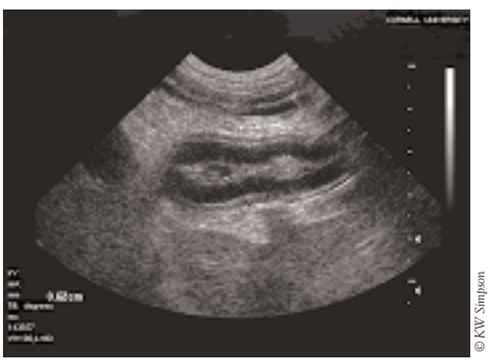

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Figure 11B - *The duodenum at the cranial flexure has a diameter of 1.6cm with a thick wall of 6.2mm . There is a moderate amount of gas in the duodenum and it has a corrugated appearance.*

Conclusions: suspect pancreatitis, focal peritonitis

> Differential diagnosis

The differential diagnosis of acute pancreatitis in dogs is usually focused on vomiting and abdominal pain **(Table 3)**.
The combined results of the history, physical examination, clinicopathological tests and diagnostic imaging are used to distinguish pancreatitis from metabolic, polysystemic infectious, toxic, neurologic and other intra-abdominal causes of vomiting.

TABLE 3 - DIFFERENTIAL DIAGNOSIS OF ABDOMINAL PAIN AND VOMITING

Causes of Abdominal Pain		Causes of vomiting	
Gastric **Intestinal**	- Dilatation/volvulus, ulceration - Obstruction, Intususception, Rupture, Torsion, Enteritis	• **Intraabdominal** Gastric	- Gastritis, Ulceration, Neoplasia, Outflow obstruction, Foreign bodies, - Motility / functional disorders
Pancreatic **Hepatic**	- Pancreatitis - Acute hepatitis, Ruptured bile duct, Hepatic neoplasia	Intestinal	- Inflammatory Bowel Disease, Neoplasia, Foreign bodies, Intussusception, Torsion, Rupture, Bacterial Overgrowth, - Functional disorders
Splenic **Urogenital**	- Torsion, Ruptured neoplasm - Nephritis, Pyelonephritis, Ruptured bladder - Ureteral / urethral calculi, Pyometra, Prostatitis	• **Non-GIT**	- Pancreas: Pancreatitis, Pancreatic Neoplasia - Liver: Cholangiohepatitis, Biliary Obstruction - Genitourinary: Pyometra, Nephritis, Nephrolithiasis, Urinary Obstruction, Prostatitis - Peritonitis
Peritoneum	- Primary or secondary peritonitis (e.g. chemical - bile and urine: septic- Ruptured viscus hollow organ e.g. bladder, gut, etc.	Metabolic/Endocrine	- Uremia, Hypoadrenocorticism, Diabetic Ketoacidosis - Hepatic Encephalopathy, Hypercalcemia, Septicemia
		Drugs	- Digoxin, Erythromycin, Chemotherapy, Apomorphine, Xylazine
Pseudoabdominal pain	- Discospondylitis, prolapsed disc	Toxins Dietary Neurologic	- Strychnine, Ethylene Glycol, Lead - Indiscretion, Intolerance, Allergy - Vestibular disease, Encephalitis, Neoplasia, Raised intra-cranial pressure
		Infectious	- Distemper, Parvovirus, Infectious Canine Hepatitis, Leptospirosis, Salmonella

Where abdominal pain is the major finding it is rapidly pursued with radiography, ultrasonography, and paracentesis, with supportive treatment provided on the basis of physical findings and initial clinicopathological testing *(Macintire,1988)*.

Diarrhea, that can be bloody, may also be observed in dogs with acute pancreatitis. Acute pancreatitis and its complications (infection, pseudocyst or abscess formation) should be considered in the differential diagnosis of icterus and pyrexia.

> Pitfalls and frequent mistakes

Pancreatitis is likely to be overdiagnosed when either clinical signs or clinicopathological tests are used as the major/sole diagnostic criteria. Acute enteritis, intestinal obstruction and a variety of causes of the acute abdomen can have very similar clinical and clinicopathological findings to those of pancreatitis.

Over-reliance on serum markers of pancreatic disease may lead to misdiagnosis. Increases in total amylase and lipase are commonly encountered in a variety of other conditions, and normal values do not exclude pancreatitis. More specific tests of pancreatic inflammation such as TLI, TAP and PLI have not been thoroughly validated at this point so caution is advised when considering them.

Changes in pancreatic echogenicity and size have to be determined by a qualified sonographer, and the sonographic findings integrated with other findings to determine if pancreatitis is a likely diagnosis. Pancreatitis has to be distinguished from neoplasia, or other causes of parenchymal fluid accumulation such as portal hypertension, or hypoproteinemia.

► Epidemiology

> Risk factors

Middle aged to old dogs (>5 years old) that are overweight appear at higher risk. There is no clear sex predisposition. Dietary indiscretion, consumption of high fat meals, and the administration of drugs (e.g. azathioprine, phenobarbital and potassium bromide) or toxins (e.g. organophosphates) have been reported to precede the development of clinical signs suggestive of pancreatitis in dogs *(Simpson, 1993; Hess et al, 1999)*.

Endocrinopathies such as hypothyroidism, diabetes mellitus and hyperadrenocorticism may also be risk factors *(Hess et al, 1999)*. Thirteen percent of 221 dogs with diabetes mellitus had histological evidence of acute pancreatitis. Hyperlipidemia is another potential risk factor *(Hess et al, 2000)*.

- ***Breed predispositions***

Miniature Schnauzers, Yorkshire and Silky Terriers and perhaps miniature Poodles may be at increased risk of developing pancreatitis.

© Hemedine

The risk of pancreatitis will be higher in Miniature Schnauzers.

► Pathophysiological mechanisms

The etiology and pathogenesis of spontaneous pancreatitis is poorly understood *(Karne & Gorelick,1999; Zyromski & Murr, 2003)*. A wide variety of factors have been implicated by association or experimentation as causes of acute pancreatitis in the dog. The potential causes of pancreatitis with a nutritional aspect are summarized in **Figure 12**.

FIGURE 12 - POTENTIAL CAUSES OF PANCREATITIS WITH A NUTRITIONAL ASPECT

Clinical	Experimental
Dietary indiscretion	High fat and high fat/ low protein diets
Obesity (a)	Ethionine™ supplementation: an analog of methionine *(Simpson, 1993)*
Hyperlipidemia (b)	CCK hyperstimulation IV free fatty acids

12a

12b

Clinically, inflammation of the pancreas can be broadly categorized as acute, recurrent acute, or chronic. Acute and recurrent acute pancreatitis are characterized by sudden episodes of inflammation and appear to be the most frequent form of pancreatitis in the dog.

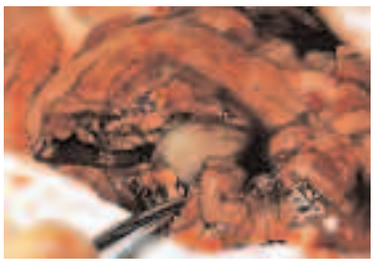


Figure 13 - Pancreatic abscess
Pancreatic abscess is a rare complication of acute pancreatitis in the dog. Treatment is generally surgical.

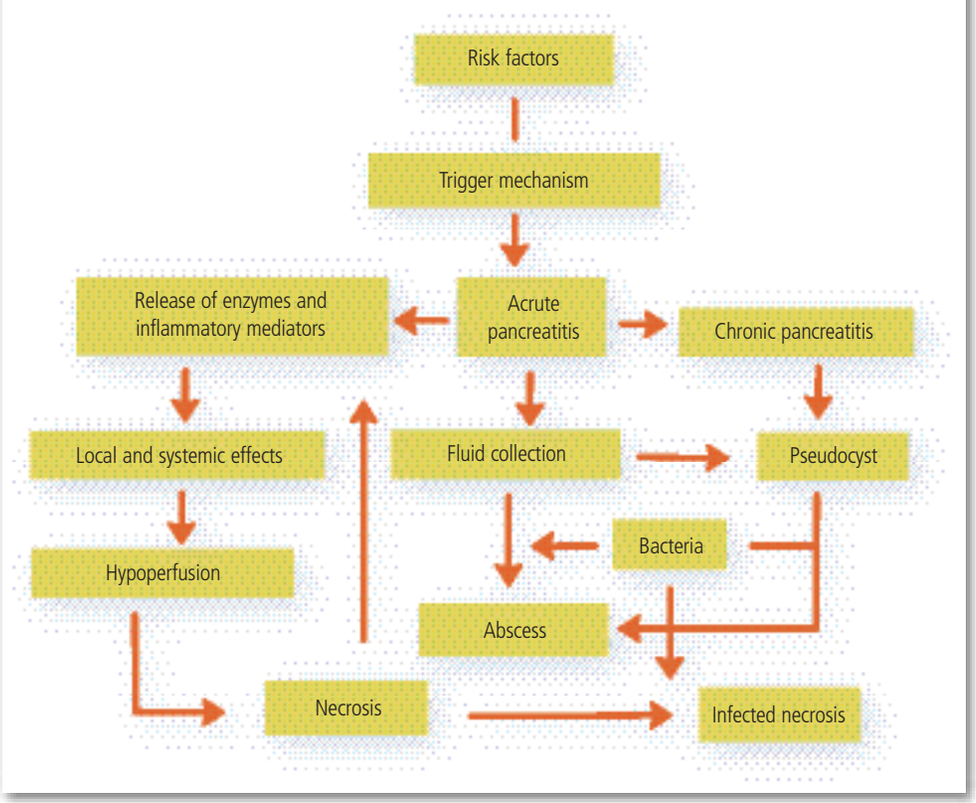
• Acute pancreatitis may resolve or may cause continued inflammation (chronic or recurrent acute) or necrosis which can be complicated by secondary infection and pseudocyst or abscess formation **(Figures 13 & 14)**.

• Chronic pancreatitis is characterized by low grade or sub-clinical inflammation and may be a factor in the development of diabetes mellitus and exocrine pancreatic insufficiency (EPI) in dogs.

Regardless of the initiating cause, pancreatitis is generally considered to occur when digestive enzymes are activated prematurely within the pancreas. Experimental pancreatic hyperstimulation with cholecystokinin (CCK) or its analogue cerulein, dietary supplementation with ethionine, and obstruction of the pancreatic duct lead to the formation of large intracellular vacuoles in acinar cells. Vacuole formation is thought to be a consequence of the uncoupling of exocytosis of zymogens and abnormal intracellular trafficking of digestive and lysosomal enzymes. These subcellular alterations are considered to precipitate the intracellular activation of digestive enzymes.

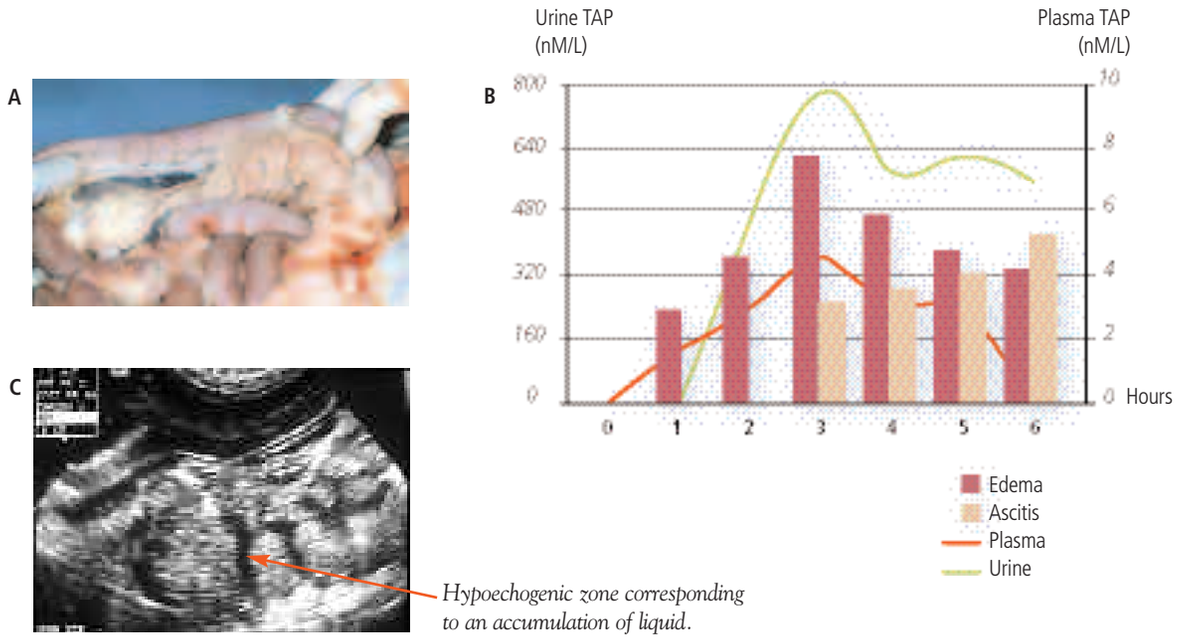
Pancreatic hyperstimulation may be of direct relevance to naturally occurring pancreatitis in dogs. CCK is normally released by cells in the duodenum in response to intraluminal fat and amino acids and coordinates and stimulates pancreatic secretion and gallbladder contraction during digestion. It is possible that high fat diets exert their effects via the excessive release of cholecystokinin and that hypercalcemia, organophosphates and high levels of circulating glucocorticoids also facilitate (potentially by changing pancreatic sensitivity to hyperstimulation), or cause pancreatic hyperstimulation; however, this is not proven.

FIGURE 14 - PROPOSED PROGRESSION OF PANCREATITIS IN DOGS
(From: Simpson & Lamb, 1995)



Edematous pancreatitis induced by CCK hyperstimulation in dogs is characterized by a rapid but self-limiting, burst of trypsinogen activation **(Figure 15)**, suggesting that the pancreas has a feedback mechanism to limiting trypsinogen synthesis and activation (see nutritional management) *(Simpson et al, 1995)*. This concept of pancreatic down regulation is important when considering nutritional intervention in acute pancreatitis.

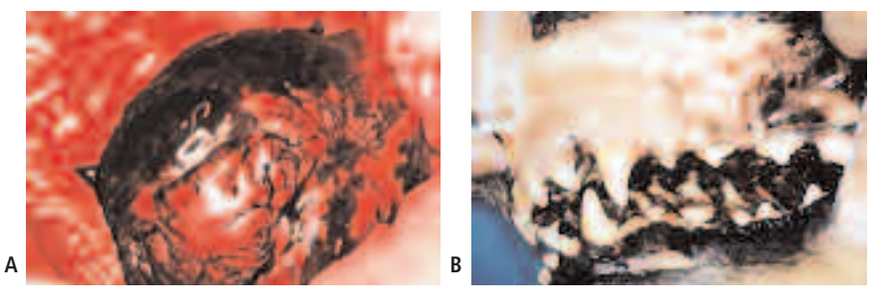
FIGURE 15 - EDEMATOUS PANCREATITIS AND INTRAPANCREATIC ACTIVATION OF TRYPINOGEN



Edematous pancreatitis is generally regarded as the mildest form of pancreatitis ***(A)****. It is associated with self-limiting trypsinogen activation and release of trypsinogen activation peptide (TAP) into the circulation* ***(B)****. In the clinical setting the accumulation of fluid within the pancreas can be detected with ultrasound* ***(C)****.*

Release of active pancreatic enzymes and inflammatory mediators from the inflamed pancreas, such as tumor necrosis factor (TNF-α) interleukin-1 (IL-1) and platelet activating factor (PAF), amplify the severity of pancreatic inflammation, and adversely affects the function of many organs (systemic inflammatory response), and cause derangement in fluid, electrolyte and acid-base balance *(Denham & Norman, 1999; Ruaux et al, 1999; Brady & Otto, 2001; Mentula et al, 2004 ; Raraty et al, 2004)*.

FIGURE 16 - PANCREATIC NECROSIS AND ITS CONSEQUENCES



Severe pancreatitis is characterized by pancreatic thrombosis and necrosis ***(A)*** *with the liberation of pancreatic enzymes and inflammatory mediators causing a systemic inflammatory response and organ dysfunction. Clinical consequences in the coagulation system are petechiation* ***(B)*** *due to thrombocytopenia and echymosis associated with disseminated intravascular coagulopathy.*

It is the development of multisystemic abnormalities that separates mild from severe, potentially fatal pancreatitis. Elucidating the systemic inflammatory response holds the promise of novel treatments for acute pancreatitis and is the focus of current research *(Johnson et al, 2004; Oruc et al, 2004)*.

► Nutritional management

> Identify and prevent, or treat, nutritional factors associated with pancreatitis

Obesity, hyperlipidemia and dietary indiscretion are reported to be associated with pancreatitis in dogs. Where these are present it would seem prudent to address their underlying cause in an attempt to prevent future bouts of pancreatitis.

> Nutrient provision to dogs with pancreatitis

Precise recommendations for the dietary management of acute pancreatitis in dogs are hampered by the absence of controlled studies, and are often based on empirical wisdom and a best guess least harm approach.

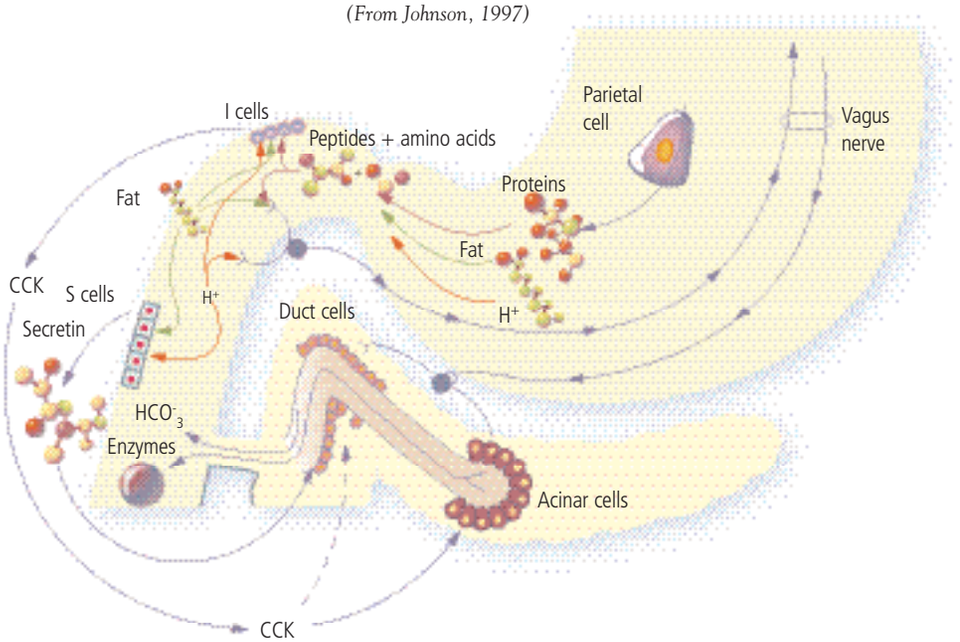
> The dilemma between feeding and stimulating the pancreas

It has been well documented that pancreatic secretion in healthy dogs occurs in response to ingested nutrients, particularly fats and amino acids delivered into the duodenum **(Figure 17)**.

Restricting oral intake, or providing nutrients intravenously, does not stimulate pancreatic secretion *(Stabile et al, 1984)*. Thus it has been largely accepted that to provide "pancreatic rest" oral intake should be withheld until clinical signs resolve, or when signs persist for approximately 72-96 hrs that parenteral nutrition is introduced. This dogma is still prevalent in veterinary and human medicine.

FIGURE 17 - REGULATION OF PANCREATIC SECRETION

(From Johnson, 1997)



Hormones such as CCK and secretin, the parasympathic system and the nerves of the duodenum and pancreas play a role in the pancreatic secretion in response to the arrival of food.

However, there is growing evidence in people and animals that enteral nutrition is superior to parenteral nutrition in the treatment of acute pancreatitis. It has been shown in both people and animals that jejunal feeding (distal to the site of pancreatic stimulation) does not exacerbate acute pancreatitis *(Vu et al, 1999; Qin et al, 2002, 2003)*.

People with acute pancreatitis fed via jejunostomy tubes (these can be oral transpyloric tubes), have lower morbidity, shorter hospital stays and less cost than those treated with TPN **(Figure 17)** *(Kalfarentzos et al, 1997; McClave et al, 1997; Windsor et al, 1998; Powell et al, 2000; Pupelis et al, 2000; Paraskeva et al, 2001; Duerksen et al, 2002)*.

Since it is now technically possible to place jejunostomy tubes non-surgically in dogs, through the nose, esophagus or stomach, clinical application of this feeding strategy is not restricted by a surgical procedure. However, it remains open to question whether patients with acute pancreatitis really require jejunal delivery of nutrients. There is evidence that the pancreas of dogs with acute experimental pancreatitis (see CCK induced pancreatitis above), and people with naturally occurring severe pancreatitis, is not as amenable to stimulation as the normal pancreas. Dogs recovering from naturally occurring pancreatitis have also been shown to have subnormal circulating TLI concentrations suggesting that pancreatic enzyme synthesis is downregulated. In addition, it appears that the major benefits of enteral support in acute pancreatitis in people and experimental dogs are due to reductions in the systemic inflammatory response and the translocation of enteric bacteria rather than a reduction in pancreatic stimulation. In this respect probiotic treatment may have a role, and it has been evaluated in people *(Olah et al, 2002)*.

Intestinal permeability and morbidity in dogs with parvovirus are positively impacted by feeding a liquid diet (41% protein, 18% fat, 3% crude fiber) through a nasoesophageal tube supporting the concept that enteral feeding in general, rather than jejunal delivery, is the reason for the beneficial effects of enteral nutrition, though this needs to be critically evaluated *(Mohr et al, 2003)*.

Despite the evidence from human clinical trials and experimental studies in dogs, resistance to enteral feeding of dogs with pancreatitis is anticipated. One common argument used to promote parenteral nutrition in dogs with pancreatitis is that they vomit too frequently to be fed enterally. However, recent studies in dogs with parvovirus should also help to allay this fear as these dogs tolerated naso-esophageal feeding despite severe vomiting and diarrhea, with enterally fed dogs showing faster recovery rates, greater body weight gains and lower intestinal permeability than dogs that were held nil per os *(Mohr et al, 2003)*.

It is not intended that parenteral nutrition be discontinued completely, but that its use be restricted to patients that really need it, for instance those in whom caloric intake is severely and persistently impaired by persistent vomiting. When parenteral nutrition is indicated a choice has to be made between total and partial parenteral nutrition. Partial parenteral nutrition (PPN) is a more practical and manageable procedure than TPN in most settings and has been shown to be a safe and effective way of providing nutrition to dogs with pancreatitis and gastrointestinal disease *(Chan et al, 2002)*. Interestingly dogs that received a combination of enteral and partial parenteral nutrition survived more often than those receiving partial parenteral nutrition exclusively *(Chan et al 2002)*.

Pancreatitis case study

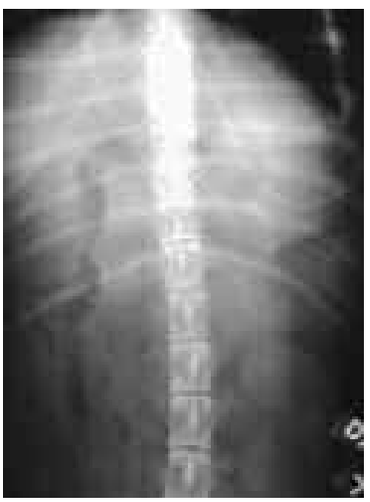
History
History of vomiting (bile), inappetence, and lethargy for 2 days. The dog is allowed free access to the backyard and has eaten trash in the past.

Physical examination
Hunched stance (A), depressed, tacky mucus membranes
Capillary refill time 1.5 secs
Heart rate 150 bpm
Temperature: 102°F
Painful abdomen

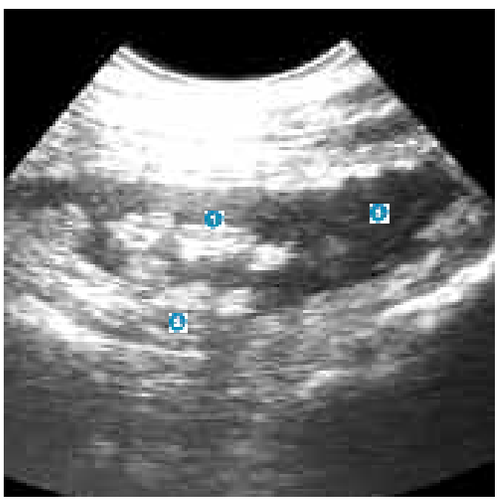
A - 8 year old female spayed mixed breed dog
The differential diagnoses are vomiting and abdominal pain (see **Table 3***). The tacky mucus membranes, fast CRT and heart rate are consistent with hypovolemia secondary to vomiting. The abdominal pain may also be causing the elevated heart rate. The initial diagnostic plan includes a minimum database (PCV, TP, azostick, glucose, urine specific gravity and dipstick), with a CBC, chemistry profile amylase and lipase submitted.*

Minimum data base	
PCV (%)	53
TP (g/dL)	7.9
BUN (mg/dL)	30-40
Glucose (mg/dL)	103
Na (mmol/L)	136
K (mmol/L)	4.5
Lipemia	evident
Urinalysis	USG 1.047, 2+ protein, pH 6

These results are interpreted as indicating hemoconcentration, with mild pre-renal azotemia. An intravenous catheter is placed and lactated ringers solution is started at twice maintenance fluid rate.



B - Abdominal radiograph



C - Abdominal ultrasound
1 - Hyperechogenic zone
2 - Fat saponification
3 - Hypoechogenic zone: liquid accumulation

Radiographs **(B)** *show a gas distended duodenum and a slight loss of abdominal detail consistent with peritonitis. An ultrasound is performed that shows an enlarged hypoechoic pancreas* **(C)** *and a small amount of free abdominal fluid.*

Results of the clinical pathology tests		
PCV (%)	52	(42-57)
MCV (fl)	72	(63-74)
WBC (thou/µL)	21.1	(6.2-14.4)
Neutrophils (thou/µL)	19	(3.4-9.7)
Band neutrophils (thou/µL)	1.1	(0-0.1)
Lymphocytes (thou/µL)	1.0	(1.3-4.7)
Platelets (thou/µL)	290	(179-483)

Coagulation cascade
Increased fibrinogen
Normal APTT, OSPT and d-dimer

Profile		
Alb (g/dL)	2.7	(3.1-4.1)
Globulin (g/dL)	3.4	(1.9-3.6)
ALP (UI/L)	750	(12-122)
ALT (UI/L)	400	(25-106)
Cholesterol (mg/dL)	400	(124-335)
Bilirubin (mg/dL)	0.4	(0.1-0.2)
Amylase (U/L)	2,400	(286-1124)
Creatinine (mg/dL)	1.8	(0-5-1.3)
Glucose (mg/dL)	131	(60-120)
Serum is lipemic		

Interpretation

No evidence of metabolic or endocrine causes of vomiting, no history of access to drugs or toxins. Static gas filled duodenum on radiographs suggests ileus secondary to intestinal disease, pancreatitis or peritonitis. Ultrasound showed no abnormalities apart from an enlarged hypoechoic pancreas. The laboratory tests showed hemoconcentration (increased PCV, and pre-renal azotemia), neutrophilia and a left shift, mild hypoalbuminemia, elevated liver enzymes, hypercholesterolemia, lipemic serum and increased fibrinogen. Taken as a whole these findings are consistent with a diagnosis of acute pancreatitis.

Treatment

A working diagnosis of pancreatitis was established. The absence of thrombocytopenia or coagulation changes argues against pancreatic necrosis. Treatment continues with crystalloids at twice maintenance fluid rate and an infusion of 10ml/kg of hetastarch. Heparin (100 u/kg SC) was given to clear the lipemia. Buprenorphine (0.01 mg/kg SC q 8hrs) was administered for abdominal pain. Ampicillin (20 mg/kg IV TID) was initiated because of the left shift. The dog is maintained NPO for 48 hrs. Vital signs, PCV and protein, electrolytes, platelet count, and body weight are monitored.

Vomiting and abdominal pain resolve on the third day and chicken broth is fed. The patient continues to improve and is weaned onto, and discharged on a fat restricted diet (due to hyperlipidemia).

Commentary

This dog has fairly classical findings associated with acute pancreatitis. The relatively rapid response to treatment along with absence of coagulation abnormalities is consistent with mild, rather than necrotizing, pancreatitis. The dietary management of this case is the conventional normal. Given recent observations in experimental dogs and people, enteral feeding could have been started through a nasogastric or nasojejunal feeding tube, however, the merits of this approach in clinical patients remains to be determined.

If the patient had presented with evidence of more severe pancreatitis or had not responded so rapidly to treatment a more aggressive therapeutic and nutritional plan would have been initiated, such as a plasma transfusion and surgical placement of a jejunostomy tube.

> What diet should be fed to dogs recovering from pancreatitis?

Free choice oral feeding is usually resumed when the appetite returns and vomiting and abdominal pain have subsided. Fat is frequently regarded as the major nutrient to be restricted as it stimulates CCK release and pancreatic secretion. However amino acids are also potent stimulators of pancreatic enzyme secretion and they are not restricted.

High-fat diets (>50 g/1000 kcal) with low protein contents (<20 g/1000 kcal) that have a nutrient profile similar to diet known to induce pancreatitis in dogs must be avoided. Obesity, a risk factor for pancreatitis, should be controlled with a balanced nutritional approach. Elemental diets cause a similar degree of pancreatic stimulation as normal diets.

The composition of a home-made diet must be adapted to the characteristics of the pancreatic disease.

- **Exocrine pancreatic insufficiency:**

Choose highly digestible ingredients. The ideal fat content can vary with individual cases:
- poor body condition: a diet designed for cachectic animals is suitable (**see chapter 13**)
- fat intolerance: a low fat-diet, suitable for hyperlipidemia is advised (**see chapter 7**)

A hypoallergenic diet can be the second choice if the animal doesn't respond or if a dietary allergy is suspected (**see Chapter 2**).

- **Acute pancreatitis:**

Choose a low fat-diet, suitable for hyperlipidemia (**see Chapter 7**).

Frequently asked questions: pancreatitis

Q	A
My dog has just recovered from pancreatitis. Is there anything I can do to avoid the dog getting pancreatitis again?	There is no simple answer to this question. Where risk factors can be eliminated the chance of recurrence is likely to be reduced. For example avoidance of dietary indiscretion or drugs (e.g phenobarbital and potassium bromide) that were thought to precipitate the bout may decrease the chance of recurrence. Where hyperlipidemia is present feeding a fat restricted diet and maintaining optimal body weight may decrease the chance of recurrence.
My dog was diagnosed with pancreatitis a week ago. He has now stopped vomiting but he is now turning yellow. Why is this happening?	The development of jaundice after acute pancreatitis is usually associated with obstruction of the bile duct by pancreatic inflammation. The diagnosis is usually made with a combination of blood tests and abdominal ultrasonography. Where the dog is otherwise happy and healthy conservative management consists of monitoring physical and biochemical parameters for approximately two weeks to see if hyperbilirubinemia and jaundice are resolving or worsening. When biliary obstruction persists for over two to three weeks it is usually relieved surgically.

References

Brady CA, Otto CM - Systemic inflammatory response syndrome, sepsis, and multiple organ dysfunction. Vet Clin North Am Small Anim Pract. 2001; 31(6): 1147-62.

Chan DL, Freeman LM, Labato MA et al - Retrospective evaluation of partial parenteral nutrition in dogs and cats. J Vet Intern Med 2002; 16(4): 440-5.

Denham W, Norman J - The potential role of therapeutic cytokine manipulation in acute pancreatitis. Surg Clin North Am 1999; 79: 767-782.

Duerksen DR, Bector S, Parry D et al - A comparison of the effect of elemental and immune enhanceing polymeric jejunal feeding on exocrine pancreatic function. J Parenter Enteral Nutr 2002; 26:205-8.

Harmoinen J, Saari S, Rinkinen M, et al - The advent of laparascopic techniques may decrease morbidity (Evaluation of pancreatic forceps biopsy by laparoscopy in healthy beagles).Vet Ther 2002; 3(1): 31-6.

Hess RS, Kass PH, Shofer FS, et al - Evaluation of risk factors for fatal acute pancreatitis in dogs. J Am Vet Med Assoc 1999; 214: 46-51.

Hess RS, Saunders HM, Van Winkle TJ et al - Clinical, clinicopathologic, radiographic, and ultrasonographic abnormalities in dogs with fatal acute pancreatitis: 70 cases (1986-1995). J Am Vet Med Assoc 1998; 213 (5): 665-670.

Hess RS, Saunders HM, Van Winkle TJ et al - Concurrent disorders in dogs with diabetes mellitus: 221 cases (1993-1998). Am Vet Med Assoc 2000; 15, 217(8):1166-73.

Jaeger JQ, Mattoon JS, Bateman SW et al - Combined use of ultrasonography and contrast enhanced computed tomography to evaluate acute necrotizing pancreatitis in two dogs. Vet Radiol Ultrasound 2003; 44(1): 72-9.

Johnson LR - Gastrointestinal Physiology:Fifth edition, 1997; Mosby-Year Book Inc. St. Louis MO: 97.

Johnson GB, Brunn GJ, Platt JL - Cutting edge: an endogenous pathway to systemic inflammatory response syndrome (SIRS)-like reactions through Tolllike receptor 4. J Immunol 2004; 172(1): 20- 4.

Kalfarentzos F, Kehagias J, Mead N et al - Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomised prospective trial. Br J Surg 1997; 84:1665-9.

Karne S, Gorelick FS - Etiopathogenesis of acute pancreatitis. Surg Clin North Am 1999; 79: 699- 710.

Lamb CR, Simpson KW, Boswood A et al - Ultrasonography of pancreatic neoplasia in the dog: a retrospective review of 16 cases. Vet Rec 1995; 137: 65-68.

Macintire DK - The acute abdomen - differential diagnosis and management. Seminars in Veterinary Medicine and Surgery Small Animal 1988; 3: 302- 310.

Mansfield CS, Jones BR - Plasma and urinary trypsinogen activation peptide in healthy dogs, dogs with pancreatitis and dogs with other systemic diseases. Aust Vet J 2000; 78(6): 416-22.

Mansfield CS, Jones BR, Spillman T - Assessing the severity of canine pancreatitis. Res Vet Sci 2003; 74(2): 137-44.

McClave SA, Greene LM, Snider HL et al. Comparison of the safety of early enteral vs parenteral nutrition in mild acute pancreatitis. J Parenter Enteral Nutr 1997; 21:14-20.

Mentula P, Kylanpaa ML, Kemppainen E et al - Plasma anti-inflammatory cytokines and monocyte human leucocyte antigen-DR expression in patients with acute pancreatitis. Scand J Gastroenterol 2004; 39(2): 178-87.

Mohr AJ, Leisewitz AL, Jacobson LS et al - Effect of early enteral nutrition on intestinal permeability, intestinal protein loss, and outcome in dogs with severe parvoviral enteritis. J Vet Intern Med 2003; 17(6): 791-8.

Olah A, Belagyi T, Issekutz A et al -Randomized clinical trial of specific lactobacillus and fibre supplement to early enteral nutrition in patients with acute pancreatitis. Br J Surg 2002; 89:1103-07.

Oruc N, Ozutemiz AO, Yukselen V et al - Infliximab: a new therapeutic agent in acute pancreatitis? Pancreas 2004; 28(1): e1-8.

Paraskeva C, Smailis D, Priovolos A et al. Early enteral nutrition reduces the need for surgery in severe acute pancreatitis. Pancreatology 2001; 1: 372. 88

Powell JJ, Murchison JT, Fearon KC - Randomized controlled trial of the effect of early enteral nutrition on markers of the inflammatory response in predicted severe acute pancreatitis. Br J Surg 2000; 87:1357- 81.

Pupelis G, Austrums E, Jansone A et al - Randomised trial of safety and efficacy of postoperative enteral feeding in patients with severe pancreatitis: preliminary report. Eur J Surg 2000; 166:383-7

Qin HL, Su ZD, Gao Q et al - Early intrajejunal nutrition: bacterial translocation and gut barrier function of severe acute pancreatitis in dogs. Hepatobiliary Pancreat Dis Int 2002; 1(1): 150-4.

Qin HL, Su ZD, Hu LG et al - Parenteral versus early intrajejunal nutrition: effect on pancreatitic natural course, entero-hormones release and its efficacy on dogs with acute pancreatitis. World J Gastroenterol 2003; 9(10): 2270-3.

Raraty MG, Connor S, Criddle DN - Acute pancreatitis and organ failure: pathophysiology, natural history, and management strategies. Curr Gastroenterol Rep 2004; 6(2): 99-103.

Ruaux CG, Atwell RB - Levels of total alphamacroglobulin and trypsin-like immunoreactivity are poor indicators of clinical severity in spontaneous canine acute pancreatitis. Res Vet Sci 1999; 67(1): 83-7.

Ruaux CG, Pennington HL, Worrall S et al - Tumor necrosis factor-alpha at presentation in 60 cases of spontaneous canine acute pancreatitis. Vet Immunol Immunopathol 1999; 72: 369-376.

Salisbury SK, Lantz GC, Nelson RW et al - Pancreatic abscess in dogs : six cases (1978-1986). J Am Vet Med Assoc 1988; 193: 1104-8.

Simpson KW - Current concepts of the pathogenesis and pathophysiology of acute pancreatitis in the dog and cat. Comp Cont Ed Prac Vet 1993; 15: 247- 253.

Simpson KW, Beechey-Newman N, Lamb CR et al - Cholecystokinin-8 induces edematous pancreatitis in dogs which is associated with a short burst of trypsinogen activation. Dig Dis Sci 1995; 40: 2152- 2161.

Simpson KW, Lamb CR - Acute pancreatitis in the dog. In Practice - Journal of Veterinary Postgraduate Clinical Study1995; 17: 328-337.

Stabile BE, Borzatta M, Stubbs RS - Pancreatic secretory responses to intravenous hyperalimentation and intraduodenal elemental and full liquid diets. J Parenter Enteral Nutr 1984; 8(4): 377- 80.

Strombeck DR, Farver T, Kaneko JJ - Serum amylase and lipase activities in the diagnosis of pancreatitis in dogs. Am J Vet Res. 1981; 42(11): 1966-70.

Vu MK, van der Veek PP, Frolich M et al - Does jejunal feeding activate exocrine pancreatic secretion? Eur J Clin Invest 1999; 29:1053-9.

Windsor AC, Kanwar S, Li AG et al. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. Gut 1998; 42: 431-5.

Zyromski N, Murr MM - Evolving concepts in the pathophysiology of acute pancreatitis. Surgery 2003; 133(3): 235-7.

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Exocrine pancreatic insufficiency affects all breeds of dog, but the syndrome is particularly common in German Shepherds and Collies around 2 years of age.

Key Points
to remember:

The role of nutrition in the treatment of pancreatic disorders

Exocrine pancreatic insufficiency syndrome (EPI) results not only from the reduced digestion of nutrients in the intestinal lumen, but also from insufficient neutralization of chyme, an alteration of enzymes of the brush border and the proliferation of intestinal bacteria. This results in abnormal activity of intestinal mucosal enzymes as well as a reduction in the transportation of sugars, amino acids, fatty acids and vitamins (particularly vitamin B12) from the intestinal lumen to the enterocytes.

The treatment of EPI consists supplementing meals with pancreatic enzymes and feeding these animals a highly digestible diet.

The most effective ways of administering enzyme supplements are:
- pancreatic powder: 3 g per meal for a 20-35-kg dog
- fresh pig or bovine pancreas: 50-100 g per meal for a medium dog.

Tablets should be avoided as they are often found intact in fecal matter.

Preincubation of the meal with the enzymes serves no purpose. The initial dose can most often be reduced to 50% as soon as the animal responds to treatment. This procedure is not insignificant given the cost of the enzyme supplements. Supplementation will be life-long for most dogs.

Oral bleeding has been reported in dogs receiving pancreatic enzyme supplements. A 50% reduction in the supplement generally eliminates the clinical signs.

1 • Pancreatic insufficiency nutritional therapy

The Traditional Approach

Traditionally, a highly-digestible low-fiber diet with a moderate fat content is generally recommended for the nutritional management of patients with EPI.

- **The low fiber content** is dictated by the need to safeguard an energy-concentrated diet (for dogs with pancreatic insufficiency that are difficult to keep in good condition). In addition, excess fiber can inhibit the action of the pancreatic enzymes.

- **Fat restriction in EPI** is recommended to prevent diarrhea which is stimulated by the presence of hydroxylated fatty acids in the intestinal lumen, which stimulates water loss. These hydroxylated fatty acids are produced by the intestinal flora, which proliferate as a result of the influx of non-digested fats in the intestine. The malabsorption of fat, is due to both the pancreatic lipase deficiency and to deconjugation of biliary acids by bacterial.

The interest of fat

However, studies have contradicted this practice. A high-fat diet (43% calories) improves fat absorption (and the clinical signs) in dogs with EPI compared with a standard maintenance diet (27% fat calories) or a low-fat diet (16% calories).

Hypothesis: a high-fat diet will result in a better conservation of lipase in the pancreatic supplement. Highly digestible diets that contain approx. 20% fat are very well tolerated by dogs with EPI. High-fat diets also favor energy consumption in underweight animals.

Selecting a highly digestible source of starch

Its very high starch digestibility makes rice the preferred cereal for dogs with EPI, who may also suffer from allergies and dietary intolerances. Preliminary observations appear to indicate that a **protein hydrolysate diet** can have a very favorable effect in dogs with EPI. The small peptides in these diets facilitate digestion and absorption.

Preventing vitamin deficiencies

Vitamin B12 and vitamin E deficiencies are very common in dogs suffering from EPI. Vitamin A and K deficiencies have also been identified. Parenteral supplementation is necessary to correct these deficiencies.

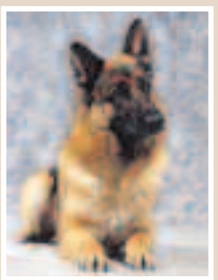
Prognosis

The quality of life for the majority of dogs suffering from EPI that receive enzyme supplements and are fed twice a day is very similar to that of healthy individuals. The prognosis for dogs with EPI associated with pancreatitis or diabetes is more reserved.

If no improvement (weight gain, reduction in diarrhea or polyphagia) is observed within 4-5 days following the start of enzyme or dietetic treatment, an antibiotic treatment should be initiated (metronidazole or tylosin) to combat bacterial proliferation.

Conclusion

Contrary to conventional wisdom, some dogs with EPI can tolerate large quantity of fat in their diet. The dietary fat permits better conservation of the enzyme supplementation while it passes through the acid environment of the stomach. Protein hydrolysate-based diets will benefit not only the digestive function but also dietary intolerance.



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In German Shepherds the transmission of endocrine pancreatic insufficiency suggests a recessive autosomal gene trait.

References

Rutz GM, Steiner JM, Williams DA - Oral bleeding due to pancreatic extract in three dogs with exocrine pancreatic insufficiency. Proc 19th ACVIM 2001 ; 875 (abst#156).

Suzuki A, Mizumoto A, Rerknimitr R et al - Effect of bacterial or porcine lipase with low- or high fat diets on nutrient absorption in pancreatic-insufficient dogs. Gastroenterology 1999 ; 116: 431-437.

Westermarck E, Junttila JT, Wiberg ME - Role of low dietary fat in the treatment of dogs with exocrine pancreatic insufficiency. Am J Vet Res 1995 ; 56: 600-605.

Wiberg ME, Lautala HM, Westermarck E - Response to long term enzyme replacement treatment in dogs with exocrine pancreatic insufficiency. J Am Vet Med Assoc 1998 ; 213: 86-90.

Wiberg M - Exocrine pancreatic insufficiency in dogs-An update. Proceeding of 12th ESVIM congress ; Munich, 2002: 103-105.

Williams DA - The pancreas. In "Strombeck's Small Animal Gastroenterology 3rd ed. Guilford, Center, Strombeck, Williams, Meyer eds, Saunders ; Philadelphia, 1996: 381-410.

2 • Exocrine pancreatic insufficiency and adverse reaction to food in dogs

Interest of a high-fat diet based on rice and soy protein isolate hydrolysate

Dermatological signs of adverse reaction to food are common in dogs suffering from EPI, especially in German Shepherd Dogs. Dogs with these two diseases respond poorly to enzyme supplementation and a diet specifically designed for EPI.

The report below describes the positive responses of 4 German Shepherd Dogs suffering from both EPI and skin disease to a rice and soy isolate hydrolysate-based extruded diet with 19% fat.

Four male German Shepherd dogs, age range 2.5-9.0 yrs, body weight 31-40 kg, and suffering from EPI (TLI 0.88 to 5.08 µg/L) were included in this study.

All dogs were suffering from recurrent diarrhea that was more or less controlled with highly digestible and/or hypoallergenic prescription diets as well as pancreatic enzyme supplementation.

All dogs were lean at presentation and showed various signs of skin diseases compatible with adverse reaction to food. The dogs presenting signs of deep pyoderma were treated with cefalexin. The dogs did not receive any other medication except for pancreatic enzyme supplementation.

After 7 days' exclusive consumption of the food described above, feces were normal in all 4 dogs and no dog showed any signs of diarrhea over a 3-month follow-up. Within 3 months, all 4 dogs were in optimal body condition after gaining 2 to 10 kg of body weight. Over the same period, the skin disease of 3 of the 4 dogs were completely controlled. Only the fourth dog still had average pruritus and some erythamtous lesions and local scabbing associated with hyperpigmentation.

A high level of fat (40.8 % of the calories) was very well tolerated by the dogs of this study and confirms earlier findings. This suggests that high fat and highly digestible diets not only are not contra-indicated in the management of EPI but could be beneficial to restore body condition.

DIETARY ANALYSIS	
Moisture	9%
Protein	21%
Fat	19%
Cellulose	2.2%
Total dietary fiber	5.4%
Ash	8%
Metabolizable energy	4182 kcal/kg

List of ingredients: *rice, soy isolate hydrolysate, animal fats, mineral salts, vegetable oils (including borage oil), zeolite, fructo-oligosaccharides, fish oil.*

Reference

Biourge VC, Fontaine J - Exocrine pancreatic insufficiency and adverse reaction to food in dogs: a positive response to a high-fat, soy isolate hydrolysate-based diet. J Nutr 2004 ; 134: 2166S–2168.

Focus on:

SOY PROTEIN ISOLATE HYDROLYSATE

Soy proteins are known as excellent quality proteins but in pet food their utilization is limited because soybeans contain:

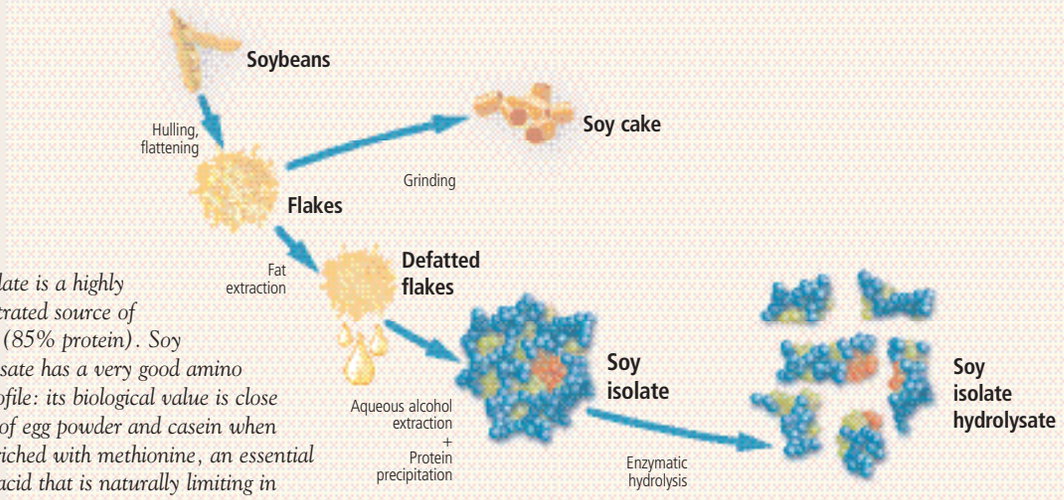
- anti-nutritional factors (e.g. antitrypsin) that inhibit protein digestion and proper absorption of nutrients
- non-digestible carbohydrates that are likely to ferment in the colon and to induce flatulence and other digestive disturbances.

Soy hydrolysate is obtained by enzymatic hydrolysis of soy isolate. Compared with intact proteins forming soy isolate, the hydrolysate contains smaller polypeptides.

During the process of obtaining soy protein isolate hydrolysate, the undesirable substances are destroyed or removed. Its main advantages are:

- very high digestibility and excellent digestive tolerance
- reduced ability to induce allergic reactions.

THE PROCESS OF OBTAINING SOY PROTEIN ISOLATE HYDROLYSATE

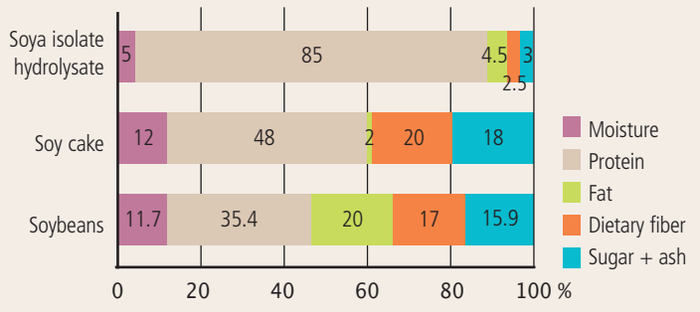


Soy isolate is a highly concentrated source of protein (85% protein). Soy hydrolysate has a very good amino acid profile: its biological value is close to that of egg powder and casein when it is enriched with methionine, an essential amino acid that is naturally limiting in soybeans.

Digestibility of **soy hydrolysate** is more than 96%, which is similar to casein and egg, other reference proteins, and better than high-quality animal proteins.

In human and animal nutrition, soy hydrolysate has become one of the reference proteins. The quality of this protein source is such that it is used as milk protein substitute for allergic infants and in protein supplements for athletes or recovering patients. In human medicine, soy hydrolysate-based diets are used to prevent the development of enteritis in patients undergoing radiotherapy and chemotherapy.

COMPARED COMPOSITION OF DIFFERENT SOY-BASED PRODUCTS



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Diabetes mellitus: nutricional strategies

1 - Diabetes in dogs 205
2 - What to feed diabetic dogs 214

Frequently asked questions regarding diabetes 223
References 225
Examples of home-prepared diets adapted to the treatment of diabetes mellitus 228
Royal Canin Nutritional Information 230

Diabetes mellitus: nutritional strategies

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Linda Fleeman graduated with honors from the University of Queensland and completed Clinical Residency training programs in Small Animal Medicine at both Murdoch University and the University of Melbourne in Australia. She is currently participating in a clinical PhD research project investigating the therapy and nutritional management of diabetes in dogs. She is currently Lecturer in Small Animal Medicine at the University of Queensland. Dr Fleeman is first author of a number of publications focusing on canine diabetes, and has lectured at many national and international conferences on this topic.

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BVSc (Hons), DVSc, Dipl ACVIM

Professor Rand graduated from the University of Melbourne (Australia) in 1975 and worked in private practice for 8 years before completing a residency and doctorate at the University of Guelph (Canada). She is currently Professor of Companion Animal Health at the University of Queensland and Director of the Centre for Companion Animal Health. Jacquie is recognized internationally as a leader in feline diabetes and nutrition research. She has authored over 100 articles, seventy abstracts and six textbook chapters. She currently has a team of 10 postgraduate students working in diabetes, obesity and nutrition research in companion animals.

Diabetes mellitus is a common endocrine disease of dogs and requires life-long therapy. Nutritional management is an important part of the treatment regimen and feeding guidelines based on evidence from well-designed clinical studies are essential. The first part of this chapter provides an understanding of the pathogenesis of diabetes in dogs, which is required before evaluation of issues relating to nutritional management. This allows comparison of the current, evidence-based, nutritional recommendations for human patients with types of diabetes analogous to canine diabetes. The second part reviews the available evidence from feeding studies in dogs and provides detailed analysis of the recommendations for dietary fiber, carbohydrate, fat, protein, and selected micronutrients in diabetic dogs. The final summary uses the American Diabetes Association grading system to rank the scientific basis of the nutritional recommendations for canine diabetes.

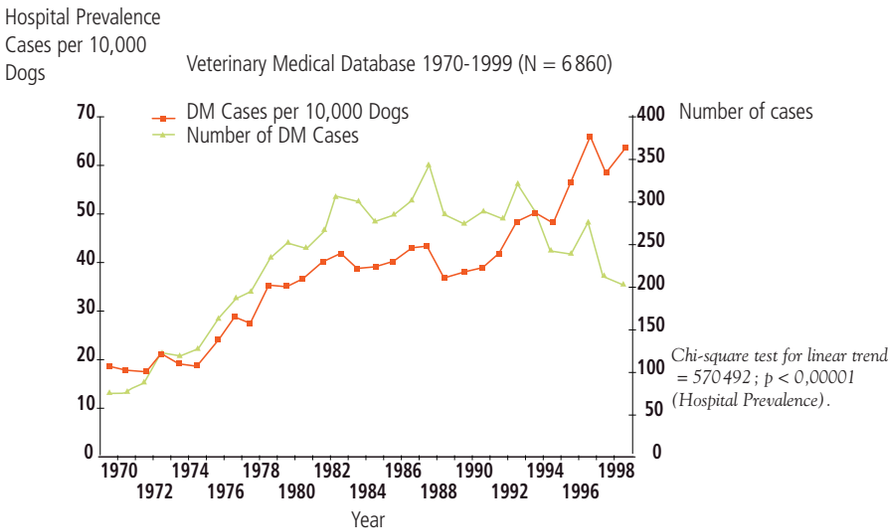
1 - Diabetes in dogs

► Prevalence of diabetes mellitus in dogs

Diabetes mellitus is one of the most frequent endocrine diseases affecting middle-aged and older dogs, and the prevalence is increasing. Thirty years ago, 19 in 10,000 dogs visiting veterinary hospitals were diagnosed with diabetes mellitus *(Marmor et al, 1982; Guptill et al, 2003)*. By 1999, the prevalence in the same veterinary hospitals had increased three-fold to 58 per 10,000 dogs **(Figure 1)** *(Guptill et al, 2003)*.

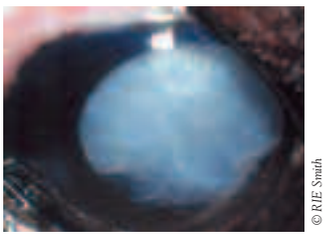
FIGURE 1 - INCREASING PREVALENCE OF CANINE DIABETES MELLITUS

Reprinted from Guptill et al, 2003, with permission from Elsevier.



Prevalence of DM increased over the study period. The number of institutions for which data are recorded is lower from 1995 to 1999 (16 institutions in 1994, 13 in 1995, 12 each in 1996-1997, 11 each in 1998-1999), therefore the number of cases per year is lower in these years.

FIGURE 2 - DIABETIC CATARACT ASSOCIATED WITH UVEITIS IN A DOG



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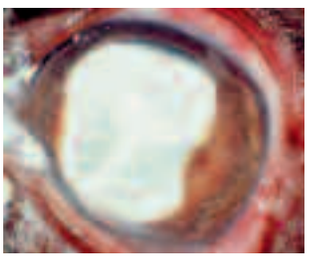
a: Advanced cataract in an aging dog. *Hyperemia is present in the sclera, indicating moderate uveitis.*



b: Severe uveitis in a diabetic dog. *The eye is red and painful, with the presence of mucopurulent ocular discharge and posterior synechia.*

► Clinical sequelae of diabetes in dogs

Insulin deficiency results in altered carbohydrate, fat, and protein metabolism. Abnormal carbohydrate metabolism manifests as hyperglycemia and glycosuria and is responsible for the polyuria, polydipsia, and cataract formation seen in diabetic dogs. The hyperlipidemia, ketone production, and hepatic changes seen in these dogs primarily results from altered fat metabolism. Decreased tissue utilization of glucose, amino acids, and fatty acids causes lethargy, weight loss, reduced stimulation of the satiety center, poor coat, and reduced immunity that is characteristic of untreated diabetic dogs.

> Cataract formation

Cataract formation is the most common, and one of the most important, long-term complications associated with diabetes in dogs *(Beam et al, 1999)* **(Figure 2)**. Cataracts are irreversible and can progress quite rapidly **(Figure 3)**. About 30% of diabetic dogs already have reduced vision at presentation *(Graham & Nash, 1997a)*. Cataracts will develop within 5-6 months of diagnosis in the majority of diabetic dogs and, by 16 months, approximately 80% will have significant cataract formation *(Beam et al, 1999)*. Importantly, the risk of cataract development seems to be unrelated to the level of hyperglycemia but increases with age *(Salgado et al, 2000)*. Thus, dietary manipulation is not likely to influence the rate or severity of cataract development in diabetic dogs.

FIGURE 3 - DEVELOPMENT OF DIABETIC CATARACTS IN A DOG

(From Fleeman & Rand 2000)

a: An eleven-year-old crossbred dog photographed shortly after diagnosis of diabetes mellitus.

b: The same dog three months after initial diagnosis of diabetes mellitus. Diabetic cataracts have rapidly developed and the dog's owner reported sudden vision loss.

c: The same dog following phacoemulsification surgery to remove the cataract from the right eye.

> Concurrent disease

Treated diabetic dogs have a similar chance of survival as compared to non-diabetic dogs of the same age and gender, although the hazard of death occurring is greatest during the first 6 months of therapy *(Graham & Nash, 1997b)*. Most diabetic dogs are middle-aged and older and are prone to diseases that commonly affect this age group. Consequently, many suffer concurrent problems that need to be managed in combination with the diabetes. For diabetic dogs receiving insulin therapy, the nutritional requirements of any concurrent disease may need to take precedence over the dietary therapy for diabetes. Regardless of the diet fed, glycemic control can still usually be maintained with exogenous insulin therapy.

If concurrent illness causes transient inappetence, it is generally advisable to administer half the usual insulin dose to reduce the risk of hypoglycemia. Diabetic dogs with a reduced appetite will often eat if they are hand-fed highly palatable food by their owner. If there is a more severe concurrent illness causing prolonged inappetence, diabetic dogs should be hospitalized for blood glucose concentration monitoring and treatment with a rapid-acting insulin preparation and intravenous fluids supplemented with glucose and potassium *(Feldman et al, 2004a)*.

► Insulin-induced hypoglycemia

Severe hypoglycemia resulting from insulin overdose can cause irreversible brain damage and death, and avoidance of insulin-induced hypoglycemia is one of the primary aims of therapy in diabetic dogs. Dietary manipulation that reduces the risk of insulin-induced hypoglycemia affords important clinical benefit for diabetic dogs. Severe hypoglycemia has been reported in a diabetic dog that was fed ad libitum and received insulin at grossly irregular intervals *(Whitley et al, 1997)*. Commercial dog foods usually result in postprandial elevation of plasma glucose for less than 90 minutes following consumption by dogs *(Nguyen et al, 1998a)* and meals should ideally be timed so that maximal exogenous insulin activity occurs during the postprandial period *(Church, 1982)*. Thus, dogs should be fed within 2 hours of administration of lente insulin or within 6 hours of protamine zinc insulin *(Stenner et al, 2004)* **(Figure 4)**. In practice, a feasible compromise is to feed the dog immediately following the insulin injection. This considerably simplifies the home treatment regimen for most dog owners while still allowing good glycemic control to be readily achieved. In addition, many owners prefer this regimen because they feel their pet is rewarded for submitting to the injection.

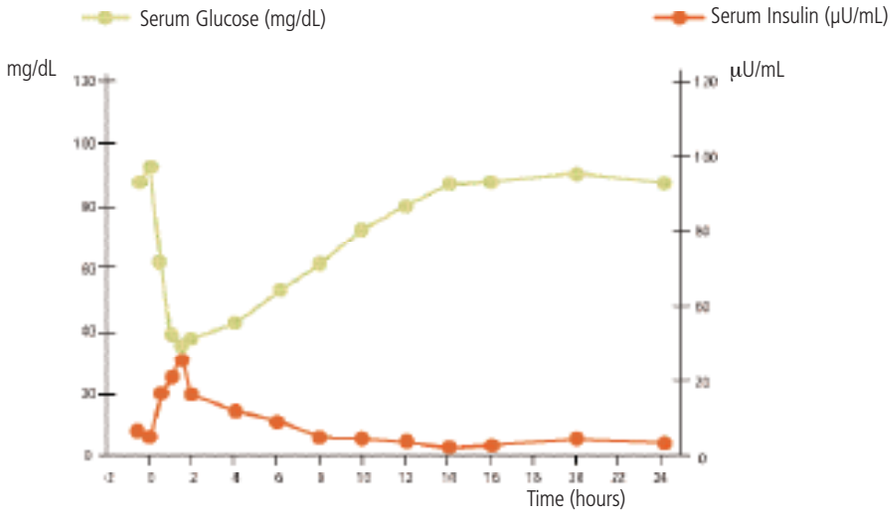
Because the daily insulin-dosing regimen tends to be fixed for diabetic dogs, it is important that a predictable glycemic response is achieved following each meal. Ideally, every meal should contain the same ingredients and calorie content, and should be fed at the same time each day. It is crucial that the diet fed is palatable so that food intake is predictable. The major determinant of the postprandial glycemic response in dogs is the starch content of the meal *(Nguyen et al, 1998b)* so particular care should be applied to ensure consistent source and content of dietary starch.

The importance of avoiding an insulin overdose cannot be over-emphasized. Every person in the diabetic dog's household needs to be aware of this life-threatening complication, which can rapid-

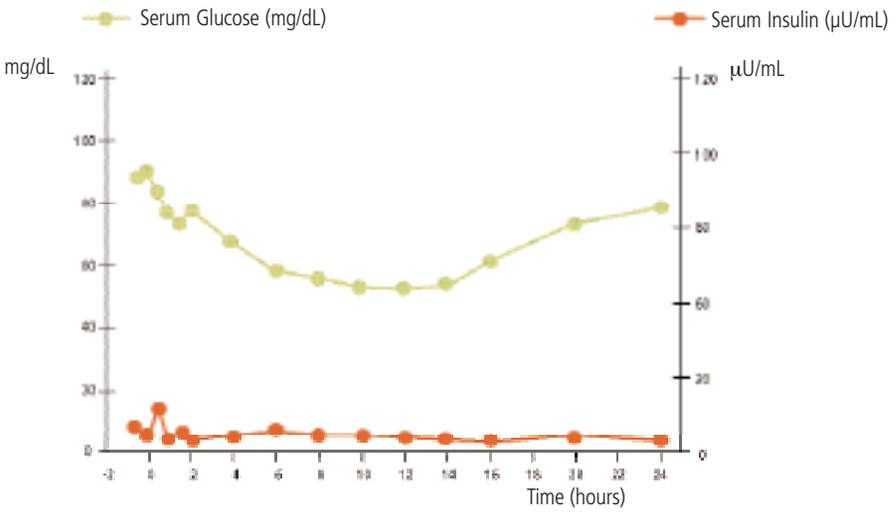
FIGURE 4 - PHARMACODYNAMICS AND PHARMACOKINETICS IN 9 HEALTHY, NON-DIABETIC DOGS FOLLOWING SUBCUTANEOUS INJECTION OF LENTE (CANINSULIN®, INTERVET) AND PROTAMINE ZINC INSULIN (PZI VET®, IDEXX) PREPARATIONS

(From Stenner et al, 2004)

Mean Serum Glucose and Insulin Concentrations vs Time in Lente Treated Dogs



Mean Serum Glucose and Insulin Concentrations vs Time in PZI Treated Dogs



For insulin-treated diabetic dogs, meals should ideally be timed so that maximal exogenous insulin activity occurs during the postprandial period. The pharmacodynamics and pharmacokinetics of two commercial veterinary insulin preparations, lente (Caninsulin®, Intervet) and protamine zinc insulin (PZI VET®, IDEXX), indicate that the maximal glucose-lowering effect occurs during the first 2 hours following subcutaneous administration for lente insulin, and within 6 hours of subcutaneous protamine zinc insulin injection. Commercial dog foods usually result in postprandial elevation of plasma glucose for less than 90 minutes following consumption, thus dogs should be fed within 30 minutes of administration of lente insulin or within 4.5 hours of protamine zinc insulin. A feasible compromise is to feed the dog immediately following the insulin injection. This considerably simplifies the home treatment regimen for most dog owners while still allowing good glycemic control to be readily achieved.

ly develop into a serious emergency. If some insulin is spilt during the injection it should never be 'topped up', even if it appears that the dog has received no insulin. If the owner is ever uncertain about whether or not to give an insulin dose, the safest option is to withhold the injection, as the consequences of missing a single insulin dose are negligible. If mild signs of hypoglycemia develop, the owner should feed a meal of the dog's usual food. If the dog is unwilling or unable to eat, syrup containing a high glucose concentration can be administered orally. Suitable syrups are marketed for use by human diabetics. When the dog recovers, food should be fed as soon as possible. No more insulin should be given to the dog and the owner should discuss the case with a veterinarian before the next injection is due. A 50% reduction in insulin dose is usually recommended in these circumstances.

Successful management of 94% of diabetic dogs is achieved with twice-daily insulin dosing *(Hess & Ward, 2000)*. High doses of insulin and episodes of hypoglycemia are more common in diabetic dogs that receive insulin only once-daily *(Hess & Ward, 2000)*. Although treatment regimens comprising once-daily insulin injections are considered by some to be simpler and more convenient, most of these regimens involve feeding two meals each day, one soon after the insulin injection and another at the time of peak insulin activity about 8 hours later. Given the length of the usual working day, it may actually be more convenient for people to feed the second meal 12 hours after the first. Experienced owners rarely report any difficulty with the administration of insulin injections and, if they are required to be at home to feed the dog, it is little more effort to give the dog an insulin injection at the same time. As a result, many clinicians favor treatment regimens that involve administration of the same dose of insulin along with feeding of the same sized meal every 12 hours.

► Pathogenesis of diabetes in dogs

The owners of diabetic dogs should be aware that a consistent insulin-dosing and feeding routine is optimal. Conservative, fixed-dose, twice-daily insulin therapy, in conjunction with a palatable diet containing a consistent content and source of dietary starch, which is fed at defined times in relation to insulin administration, is likely to be associated with reduced risk of hypoglycemia in diabetic dogs.

Evidence is mounting for a genetic basis for canine diabetes. An association with major histocompatibility complex alleles on the dog leukocyte antigen gene strongly suggests that the immune response has a role in the pathogenesis of diabetes mellitus *(Kennedy et al, 2003; Davison et al, 2003a; Rand et al, 2004)*.

The current classification of human diabetes mellitus is based on pathogenesis, and thus provides a rational foundation for understanding treatment issues. Adoption of these criteria for canine diabetes will afford a similar benefit for veterinarians. Human diabetes is divided into type 1, type 2, other specific types of diabetes, and gestational diabetes *(The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997)*. At present, there are no internationally accepted criteria for the classification of canine diabetes. If the criteria established for human diabetes were applied to dogs, at least 50% of diabetic dogs would be classified as type 1. The remainder are likely to have 'other specific types of diabetes' resulting from pancreatic destruction or chronic insulin resistance, or they have diestrus-induced diabetes.

> Type 1 diabetes

Type 1 diabetes appears to be the most common form of diabetes in dogs, and is characterized by pancreatic beta cell destruction leading to absolute insulin deficiency. In people, this usually occurs via cell-mediated, autoimmune processes and is associated with multiple genetic predispositions and poorly defined environmental factors *(The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997)*. The majority of diabetic dogs have absolute insulin deficiency *(Montgomery et al, 1996)*. The etiology of beta cell destruction is often unknown, although there is evidence that in approximately 50% of diabetic dogs it is caused by immune-mediated processes similar to human type 1 diabetes *(Alejandro et al, 1988; Hoenig & Dawe; 1992; Davison et al, 2003a, 2003b)*.

Although genetic susceptibility appears to be a prerequisite, multiple environmental factors likely initiate beta cell autoimmunity, which once begun, then proceed by common pathogenic pathways *(Kukreja & Maclaren, 1999)*. Similar to canine diabetes, the incidence rate of type 1 diabetes in people is rising *(Onkamo et al, 1999)*, a trend that has been explained on the basis of increased contacts with adverse environmental factors *(Kukreja & Maclaren, 1999)*. There is a highly significant seasonal incidence of diagnosis of both human type 1 diabetes *(Gamble & Taylor, 1969; Fleegler et al, 1979)* and canine diabetes *(Atkins & MacDonald, 1987)*, with the incidence peaking

in winter, indicating that environmental influences may have a role in disease progression just prior to diagnosis.

The rate of progression to absolute insulin deficiency is quite variable in human patients. It can be rapid in young children and much slower in middle-aged and older people. This latter group has the latent autoimmune diabetes of adults (LADA) form of type 1 diabetes, which is characterized by gradual beta cell destruction over months or years and is not associated with obesity *(Zimmet et al, 1994)*. Distinct autoantibody patterns are recognized in the acute onset and slowly progressive (LADA) forms of human type 1 diabetes *(Zimmet et al, 1994; Seissler et al, 1998)*, indicating a different pathogenesis for the two forms of the disease.

The rate of progression to absolute insulin deficiency has not been studied in dogs, but epidemiological factors closely match those of human patients with the LADA form of type 1 diabetes, who are usually not obese and tend to be middle-aged and older. Most affected dogs are over 7 years of age and the onset of clinical signs is typically insidious, ranging from weeks to months in duration *(Ling et al, 1977)*. This has prompted speculation that there may also be similarities between the pathogenesis of canine diabetes and human LADA.

> Other types of canine diabetes

• *Association between diabetes and pancreatitis in dogs*

Extensive pancreatic damage, which likely results from chronic pancreatitis, is responsible for the development of diabetes in approximately 28% of diabetic dogs *(Alejandro et al, 1988)* and thus is the most common 'other specific type' of diabetes in dogs. Beta cell loss is being investigated in non-diabetic dogs with chronic pancreatitis and preliminary findings indicate that some have reduced beta cell function and appear to be pre-diabetic *(Watson & Herrtage, 2004)*. Serum canine pancreatic lipase immunoreactivity (cPLI) is a sensitive marker for pancreatic inflammation in dogs *(Steiner, 2003)*. Increases in serum cPLI concentration have been reported in 5 of 30 (17%) newly diagnosed diabetic dogs, although none of these dogs had serum cPLI concentrations above the diagnostic cut-off value for pancreatitis *(Davison et al, 2003b)*.

In long-term diabetic dogs with no clinical evidence of exocrine pancreatic disease, serum cPLI concentrations in the diagnostic range for pancreatitis were found in 2 of 12 (17%) dogs, with a further 4 (33%) dogs recording increases in cPLI that did not reach the diagnostic cut-off value for pancreatitis, and an additional 2 (17%) dogs having laboratory evidence of exocrine pancreatic insufficiency (unpublished data). This indicates that subclinical exocrine pancreatic disease is common in diabetic dogs.

The association between canine diabetes and pancreatitis warrants particular attention because beta cell autoimmunity, pancreatic inflammation, and regulation of gut immunity might be linked in disease pathogenesis. The gut immune system likely plays a central role in the pathogenesis of human type 1 diabetes because accumulating evidence suggests that affected persons have aberrant regulation of gut immunity *(Vaarala, 1999, Akerblom et al, 2002)*. The gut and the pancreas are probably immunologically linked, as well as anatomically linked, and influenced by environmental factors such as intestinal microflora, infections, and dietary factors *(Vaarala, 1999)*.

Hypertriglyceridemia has been proposed as a possible inciting cause of canine pancreatitis *(Williams, 1994)* and is commonly seen in diabetic dogs *(Ling et al, 1977)*. Obesity affects one-quarter to one-third of dogs presented to veterinary practices *(Edney & Smith, 1986)*, and is also associated with an increased risk of pancreatitis *(Hess et al, 1999)*. Environmental factors such as feeding high-fat diets, lipemia and disturbances in lipid metabolism, have been implicated as potential etiological factors in dogs with obesity-associated pancreatitis *(Simpson, 1993)*, and likely play a role in the development of pancreatitis in diabetic dogs. More detailed discussion on canine pancreatitis and hyperlipidemia can be found in chapters 5 and 7 of this encyclopedia.

Adult Dachshund presenting an excess of weight
No epidemiological data examining the relationship between canine diabetes and obesity have been published since 1960 (Krook et al), and an association between obesity and diabetes in dogs is not currently recognized.

• *Role of insulin resistance in canine diabetes*

Diabetes induced by insulin resistance states are less common 'other specific types' of canine diabetes.

Disease conditions such as hyperadrenocorticism *(Peterson, 1984)* and acromegaly *(Selman et al, 1994)* result in insulin resistance, and may induce diabetes in dogs. Iatrogenic causes of insulin resistance that might lead to induced diabetes include chronic corticosteroid therapy *(Campbell & Latimer, 1984)*. As most dogs do not develop overt diabetes with chronic corticosteroid therapy or spontaneous hyperadrenocorticism, for overt diabetes to develop it might require underlying reduced beta cell function resulting from immunological processes or chronic pancreatitis.

Although obesity causes insulin resistance in dogs, there are no published data clearly indicating that obesity is a risk factor for canine diabetes.
Obesity is a well-established risk factor for type 2 diabetes in cats and people. In contrast, there are no well-documented studies demonstrating convincingly that type 2 diabetes is a significant disease entity in dogs. In dogs, obesity causes insulin resistance *(Rocchini et al, 1999; Villa et al, 1999, Mittelman et al, 2002)*, which leads to hyperinsulinemia and impaired glucose tolerance *(Mattheeuws et al, 1984, Henegar et al, 2001)*. These effects are particularly pronounced when obesity is induced by feeding a diet high in saturated fat *(Truett et al, 1998)*. Dogs fed a high-fat diet develop insulin resistance that is not compensated for by increased insulin secretion, resulting in more severe glucose intolerance *(Kaiyala et al, 1999)*. Despite the evidence that obesity causes impaired glucose tolerance, it appears that very few dogs develop overt diabetes as a consequence of obesity-induced insulin resistance.

Diestrus- and gestation-associated diabetes

Gestational diabetes is another classification of diabetes recognized in human patients. In women, it is defined as any degree of glucose intolerance with onset or first recognition during pregnancy *(The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997)*. If overt diabetes persists after the pregnancy ends, then it is reclassified as type 1, type 2, or another specific type of diabetes. Reduced insulin sensitivity occurs in healthy bitches by day 30-35 of gestation *(McCann, 1983)* and becomes more severe during late pregnancy *(Concannon, 1986)*. The luteal phase of the non-pregnant cycle of the bitch is similar in duration to the 9 weeks of pregnancy and it is generally agreed that the hormone profiles during diestrus and pregnancy, are essentially identical *(Concannon et al, 1989; Feldman et al, 2004b)*. Progesterone elevation causes glucose intolerance and overt diabetes during diestrus in bitches *(Eigenmann et al, 1983, Scaramal et al, 1997)*. Progesterone also stimulates the mammary gland of bitches to produce growth hormone, which is a potent inducer of insulin resistance *(Selman et al, 1994)*.

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If diabetes is diagnosed in a bitch during either pregnancy or diestrus, it probably should be classified as being comparable to human gestational diabetes. If diabetes persists after pregnancy or diestrus ends, then it should be reclassified as type 1 or another specific type of diabetes.

The periodic influence of diestrus-associated insulin resistance might contribute to the increased risk of female compared with male dogs for developing diabetes *(Marmor et al, 1982; Guptill et al, 2003)*.

Classification of canine diabetes based on the current understanding of pathogenesis is summarized in **Table 1**.

Table 1 - Classification of canine diabetes mellitus based on current understanding of pathogenesis

Form of canine diabetes mellitus	Analogous form of human diabetes mellitus	Estimated proportion of diabetic dogs	Pathogenesis	Clinical features
Type 1 diabetes	Latent Autoimmune Diabetes of Adults (LADA) form of type 1 diabetes	50%	• Autoimmune destruction of pancreatic beta cells • Genetic susceptibility related to the major histocompatibility complex on the dog leukocyte antigen gene • Most likely initiated in susceptible individuals by environmental factors that interact with gut immunity	• Middle-aged and older dogs • Not associated with obesity • Permanent, absolute insulin deficiency
Extensive damage from chronic pancreatitis	Other specific types of diabetes	30%	• Chronic pancreatitis causing widespread destruction of both endocrine and exocrine pancreatic tissue	• Onset of diabetes typically occurs many months before onset of exocrine insufficiency • Permanent, absolute insulin deficiency
Diabetes associated with insulin-resistant states	Other specific types of diabetes	20%	• Concurrent disease or therapy causing insulin resistance • Some dogs developing diabetes in association with insulin-resistant states might have underlying reduced beta cell function because of autoimmune destruction or chronic pancreatitis	• Occurs in dogs with insulin resistance, e.g. hyperadrenocorticism, corticosteroid therapy • Absolute or relative insulin deficiency
Diestrus-associated diabetes	Gestational diabetes	Prevalence dependent on proportion of intact bitches in the population	• Progesterone causes insulin resistance • Progesterone also stimulates growth hormone production by the mammary gland, which further contributes to insulin resistance • Might have underlying reduced beta cell function due to autoimmune destruction or chronic pancreatitis	• Occurs in intact bitches during diestrus or pregnancy • Absolute or relative insulin deficiency • Remission of diabetes is possible when diestrus or pregnancy ends
Not reported in dogs	Type 2 diabetes	0%	• Impaired insulin secretion and insulin resistance • Obesity is a risk factor • Although overt type 2 diabetes is not reported in dogs, the insulin resistance of obesity might have the potential to precipitate signs of overt diabetes in dogs with beta cell destruction associated with other forms of diabetes, such as chronic pancreatitis	-

► Nutritional perspectives based on pathogenesis of diabetes in dogs

Understanding the pathogenesis of diabetes in dogs provides a logical foundation for understanding issues relating to nutritional management of this disease. Recently, the American Diabetes Association released a position statement comprising a large meta-analysis presenting evidence-based nutrition principles and recommendations for the treatment and prevention of human diabetes *(Franz et al, 2002a)*. Consideration of the evidence-based recommendations for human patients with types of diabetes comparable to canine diabetes provides a rational perspective for dietary recommendations for diabetic dogs.

> Dietary carbohydrate and type 1 diabetes

Perspective gained from the dietary carbohydrate recommendations for human type 1 diabetics provide relevant perspective for canine diabetics because at least 50% of diabetic dogs appear to have analogous disease. Most relevant is perhaps the current recommendation regarding consumption of dietary fiber by human type 1 diabetics. After decades spent researching the effects of dietary fiber on the glycemic and lipemic responses of diabetic people, it is interesting that the current recommendation is that consumption of fiber is to be encouraged in all people and that those with type 1 diabetes require no more dietary fiber than non-diabetic people *(Franz et al, 2002a)*. This suggests that there might also be no clinical benefit of feeding a diet with increased levels of fiber to diabetic dogs compared with feeding 'typical', moderate-fiber diets formulated for adult maintenance.

With regard to the glycemic effects of carbohydrates, there is strong evidence in human diabetics that the total amount of carbohydrate in meals and snacks is more important than the source or type *(Franz et al, 2002a)*. Additionally, there is a strong association between the pre-meal insulin dosage required and the postprandial glycemic response to the carbohydrate content of the meal, regardless of the glycemic index, fiber, fat, or caloric content of the meal *(Franz et al, 2002a)*. As a regimen of fixed daily insulin dosages is typically used to manage diabetic dogs, it is rational to provide a consistent amount of carbohydrate in the meals fed each day.

> Dietary fat and type 1 diabetes

The primary goal regarding dietary fat in human patients with diabetes is to decrease intake of saturated fat and cholesterol to reduce the risk of coronary heart disease *(Franz et al, 2002a)*. As coronary heart disease is not recognized as a significant clinical entity in dogs, it might not be relevant to extrapolate dietary fat recommendations for human patients to diabetic dogs. For most human type 1 diabetics, effective insulin therapy returns serum lipid levels to normal and usually lowers plasma triglyceride concentrations *(Franz et al, 2002a)*. However, for obese individuals with type 1 diabetes, there is strong evidence that restricted intake of saturated fats, incorporation of monounsaturated fats into the diet, modest weight loss, and increased physical activity may be beneficial *(Franz et al, 2002a)*. The same recommendations might afford clinical benefit for obese diabetic dogs.

> Dietary protein and type 1 diabetes

The protein composition of the recommended diet for people with diabetes is the same as that recommended for the non-diabetic population *(Franz et al, 2002a)*. However, if microalbuminuria or persistent proteinuria develop, then protein restriction might help slow the progression of diabetic nephropathy in these people *(EASD, 1995)*.

> Diabetes with exocrine pancreatic disease

Approximately 60% of human type 1 diabetics have reduced exocrine pancreatic function and it is now recognized that diabetes secondary to exocrine pancreatic disease might be more frequent in people than previously realized *(Hardt et al, 2000)*. Despite this, no specific dietary recommendations are given in the current American Diabetes Association position statement regarding diabetic patients with concurrent exocrine pancreatic disease. Human diabetics with hypertriglyceridemia have increased risk of acute pancreatitis and current management recommendations include a fat-restricted diet *(Athyros et al, 2002)*.

> Dietary recommendations for gestational diabetes

In the supplemental American Diabetes Association position statement focusing on gestational diabetes *(Franz et al, 2002b)*, it is noted that restriction of dietary carbohydrate has been shown to decrease maternal postprandial glucose levels *(Major et al, 1998)*. Similarly, bitches with diestrus-associated insulin resistance might benefit from a carbohydrate-restricted diet. This would likely reduce postprandial blood glucose fluctuations, helping to alleviate the hyperinsulinemia associated with diestrus, thus preserving beta cell function and reducing the risk of overt diabetes. There is some evidence that reduced intake of total fat, particularly saturated fat, in people might improve insulin sensitivity and reduce the risk for insulin resistance-associated diabetes *(Franz et al, 2002a)*. Potentially, feeding a fat-restricted diet to bitches with diestrus-associated insulin resistance might improve insulin sensitivity and reduce the risk of overt diabetes. As both fat and carbohydrate restriction may be recommended for these animals, a high-protein diet is a rational choice.

Importantly, nutrient-restricted diets should never be recommended for pregnant bitches unless there is strong scientific evidence for both maternal and fetal benefit.

> Dietary recommendations for older diabetics

There are no evidence-based nutritional recommendations for aging diabetic persons and they must be extrapolated from what is known for the general population *(Franz et al, 2002a)*. There is strong evidence that energy requirements for older adults are less than those for younger adults, however it is pointed out that under-nutrition is more likely than over-nutrition in elderly people. Therefore, caution should be exercised when prescribing weight-loss diets *(Franz et al, 2002a)*.

There are no evidence-based nutritional recommendations for aging diabetic dogs. Caution should be exercised when prescribing low-calorie diets to older dogs because this might result in excessive loss of body condition.

TABLE 2 - WHAT TO FEED DIABETIC DOGS: EVIDENCE RANKING SYSTEM

System used to rank scientific evidence on feeding recommendations for diabetic dogs	
1. Highest ranking	Randomized, controlled, clinical trials in diabetic dogs
	Other clinical trials in diabetic dogs
	Randomized, controlled clinical trials in non-diabetic dogs
4. Lower ranking	Expert opinion, clinical experience, and pathophysiological rationale

2 - What to feed diabetic dogs

► Evidence-based approach

Recommendations for feeding diabetic dogs should ideally be based on evidence provided by results of randomized, controlled clinical trials that clearly document significant clinical value of the test diet. Whenever this is lacking, clinicians must assess the best evidence that is available and interpret this in the light of expert clinical experience and knowledge of current pathophysiological concepts.

To assist this process, evidence in the following review has been ranked into categories **(Table 2)**:

1. Randomized, controlled, clinical trials in diabetic dogs
2. Other clinical trials in diabetic dogs
3. Randomized, controlled, clinical trials in non-diabetic dogs
4. Expert opinion, clinical experience, and pathophysiological rationale

► General goals of nutritional therapy for diabetic dogs

- ***Evidence based on expert opinion, clinical experience, and pathophysiological rationale***

The diet of diabetic dogs should provide adequate calories to achieve and maintain optimal body condition. Dogs with poorly controlled diabetes have a decreased ability to metabolize the nutrients absorbed from their gastrointestinal tract and lose glucose in their urine and so may require more calories for maintenance than healthy dogs. The diet fed should be nutritionally balanced and needs to be palatable so that food intake is predictable. Meals should ideally be timed so that maximal exogenous insulin activity occurs during the postprandial period *(Church, 1982)*. Because the daily insulin-dosing regimen tends to be fixed for diabetic dogs, it is also important that a predictable glycemic response is achieved following each meal. Consequently, every meal should contain roughly the same ingredients and calorie content, and should be fed at the same time each day. **The owners of diabetic dogs should be aware that a consistent insulin-dosing and feeding routine is optimal.**

► Dietary fiber and canine diabetes

> Total dietary fiber

- ***Evidence based on various clinical trials in diabetic dogs***

Some studies in diabetic dogs have indicated that high-fiber diets might be associated with improved glycemic control. However, these studies have compared high-fiber (56-73 g/1000kcal and 15%DM) with lower-fiber (16-27 g/1000 kcal) diets without including comparison with a control diet formulated for typical canine adult maintenance. Thus, there has not been a clear demonstration of clinical benefit for diabetic dogs fed a high-fiber formulation compared with feeding a typical adult maintenance diet.

Additionally, low-fiber diets typically contain increased dietary starch content, which might be a confounding factor when comparing the glycemic responses of diabetic dogs to high- and low-fiber diets. Regardless of the composition of the high-fiber diet or the length of time over which the diabetic dogs were monitored, no significant difference in daily insulin requirement *(Nelson*

et al, 1991; Graham et al, 1994; Nelson et al, 1998, 2000; Kimmel et al, 2000; Graham et al, 2002) or fasting triglyceride levels *(Nelson et al, 1991, 1998; Graham et al, 2002)* between groups of diabetic dogs fed low-fiber and high-fiber diets has been found.

Importantly, there seems to be marked variation between the responses of individual diabetic dogs to dietary fiber. In one study *(Nelson et al, 1998)*, significant improvement of all indices of glycemic control, including lowered daily insulin requirement, was seen in 9 of 11 dogs when they were fed a high-fiber diet (64.4g/1000kcal). The remaining 2 dogs were found to have improved glycemic control on the lower-fiber diet (27.0g/1000kcal or 11% in 4000kcal/kg of food).

In another study of 12 diabetic dogs *(Nelson et al, 2000)*, glycemic control was best in 6 dogs when fed a soy-based, moderate-fiber diet (total dietary fiber 8% DMB), in 4 dogs when fed a cellulose-based, high-fiber diet (total dietary fiber 16% DMB), in 1 dog when fed a cellulose-based, moderate-fiber diet (total dietary fiber 8% DMB), and glycemic response to diet could not be ranked in the remaining dog. A similar situation exists for people because high-fiber diets do not have a uniform effect in all diabetic subjects *(EASD, 1988)*. This might be partly due to the side effects that are sometimes associated with high-fiber diets, which include poor palatability, poor weight gain, poor hair coat, vomiting, voluminous feces, flatulence, diarrhea, and constipation. Individual tolerance to dietary fiber is dependent on a large number of factors, including the quality and type of the fiber.

- ***Evidence based on a randomized, controlled, clinical trial in diabetic dogs***

A randomized, controlled, trial was performed to assess the influence of canned, high-fiber, moderate-starch diets on insulin requirement and glycemic control in dogs with stabilized diabetes *(Fleeman & Rand, 2003)*. The two trial diets had high-fiber (50g/1000kcal) and moderate-starch (26% ME) content, but varied in fat content (31% ME and 48% ME). The control diet was a commercial dog food formulated for adult maintenance with moderate-fiber (35g/1000kcal), low-starch (2.3% ME), and higher fat (61% ME) content.

Diabetic control evaluated every 2 weeks included history, physical examination, and 2-hourly blood glucose measurements over 12 hours. Insulin dose was adjusted based on standardized criteria to maintain control of glycemia. At the end of each 2 month feeding period, glycemic control was evaluated by plasma fructosamine, glycosylated hemoglobin, and 48 hour serial blood glucose measurements. No significant differences in insulin requirement or glycemic response among diets were found. It was concluded that, for stable diabetic dogs, high-fiber, moderate-starch diets offer no significant advantage for insulin requirement or glycemic control compared with a commercial diet formulated for adult maintenance with moderate-fiber and low-starch content.

> Different types of dietary fiber

- ***Evidence based on pathophysiological rationale***

Soluble fiber: Dietary fiber can be characterized by degree of solubility, which is a reflection of its properties in an aqueous media. Soluble fiber, as provided by guar gum and psyllium, has great water-holding capacity, and forms a viscous solution in the intestine.

Dogs fed diets with increased viscosity might have more rapid postprandial glucose absorption, resulting in higher total postprandial glucose absorption and are more likely to develop secretory diarrhea than dogs fed diets with lower viscosity *(Nelson & Sunvold, 1998b)*.

This suggests that only diets with an intermediate viscosity (solubility) level might be associated with a delay in gastrointestinal transit time and optimal glucose homeostasis in dogs.
Soluble fiber, with the exception of psyllium, is usually also fermentable fiber.

Psyllium grains
The outer husk is high in non-fermentable mucilage that is soluble in water.

Fermentable fiber: Dietary fiber can be characterized by degree of fermentability, as well as solubility. Fermentable fiber is readily degraded by colonic microflora in dogs to produce short-chain fatty acids that are absorbed across the intestinal mucosa.

Fermentable dietary fiber is associated with increased intestinal glucose transport capacity, increased glucagon-like-peptide-1, and increased insulin secretion in non-diabetic dogs *(Massimino et al, 1998)*. **The overall effect is a significant reduction of the area under the blood glucose concentration versus time curve during oral glucose tolerance testing. As diabetic dogs lack the capacity to increase insulin secretion and match increased intestinal glucose transport, it needs to be investigated whether they benefit from diets containing high levels of fermentable fiber or whether these diets may actually contribute to glucose intolerance.**

Insoluble, non-fermentable fiber: Dogs cannot digest the insoluble fiber component of their diet and it is excreted in the feces. In contrast to soluble fiber, **insoluble fiber such as purified cellulose seems to exert relatively little physiological effect in the canine gut and can be tolerated in fairly high dietary levels** *(Bauer & Maskell, 1995)*.

- ***Evidence based on a randomized, controlled, trial in non-diabetic dogs***

A randomized controlled evaluation in non-diabetic dogs of the effects of diets containing different fiber types (highly-soluble, highly-fermentable guar gum, poorly-soluble, poorly-fermentable cellulose, and mixed soluble-insoluble, moderately-fermentable sugar beet pulp fiber) at three different dietary concentrations has helped to clarify some of the issues relating to the putative glucoregulatory effects of dietary fiber in dogs *(Hoenig et al, 2001)* **(Figure 5)**. The different test diets were obtained by substituting 3.5%DM of cornstarch in the control diet with the fiber sources mentioned above. The total dietary fiber level varied between 4.9% and 17.2%DM *(Hoenig et al, 2001)*.

Compared with the control diets (total dietary fiber 3.5% and 4.4%DM), **there were no significant differences in physical findings, serum glucose and insulin concentrations during oral glucose tolerance testing, serum triglyceride concentrations, or cholesterol content of HDL, LDL, and VLDL associated with feeding any of the fiber-modified diets. The only significant findings were that total serum cholesterol concentrations were lower in dogs fed sugar beet fiber and higher in dogs fed cellulose fiber, compared with control diets. Although it was not objectively measured, it was noted that the dogs' coat hairs seemed to become dull and lusterless when they consumed the fiber-modified diets.**

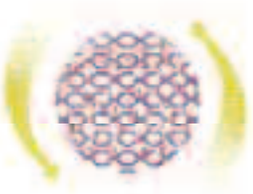
FIGURE 5 - A MIXTURE OF BEET PULP AND CELLULOSE (BRAN)

Fermentable dietary fiber stimulates insulin secretion in non-diabetic dogs. A surplus of fermentable fiber might however lead to osmotic complaints that increase fecal moisture.

Beet pulp

Cellulose

Insoluble and non-fermentable fiber is very well tolerated, even at a high level in the food.



Glycemic control is statistically similar when diabetic dogs are fed diets containing different quantities of fiber and different fiber sources, although results suggest that a blend of soluble and insoluble fiber such as soy or beet pulp might be preferable to insoluble fiber such as cellulose in lower-fiber diets (total dietary fiber 8%DM) (Nelson et al, 2000).

The authors proposed that this might have been due to an inhibitory effect of fiber on the absorption of minerals and vitamins.

- ***Evidence based on various clinical trials in diabetic dogs***

When dogs were fed a single meal containing added soluble fiber or added insoluble fiber, a greater reduction of postprandial hyperglycemia was seen with the meal containing soluble fiber *(Blaxter et al, 1990)* although the dietary fiber composition of the diets was not reported and were probably not comparable *(Davis, 1990)*.

When comparisons were made following long-term feeding for 1 or 2 months of diets high in soluble fiber or insoluble fiber (34g/1000kcal soluble fiber versus 60g/1000kcal insoluble fiber) *(Nelson et al, 1991)*; 10g/1000kcal soluble fiber versus 73g/1000kcal insoluble fiber *(Kimmel et al, 2000)*), a tendency for improved glycemic control and fewer side effects was seen with the diets containing increased insoluble fiber. In particular, significantly lower glycosylated hemoglobin *(Nelson et al, 1991)* or fructosamine *(Kimmel et al, 2000)* levels were recorded. The current evidence regarding dietary fiber and canine diabetes mellitus is summarized in **Table 3**.

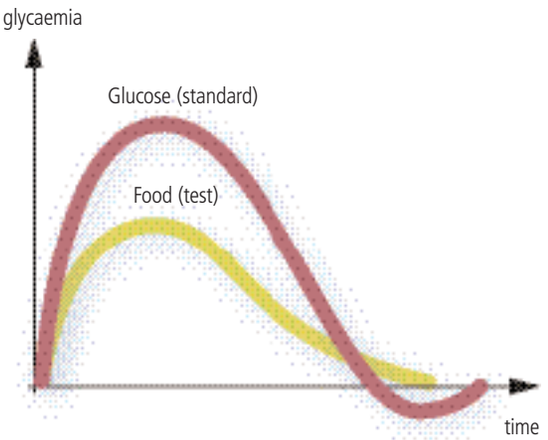
TABLE 3 - SUMMARY OF CURRENT EVIDENCE REGARDING DIETARY FIBER AND CANINE DIABETES MELLITUS

Perspective gained from current, evidence-based, dietary fiber recommendations for human type 1 diabetics	• Meta-analysis of all available evidence reveals that people with type 1 diabetes require no more dietary fiber than non-diabetic people
Evidence-based recommendations regarding canine diabetes and total dietary fiber	• There has been no clear demonstration of clinical benefit for diabetic dogs of feeding high-fiber formulations compared with feeding typical adult maintenance diets • Regardless of the composition of the high-fiber diet or the length of time over which the diabetic dogs were monitored, no significant difference in insulin requirement between groups of diabetic dogs fed low-fiber and high-fiber diets has been found • Some diabetic dogs might have improved glycemic control when fed diets with increased fiber content, although there is marked variation among the responses of individual dogs to dietary fiber
Evidence-based recommendations regarding the type of dietary fiber fed to diabetic dogs	• For non-diabetic dogs, there are no significant differences in physical findings, serum glucose and insulin concentrations during oral glucose tolerance testing, serum triglyceride concentrations, or cholesterol content of HDL, LDL, and VLDL associated with feeding diets containing different quantities of fiber and fiber sources • In diabetic dogs fed high-fiber diets, there is a tendency for improved glycemic control and fewer side effects when diabetic dogs are fed diets containing increased insoluble fiber, compared with increased soluble fiber • In diabetic dogs fed moderate-fiber diets, a blend of soluble and insoluble fiber such as soy or beet pulp might be preferable to insoluble fiber alone (such as cellulose)
Summary	• The most suitable dietary fiber recommendation for diabetic dogs might be moderate-fiber formulations (for example, 35 g/1000kcal) containing a blend of soluble and insoluble fiber, such as soy or sugar beet pulp • Further research is required to demonstrate clinical benefit of this formulation for diabetic dogs compared with typical commercial dog foods formulated for adult maintenance

FIGURE 6 - WHAT IS THE GLYCEMIC INDEX ?

Amount of food, equivalent to 50 g carbohydrate -eaten within 13 minutes
Blood glucose levels are measured in the next 2 to 3 hours: measurement of the Area Under the Curve (AUC)
Trial replicated with 8 - 10 individuals
Glycaemic Index (GI) = Ratio of curve integrals compared to a control (Glucose = 100%)

Classification:
< 55 : low GI
Between 55 and 70: medium GI
> 70 : high GI



In man, GI does not necessarily represent a practical guide for evaluating foods because data can be in conflict depending on the composition of the meal, the processing method, cooking, etc. Answers can also vary amongst individuals. In animals, results are more reliable because the diet can be better controlled.

► Dietary carbohydrate and canine diabetes

> Total dietary carbohydrate

- ***Evidence based on randomized trials in non-diabetic dogs***

The amount of starch in the diet has been shown to be the major determinant of the postprandial glycemic response of healthy dogs across 15 typical commercial dog foods (dietary starch 0.4-52.7% DMB), regardless of the carbohydrate source or type, or of the composition profile of other macronutrients *(Nguyen et al, 1998b)*. Although similar studies have not been performed in diabetic dogs, there is very good evidence in diabetic people for a strong association between the insulin dosage requirement and the carbohydrate content of the meal, regardless of the glycemic index **(Figure 6)**, the carbohydrate source or type, or the composition profile of other macronutrients *(Franz et al, 2002a)*. The same might be true for diabetic dogs.

> Different types of dietary carbohydrate

- ***Evidence based on physiological rationale***

The postprandial glycemic response to dietary carbohydrate might be potentially influenced by the type of carbohydrate and by the way it has been processed. Digestion of dietary carbohydrate occurs in the small intestine of dogs and results in the breakdown of starch to glucose, fructose, and galactose. The postprandial glycemic response is directly dependent on the absorption of glucose, because fructose and galactose require hepatic metabolism for conversion to glucose. Thus, the type of starch contained in the dietary carbohydrate fed might influence the postprandial glycemic response. Carbohydrate sources that predominantly breakdown to glucose during digestion are likely to result in the greatest postprandial glycemic response.

The digestibility of whole cereal grains (in this case rice) is lower than that of the same cereal ground into meal.

Studies assessing the digestibility in dogs of different dietary carbohydrate substrates *(Murray et al, 1999; Bednar et al, 2000; Twomey et al, 2002)*, have found that the processing method as well as the carbohydrate source significantly influences digestibility *(Bednar et al, 2000)*. For example, barley flour is approximately five times more digestible in dogs compared with barley grain, while rice flour is almost ten times more digestible than white rice grain *(Bednar et al, 2000)*. When commercial dog foods are formulated, the dietary starch is usually in the form of flours prepared using a combination of roller milling, sieving, and steam cooking *(Murray et al, 1999)*. The extrusion process then tends to gelatinize the starch and make it even more digestible *(Camire, 1998)*, so that starch digestibility is essentially 100% for most carbohydrate sources included in commercial dry dog foods *(Murray et al, 1999; Twomey et al, 2002)*. **There is some evidence that the gelling agents used in canned commercial dog foods may similarly increase digestibility** *(Karr-Lilienthal et al, 2002)***. Thus, for most commercial dog foods, processing effects likely have minimal influence on the postprandial glycemic response and the major potential influence on the postprandial glycemic response is likely the dietary carbohydrate source.**

- ***Evidence based on a randomized trial in non-diabetic dogs***

Little is known about the glycemic responses of diabetic dogs to different sources of dietary carbohydrate. However, a study in non-diabetic dogs that examined the postprandial effects of five diets with equivalent starch content (30% DMB) from different cereal sources found marked differences in the glucose and insulin responses *(Sunvold & Bouchard, 1998; Bouchard & Sunvold, 2001)*. **The rice-based diet resulted in significantly higher postprandial glucose and insulin responses. Sorghum generally caused the lowest postprandial glucose response while barley produced the lowest insulin response.** These findings form an interesting basis for future study on the effects of diets containing sorghum in diabetic dogs, but more work is required before specific recommendations can be made. Caution is required when extrapolating the results of dietary carbohydrate studies in non-diabetic dogs to clinical recommendations for diabetic dogs. This is because all diabetic dogs require exogenous insulin therapy, which has an overwhelming effect on carbohydrate metabolism and the postprandial glycemic response. It is also worth noting that studies in people have found a marked variability in the glycemic response to different types of barley *(Liljeberg et al, 1996)* and rice *(Jarvi et al, 1995)*. The same is likely true for dogs.

The current evidence regarding dietary carbohydrate and canine diabetes mellitus is summarized in **Table 4**.

TABLE 4 - SUMMARY OF CURRENT EVIDENCE REGARDING DIETARY CARBOHYDRATE AND CANINE DIABETES MELLITUS

Perspective gained from current, evidence-based, dietary carbohydrate recommendations for human type 1 diabetics	• Meta-analysis of all available evidence reveals a very strong association between the insulin dosage requirement and the carbohydrate content of the meal, regardless of the glycemic index, the carbohydrate source or type, or the composition profile of other macronutrients
Evidence-based recommendations regarding canine diabetes and total dietary carbohydrate	• For non-diabetic dogs, the amount of starch in the diet has been shown to be the major determinant of the postprandial glycemic response across a wide range of typical commercial dog foods (dietary starch 0.4-52.7% DMB), regardless of the carbohydrate source or type, or of the composition profile of other macronutrients
Evidence-based recommendations regarding the type of dietary carbohydrate fed to diabetic dogs	• For most commercial dog foods, processing effects likely have minimal influence on the postprandial glycemic response and the major potential influence is likely the dietary carbohydrate source • In non-diabetic dogs, a sorghum-based diet generally resulted in the lowest postprandial glucose response • In non-diabetic dogs, a barley-based diet produced the lowest postprandial insulin response • In non-diabetic dogs, a rice-based diet resulted in significantly higher postprandial glucose and insulin responses
Summary	• As a regimen of fixed daily insulin dosages is typically used to manage diabetic dogs, it is rational to provide a very consistent amount of carbohydrate in the meals fed each day • Rice should be avoided in diets for diabetic dogs, while sorghum and barley are likely more suitable carbohydrate sources • Further research is required to demonstrate clinical benefit of these formulations for diabetic dogs and bitches in diestrus, compared with typical commercial dog foods formulated for adult maintenance

► Dietary fat

and canine diabetes

> Evidence based on expert opinion, clinical experience, and pathophysiological rationale

Altered lipid metabolism occurs with insulin deficiency in dogs, yet there are minimal published data on the influence of dietary fat on diabetic dogs. In human patients, the lipid disorders that occur in association with diabetes are atherogenic and predispose to coronary artery disease *(Stamler et al, 1993)*. Restricted-fat diets reduce cardiovascular morbidity and mortality in diabetic people. Although atherosclerosis and coronary artery disease are not usually a clinical concern in diabetic dogs, atherosclerosis does occur in association with spontaneous canine diabetes *(Sottiaux, 1999; Hess et al, 2003)*. Perhaps of greater clinical relevance is that diabetes secondary to exocrine pancreatic disease appears to be common in dogs, and the diabetic state might also be a risk factor for pancreatitis. High-fat diets and hypertriglyceridemia have been proposed as possible inciting causes of canine pancreatitis *(Simpson, 1993; Williams, 1994)*. Low-fat diets (for example fat < 20% ME) are recommended for dogs with chronic pancreatitis. As it can be difficult to identify those diabetic dogs with subclinical pancreatitis *(Wiberg et al, 1999)*, **it might be prudent to consider feeding a restricted-fat diet (for example fat< 30% ME) to all diabetic dogs**. This might have the added benefit of improving insulin sensitivity in animals with insulin resistance-associated diabetes and reducing the risk of overt diabetes in bitches during diestrus. However, greater levels of energy restriction might lead to undesirable weight loss

> Evidence based on a randomized, controlled, clinical trial in diabetic dogs

The same randomized, controlled trial that assessed the influence of canned, high-fiber, moderate-starch diets on insulin requirement and glycemic control of dogs with stabilized diabetes also assessed the influence of dietary fat *(Fleeman & Rand, 2003)*. Different amounts of dietary fat in the high-fiber (50 g/1000 kcal), moderate starch (26 % ME) diets had no significant influence on insulin requirement or glycemic control of the dogs. Lower dietary fat content (31% ME compared with 48% ME) was associated with significantly improved lipid profiles. The low fat, high fiber, moderate starch diet resulted in significantly lower mean total cholesterol concentration compared with either of the other diets, and significantly lower mean glycerol and free fatty acids than the commercial diet. It is unknown whether any health benefits for dogs might be attributed to these improvements in the lipid profile. Significant weight loss occurred when the dogs were fed the low-fat, high-fiber, moderate-starch diet, whereas maintenance of weight was achieved with both of the other diets. It was concluded that **diets with lower fat content may result in improved lipid profiles in diabetic dogs, but might contribute to undesirable weight loss.** Therefore, restricted-fat diets should not routinely be recommended for diabetic dogs with thin body condition.

The current evidence regarding dietary fat and canine diabetes mellitus is summarized in **Table 5**.

► Dietary protein and canine diabetes

> Evidence based on pathophysiological rationale

The optimal dietary protein for diabetic dogs has not been determined and **it is rational that recommendations would be no different than for non-diabetic dogs.** As restriction of dietary carbohydrate might reduce postprandial hyperglycemia in diabetic dogs and dietary fat restriction might be beneficial if there is concurrent pancreatitis, there will be a tendency for suitable diets to have higher protein levels (>30%ME).

Microalbuminuria and proteinuria do occur in diabetic dogs *(Struble et al, 1998)* and lower dietary protein intake may be indicated in diabetic dogs with microalbuminuria.

TABLE 5 - SUMMARY OF CURRENT EVIDENCE REGARDING DIETARY FAT AND CANINE DIABETES MELLITUS

Perspective gained from current, evidence-based, dietary fat recommendations for human type 1 diabetics	• The primary goal regarding dietary fat restriction in human diabetics is to reduce the risk of coronary heart disease • As coronary heart disease is not recognized as a significant clinical entity in dogs, it might not be relevant to extrapolate dietary fat recommendations for human patients to diabetic dogs
Evidence-based recommendations regarding canine diabetes and dietary fat	• Diabetes secondary to exocrine pancreatic disease appears to be common in dogs, and the diabetic state might also be a risk factor for pancreatitis. As low-fat diets (for example fat< 20% ME) are recommended for dogs with chronic pancreatitis, in addition, since it can be difficult to identify those diabetic dogs with subclinical pancreatitis, it might be prudent to consider feeding a fat-restricted diet (for example fat< 30% ME) to all diabetic dogs • However, results of a randomized, controlled clincial trial in diabetic dogs indicate that diets with lower fat content (31% ME compared with 48% ME) may result in improved lipid profiles but may contribute to undesirable weight loss
Summary	• Although evidence of clinical benefit of feeding fat-restricted diets (< 30% ME) to diabetic dogs is lacking, this option may be considered for diabetic dogs with concurrent pancreatitis • To avoid undesirable weight loss, restricted-fat diets (< 30% ME) should not routinely be recommended for diabetic dogs in poor body condition

► Dietary L-carnitine and canine diabetes

> Evidence based on pathophysiological rationale

L-Carnitine is a conditionally essential, vitamin-like nutrient that plays a pivotal role in fatty acid metabolism. Supplemental L-Carnitine suppresses acidosis and ketogenesis during starvation in dogs *(Rodriguez et al, 1986)*. L-Carnitine supplementation at 50 ppm of diets fed to dogs enhances energy conversion from fatty acid oxidation and protects muscles from catabolism during weight loss *(Gross et al, 1998; Sunvold et al, 1999; Center, 2001)*. Dogs with poorly controlled diabetes experience weight loss, altered fat metabolism, ketogenesis, and hepatic changes, and so are likely to benefit from dietary L-carnitine supplementation. The majority of diabetic dogs are middle-aged and older and can be expected to already have reduced lean body mass *(Kealy et al, 2002)* before the onset of diabetes-associated weight loss. Consequently, it is important to consider any dietary intervention, such as L-carnitine supplementation, that promotes maintenance of lean body mass in these animals.

► Dietary chromium and canine diabetes

> Evidence based on pathophysiological rationale and a controlled clinical trial in diabetic dogs

Chromium tripicolinate is a dietary mineral supplement that has been shown to increase the clearance rate of glucose from the blood by approximately 10% in healthy dogs *(Spears et al, 1998)*. However this potential benefit is only possible if there is chromium deficiency because chromium is a nutrient, not a drug. Thus, supplementation may only result in benefits if the individual is deficient or marginally deficient in chromium.

It is now clear that dietary chromium levels of people in industrialized countries are sub-optimal *(Anderson, 1998)*. Similar information is not available for dogs and further studies are warranted to try and establish the minimum recommended dietary chromium intake for healthy dogs.

Chromium is thought to potentiate insulin's ability to store glucose and would theoretically be useful in dogs with insulin resistance or as an adjunct to exogenous insulin therapy. It is also possible that inadequate dietary intake of chromium by dogs might increase their risk of developing diabetes. It has been postulated that some insulin-dependent diabetic people might lose their ability to convert inorganic chromium to the biologically active form and might actually need to consume foods that contain active forms of chromium *(Anderson, 1992)*. At this stage, there is little information available on the effects of chromium supplementation in human patients requiring insulin therapy *(Ravina et al, 1995; Fox et al, 1998)*. Supplementation with chromium picolinate capsules has not been found to improve glycemic control in insulin-treated dogs *(Schachter et al, 2001)*. The influence of chromium supplementation on bitches with diestrus-induced insulin resistance is unknown.

Dietary chromium supplements usually contain low molecular weight chromium salts such as trivalent chromium [Cr(III)], which has a large safety margin but can be toxic at very high doses *(Jeejeebhoy, 1999)*. In contrast, oral hexavalent chromium [Cr(VI)] appears to be 10-100 times more toxic than trivalent chromium compounds and is an unsuitable dietary supplement *(Katz & Salam, 1993)*.

Summary of dietary recommendations for canine diabetics

The American Diabetes Association uses a grading system to rank the scientific principles of their nutritional recommendations.
- The highest ranking, Grade A, is assigned when there is supportive evidence from multiple, well-conducted studies
- Grade B is an intermediate rating
- Grade C is a lower ranking
- Grade E represents recommendations based on expert consensus.

If this grading system is used to rank the scientific basis of the nutritional recommendations for canine diabetes, current evidence can be summarized in the following fashion.

Grade B evidence
- Controlled evaluation in non-diabetic dogs of diets with different amounts and types of fiber indicate that increased fiber intake has no significant influence on glucose homeostasis, compared with typical diets formulated for canine adult maintenance.
- Several studies in diabetic dogs indicate that high-fiber diets, compared with low-fiber diets, might be associated with improved glycemic control. However, randomized, controlled comparison identified no measurable benefit for insulin requirement or glycemic control in diabetic dogs, compared with a conventional, moderate-fiber diet formulated for adult maintenance (Grade C evidence).
- There seems to be marked variation between the responses of individual diabetic dogs to dietary fiber.
- High-fiber diets do not significantly improve hypertriglyceridemia in diabetic dogs but might lower serum cholesterol concentrations.
- Supplementation with chromium capsules has not been found to improve glycemic control in insulin-treated dogs.

Grade C evidence
- When lower-fiber diets are fed to diabetic dogs, a blend of soluble and insoluble fibers (such as soy fiber or beet pulp) might be preferable to insoluble fiber alone.
- Comparison in non-diabetic dogs found that a rice-based diet resulted in significantly higher postprandial glucose and insulin responses, while a sorghum-based diet caused reduced glucose responses, and barley produced lower insulin responses.
- Diabetic dogs might benefit from dietary L-carnitine supplementation.
- Diets with lower fat content might result in improved lipid profiles in diabetic dogs, but might also contribute to undesirable weight loss.

Grade E evidence
- The diet fed to diabetic dogs should be palatable so that food intake is predictable
- The diet fed to diabetic dogs should be nutritionally balanced.
- The nutritional requirements of any concurrent disease may need to take precedence over the dietary therapy for diabetes.
- As a regimen of fixed daily insulin dosages is typically used to manage diabetic dogs, it is rational to provide a consistent amount of carbohydrate in the meals fed each day.
- The optimal dietary protein for diabetic dogs has not been determined. Lower dietary protein might be indicated only in diabetic dogs with microalbuminuria or proteinuria.

Frequently asked questions regarding diabetes

Q	A
Do diabetic dogs have significant postprandial hyperglycemia? If they do, how long does it last?	Yes. In non-diabetic dogs, commercial dog foods usually result in postprandial elevation of blood glucose concentration for less than 90 minutes. Diabetic dogs lack endogenous insulin secretion, resulting in failure of the major physiological mechanism for counter-regulation of increasing blood glucose concentration. Consequently, **postprandial hyperglycemia in diabetic dogs is of greater magnitude and duration compared with non-diabetic dogs.**
When should diabetic dogs be fed in relation to administration of insulin injections?	Therapy with exogenous insulin has a marked effect on postprandial hyperglycemia. Insulin administration and meal feeding should ideally be timed so that maximal exogenous insulin activity occurs during the postprandial period. Thus, dogs should be fed within 2 hours of subcutaneous administration of lente insulin or within 6 hours of protamine zinc insulin **(Figure 2). A feasible compromise is to feed the dog immediately following the insulin injection.** This considerably simplifies the home treatment regimen for most dog owners while still allowing good glycemic control to be readily achieved. In addition, many owners prefer this regimen because they feel their pet is rewarded for submitting to the injection.
What should be done if a diabetic dog will not eat?	It is crucial that the food fed to diabetic dogs is highly palatable so that food intake is predictable. If the diet is not palatable, it should be changed to a formulation that is more acceptable to the dog. Whenever an individual diabetic dog does not reliably consume meals when they are fed, it should be recommended that insulin injections are administered immediately after meal feeding. If the dog consumes the meal, the full insulin dose can be administered. **If the dog refuses to eat, then administration of half the usual insulin dose should be recommended to reduce the risk of hypoglycemia.** If a diabetic dog refuses to eat a meal that it usually finds palatable, the possibility of concurrent illness should be considered and veterinary examination is recommended.
Can diabetic dogs be fed ad libitum or should they all be meal fed?	**Diabetic dogs should ideally be fed a set number of meals per day.** The daily insulin-dosing regimen tends to be fixed for diabetic dogs, and the timing of meals should be matched to insulin administration so that a predictable glycemic response occurs at the time of maximal exogenous insulin activity. Thus, meals should be fed at the same times each day. Severe hypoglycemia has been reported in a diabetic dog that was fed ad libitum and received insulin at grossly irregular intervals *(Whitley et al, 1997)*. The majority of diabetic dogs will readily consume meals twice-daily if the meals are highly palatable and contain half the daily caloric requirement. For finicky eaters, the meal should be fed at the time of insulin administration and remain available until the expected end of the period of maximal exogenous insulin activity.
Can the meals fed to a diabetic dog be varied from day to day?	Ideally, **every meal should contain the same ingredients and calorie content.** This is an important aspect of diabetes management in dogs and owner compliance should be encouraged. However, care should be taken to consider each case individually. It is usually possible to allow some changes in the feeding regimen without compromising the clinical response of the dog.

Q	A
What is the recommended fiber content of diets fed to diabetic dogs?	There is no evidence of clinical benefit for diabetic dogs of feeding a high-fiber formulation compared with feeding a typical adult maintenance diet. There is marked variation between the responses of individual diabetic dogs to dietary fiber. Some diabetic dogs will have improved glycemic control when fed diets with an increased amount of dietary fiber, while others will not. The response to dietary fiber must be individually assessed in each case. Increased dietary fiber intake is not recommended for diabetic dogs that are underweight, or for dogs for which fiber-supplemented formulations are unpalatable or associated with unacceptable gastrointestinal side-effects. **The most suitable general dietary fiber recommendation for diabetic dogs may be moderate-fiber formulations** (for example, 35 g/1000kcal), although further research is required to demonstrate clinical benefit of this formulation for diabetic dogs compared with typical commercial dog foods formulated for adult maintenance.
Is a low-carbohydrate, high-protein diet now recommended for diabetic dogs similar to the current recommendation for diabetic cats?	Dogs and cats are prone to different types of diabetes and also have different basic macronutrient requirements. Diabetic dogs have forms of diabetes analogous to both human type 1 diabetes and end-stage pancreatitis, while diabetic cats have a form analogous to human type 2 diabetes. There is no evidence that type 2 diabetes occurs in dogs, so it is not valid to extrapolate information on either this disease or feline diabetes to dogs. Unlike dogs, a large proportion of diabetic cats have sufficient beta cells to allow diabetic remission if glucose toxicity and its associated insulin resistance can be reversed, and there is evidence that remission rates are higher if diabetic cats are fed a low-carbohydrate diet. This does not apply to dogs. Diabetic dogs have absolute insulin deficiency and require life-long therapy with exogenous insulin. **As a regimen of fixed daily insulin dosages is typically used to manage diabetic dogs, it is rational to provide a very consistent amount of starch in the meals fed each day.**
What is the best method to achieve body weight gain in a thin diabetic dog, and weight loss in an overweight diabetic dog?	Caloric intake in diabetic dogs should be adjusted to achieve and maintain an ideal body condition. Dogs with poorly controlled diabetes have a decreased ability to metabolize the nutrients absorbed from their gastrointestinal tract and loose glucose in their urine, so require more calories for maintenance than healthy dogs. Most dogs have weight loss by the time diabetes is diagnosed. Many will be underweight while others might still be obese even though they will have experienced weight loss. Insulin therapy ends this state of catabolism and weight loss will soon be arrested. At this stage, a weight management program can be initiated. **Body weight and body condition should be monitored regularly in all diabetic dogs and caloric intake should be adjusted at each re-evaluation until the desired rate of gain or loss is achieved**. If a diabetic dog fails to gain weight when there is good glycemic control and adequate caloric intake, concurrent disease such as exocrine pancreatic insufficiency should be considered. Conversely, a possible cause of obesity in treated diabetic dogs is excessive insulin dose, because insulin has an anabolic action on adipose tissue.
What diet is recommended for diabetic dogs with recurring pancreatitis or exocrine pancreatic insufficiency?	**Dietary therapy for recurring pancreatitis or exocrine pancreatic insufficiency is usually a higher clinical priority than dietary therapy for diabetes.** The prognosis might be improved if these concurrent conditions are recognized early in diabetic dogs and specific nutritional and medical therapy instituted. The dietary recommendations for exocrine pancreatic diseases can be found in **Chapter 5** of this encyclopedia.

References

Akerblom HK, Vaarala O, Hyoty H et al - Environmental factors in the etiology of type 1 diabetes. Am J Med Genet. 2002 ; 115: 18-29.

Alejandro R, Feldman E, Shienvold FL et al - Advances in canine diabetes mellitus research: Etiopathology and results of islet transplantation. J Am Vet Med Assoc 1988 ; 193: 1050-1055.

Anderson RA - Chromium, glucose tolerance, and diabetes. Biol Trace Elem Res 1992 ; 32: 19-24.

Anderson RA - Chromium, glucose intolerance and diabetes. J Am Coll Nutr 1998 ; 17: 548-555.

Athyros VG, Giouleme OI, Nikolaidis NL et al - Long-term follow-up of patients with acute hypertriglyceridemia-induced pancreatitis. J Clin Gastroenterol 2002 ; 34: 472-475.

Atkins CE, MacDonald MJ - Canine diabetes mellitus has a seasonal incidence: Implications relevant to human diabetes. Diabetes Res 1987 ; 5: 83-87.

Bauer JE, Maskell IE - Dietary fibre: Perspectives in clinical management. In Wills JM, Simpson KW (eds). The Waltham book of clinical nutrition of the dog and cat. Oxford, New York, Tokyo: Pergamon, 1995 ; 87-104.

Beam S, Correa MT, Davidson MG - A retrospective-cohort study on the development of cataracts in dogs with diabetes mellitus: 200 cases. Vet Ophtalmol 1999 ; 2: 169-172.

Bednar GE, Patil AR, Murray SM et al - Starch and fiber fractions in selected food and feed ingredients affect their small intestinal digestibility and fermentability and their large bowel fermentability in vitro in a canine model. J Nutr 2000 ; 131: 276-286.

Blaxter AC, Cripps PJ, Gruffydd-Jones TJ - Dietary fibre and post prandial hyperglycaemia in normal and diabetic dogs. J Small Anim Pract 1990 ; 31: 229-233.

Bouchard GF, Sunvold GD - Implications for starch in the management of glucose metabolism. In current perspectives in weight management, in Proceedings. 19th Annual Veterinary Medical Forum of the American College of Veterinary Internal Medicine ; 2001: 16-20.

Camire ME - Chemical changes during extrusion cooking. Recent Advances. Adv Exp Med Biol 1998 ; 434: 109-121.

Campbell KL, Latimer KS - Transient diabetes mellitus associated with prednisone therapy in a dog. J Am Vet Med Assoc 1984 ; 185: 299-301.

Center SA - Carnitine in weight loss. In: Current perspectives in weight management, in Proceedings ; 19th Annual Veterinary Medical Forum of the American College of Veterinary Internal Medicine 2001: 36-44.

Church DB - Canine diabetes mellitus: Some therapeutic considerations. In Veterinary Annual. 22nd edition ; Bristol: Scientechnica 1982: 235-240.

Concannon PW - Canine pregnancy and parturition. Vet Clin North Am Small Anim Pract 1986 ; 16: 453-475.

Concannon PW, McCann JP, Temple M - Biology and endocrinology of ovulation, pregnancy and parturition in the dog. J Reprod Fertil Suppl 1989 ; 39: 3-25.

Davis M - Dietary fibre and post prandial hyperglycaemia. J Small Anim Pract 1990 ; 31: 461.

Davison LJ, Fleeman LM - Pathogenesis of canine diabetes mellitus: Current research directions (abstract), in Proceedings. Annual meeting of the Society for Comparative Endocrinology 2003a.

Davison LJ, Herrtage ME, Steiner JM et al - Evidence of anti-insulin autoreactivity and pancreatic inflammation in newly diagnosed diabetic dogs (abstract). J Vet Intern Med 2003b ; 17: 395.

EASD (Diabetes and Nutrition Study Group of the EASD) - Nutritional recommendations for individuals with diabetes mellitus. Diab Nutr Metab 1988 ; 1: 145-149.

EASD (Diabetes and Nutrition Study Group of the EASD) - Recommendations for the nutritional management of patients with diabetes mellitus. Diab Nutr Metab 1995 ; 8: 1-4.

Edney ATB, Smith PM - Study of obesity in dogs visiting veterinary practices in the United Kingdom. Vet Rec 1986 ; 118: 391-396.

Eigenmann JE, Eigenmann RY, Rijnberk A et al - Progesterone-controlled growth hormone overproduction and naturally occurring canine diabetes and acromegaly. Acta Endocrinol 1983 ; 104: 167-176.

Feldman EC, Nelson RW - Diabetic ketoacidosis. In Canine and feline endocrinology and reproduction. 3rd edition. St Louis: Saunders, 2004a ; 580-615.

Feldman EC, Nelson RW - Ovarian cycle and vaginal cytology. In Canine and feline endocrinology and reproduction. 3rd edition. St Louis ; Saunders, 2004b: 752-774.

Fleegler FM, Rogers KD, Drash A et al - Age, sex, and season of onset of juvenile diabetes in different geographic areas. Pediatrics 1979 ; 63: 374-379.

Fleeman LM, Rand JS - Long-term management of the diabetic dog. Waltham Focus 2000 ; 10:1 6-23.

Fleeman LM, Rand JS - Diets with high fiber and moderate starch are not advantageous for dogs with stabilized diabetes compared to a commercial diet with moderate fiber and low starch (abstract). J Vet Intern Med 2003 ; 17: 433.

Fox GN, Sabovic Z - Chromium picolinate supplementation for diabetes mellitus. J Fam Pract 1998 ; 46: 83-86.

Franz MJ, Bantle JP, Beebe CA et al - Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications (technical review). Diabetes Care 2002a ; 25: 148-198.

Franz MJ, Bantle JP, Beebe CA et al - Gestational diabetes mellitus (position statement). Diabetes Care 2002b ; 25: S94-S96.

Gamble DR, Taylor KW - Seasonal incidence of diabetes mellitus. BMJ 1969 ; 3: 631-633.

Graham PA, Maskell IE, Nash AS - Canned high fiber diet and postprandial glycemia in dogs with naturally occurring diabetes mellitus. J Nutr 1994 ; 124: 2712S-2715S.

Graham PA, Maskell IE, Rawlings JM et al - Influence of a high fibre diet on glycaemic control and quality of life in dogs with diabetes mellitus. J Small Anim Pract 2002 ; 43: 67-73.

Graham PA, Nash AS - Rates of blindness and other complications in diabetic dogs (abstract). J Vet Intern Med 1997a ; 11: 124.

Graham PA, Nash AS - Survival data analysis applied to canine diabetes mellitus (abstract). J Vet Intern Med. 1997b ;11:142.

Gross KL, Wedekind K, Kirk CA, et al - Effect of dietary carnitine or chromium on weight loss and body composition of obese dogs (abstract). J Anim Sci 1998 ; 76: 175.

Guptill L, Glickman L, Glickman N - Time trends and risk factors for diabetes mellitus in dogs:

Analysis of veterinary medical data base records (1970-1999). Vet J 2003 ; 165: 240-247.

Hardt PD, Krauss A, Bretz L et al - Pancreatic exocrine function in patients with type 1 and type 2 diabetes mellitus. Acta Diabetol 2000 ; 37: 105-110.

Henegar JR, Bigler SA, Henegar LK et al - Functional and structural changes in the kidney in the early stages of obesity. J Am Soc Nephrol 2001 ; 12: 1211-1217.

Hess RS, Kass PH, Shofer FS et al - Evaluation of risk factors for fatal acute pancreatitis in dogs. J Am Vet Med Assoc 1999 ; 214: 46-51.

Hess RS, Ward CR - Effect of insulin dosage on glycemic response in dogs with diabetes mellitus: 221 cases (1993-1998). J Am Vet Med Assoc 2000 ; 216: 217-221.

Hess RS, Kass PH, van Winkle TJ - Association between diabetes mellitus, hypothyroidism or hyperadrenocorticism, and atherosclerosis in dogs. J Vet Intern Med 2003: 17: 489-494.

Hoenig M, Dawe DL - A qualitative assay for beta cell antibodies. Preliminary results in dogs with diabetes mellitus. Vet Immunol Immunopathol 1992 ; 32: 195-203.

Hoenig M, Laflamme DP, Klaser DA et al - Glucose tolerance and lipid profiles in dogs fed different fiber diets. Vet Ther 2001 ; 2: 160-169.

Jarvi AE, Karlstrom BE, Granfeldt YE et al - The influence of food structure on postprandial metabolism in patients with non-insulin-dependent diabetes mellitus. Am J Clin Nutr 1995 ; 61: 837-842.

Jeejeebhoy KN - The role of chromium in nutrition and therapeutics and as a potential toxin. Nutr Rev 1999 ; 57: 329-335.

Kaiyala KJ, Prigeon RL, Kahn SE et al - Reduced beta-cell function contributes to impaired glucose tolerance in dogs made obese by high-fat feeding. Am J Physiol 1999 ; 277: E659-E667.

Karr-Lilienthal LK, Merchen NR, Grieshop CM et al - Selected gelling agents in canned dog food affect nutrient digestibilities and fecal characteristics of ileal cannulated dogs. J Nutr 2002 ; 132: 1714S-1716S.

Katz SA, Salem H - The toxicology of chromium with respect to its chemical speciation: a review. J Appl Toxicol 1993 ; 13: 217-224.

Kealy RD, Lawler DF, Ballam JM et al - Effects of diet restriction on life span and age-related changes in dogs. J Am Vet Med Assoc 2002 ; 220: 1315-1320.

Kennedy LJ, Davison LJ, Barnes A et al - Susceptibility to canine diabetes mellitus is associated with MHC class II polymorphism (abstract), in Proceedings. 46th Annual Congress of the British Small Animal Veterinary Association 2003: 563.

Kimmel SE, Michel KE, Hess RS et al - Effects of insoluble and soluble dietary fiber on glycemic control in dogs with naturally occurring insulin-dependent diabetes mellitus. J Am Vet Med Assoc 2000 ; 216: 1076-1081.

Krook L, Larsson S, Rooney JR - The interrelationship of diabetes mellitus, obesity, and pyometra in the dog. Am J Vet Res 1960 ; 21: 121-124.

Kukreja A, Maclaren NK - Autoimmunity and diabetes. J Clin Endocrinol Metab 1999 ; 84: 4371-4378.

Liljeberg HG, Granfeldt YE, Bjorck IM - Products based on a high fiber barley genotype, but not on common barley and oats, lower postprandial glucose and insulin responses in healthy humans. J Nutr 1996 ; 126: 458-466.

Ling GV, Lowenstine LJ, Pulley T et al - Diabetes mellitus in dogs: A review of initial evaluation, immediate and long-term management, and out-come. J Am Vet Med Assoc 1977 ; 170: 521-530.

Major CA, Henry MJ, De Veciana M et al - The effects of carbohydrate restriction in patients with diet-controlled gestational diabetes. Obstet Gynecol. 1998 ; 91: 600-604.

Marmor M, Willeberg P, Glickman LT et al - Epizootiologic patterns of diabetes mellitus in dogs. Am J Vet Res 1982 ; 43: 465-470.

Massimino SP, McBurney MI, Field CJ et al - Fermentable dietary fiber increases GLP-1 secretion and improves glucose homeostasis despite increased gastrointestinal glucose transport capacity in healthy dogs. J Nutr 1998 ; 128: 1786-1793.

Mattheeuws D, Rottiers R, Kaneko JJ et al - Diabetes mellitus in dogs: Relationship of obesity to glucose tolerance and insulin response. Am J Vet Res 1984 ; 45: 98-103.

McCann JP, Concannon PW - Effects of sex, ovarian cycles, pregnancy and lactation on insulin and glucose response to exogenous glucose and glucagon in dogs (abstract). Biol Reprod 1983 ; 28: 41.

Mittelman SD, Van-Citters GW, Kirkman EL et al - Extreme insulin resistance of the central adipose depot in vivo. Diabetes 2002 ; 51: 755-761.

Montgomery TM, Nelson RW, Feldman EC et al - Basal and glucagon-stimulated plasma c-peptide concentrations in healthy dogs, dogs with diabetes mellitus, and dogs with hyperadrenocorticism. J Vet Intern Med 1996 ; 10: 116-122.

Murray SM, Fahey GCJr, Merchen NR et al - Evaluation of selected high-starch flours as ingredients in canine diets. J Anim Sci 1999 ; 77: 2180-2186.

Nelson R, Briggs C, Scott-Moncrieff JC et al - Effect of dietary fiber type and quantity on control of glycemia in diabetic dogs (abstract). J Vet Intern Med 2000 ; 14: 376.

Nelson RW, Duesberg CA, Ford SL et al - Effect of dietary insoluble fiber on control of glycaemia in dogs with naturally acquired diabetes mellitus. J Am Vet Med Assoc 1998 ; 212: 380-386.

Nelson RW, Ihle SL, Lewis LD et al - Effects of dietary fiber supplementation on glycemic control in dogs with alloxan-induced diabetes mellitus. Am J Vet Res 1991 ; 52: 2060-2066.

Nelson RW, Sunvold GD - Effect of carboxymethylcellulose on postprandial glycaemic response in healthy dogs. In Reinhart GA, Carey DP (eds). Recent advances in canine and feline nutrition. Vol II. Wilmington, USA ; Orange Frazer Press, 1998: 97-102.

Nguyen P, Dumon H, Biourge V et al - Measurement of postprandial incremental glucose and insulin changes in healthy dogs: Influence of food adaptation and length of time of blood sampling. J Nutr 1998a ; 128: 2659S-2662S.

Nguyen P, Dumon H, Biourge V et al - Glycemic and insulinemic responses after ingestion of commercial foods in healthy dogs: Influence of food composition. J Nutr 1998b ; 128: 2654S-2658S.

Onkamo P, Vaananen S, Karvonen M et al - Worldwide increase in incidence of type 1 diabetes - the analysis of the data on published incidence trends. Diabetologia 1999 ; 42: 1395-1403.

Peterson ME - Decreased insulin sensitivity and glucose tolerance in spontaneous canine hyperadrenocorticism. Res Vet Sci 1984 ; 36: 177-182.

Rand JS, Fleeman LM, Farrow HA et al - Canine and feline diabetes: Nature or nurture? J Nutr 2004 ; 134: 2072S-2080S.

Ravina A, Slezak L, Rubal A et al - Clinical use of the trace element chromium (III) in the treatment of diabetes mellitus. J Trace Elem Exp Med 1995 ; 8: 183-190.

Rocchini AP, Mao HZ, Babu K et al - Clonidine prevents insulin resistance and hypertension in obese dogs. Hypertension 1999 ; 33: 548-553.

Rodriguez J, Bruyns J, Askanazi J et al - Carnitine metabolism during fasting in dogs. Surgery 1986 ; 99: 684-687.

Salgado D, Reusch C, Spiess B - Diabetic cataracts: Different incidence between dogs and cats. Schweiz Arch Tierheilkd 2000 ; 142: 349-353.

Scaramal JD, Renauld A, Gomez NV et al - Natural estrous cycle in normal and diabetic bitches in relation to glucose and insulin tests. Medicina (Buenos Aires) 1997 ; 57: 169-180.

Schachter S, Nelson RW, Kirk CA - Oral chromium picolinate and control of glycemia in insulin-treated diabetic dogs. J Vet Intern Med 2001 ; 15: 379-384.

Seissler J, de Sonnaville JJ, Morgenthaler NG et al - Immunological heterogeneity in type 1 diabetes: Presence of distinct autoantibody patterns in patients with acute onset and slowly progressive disease. Diabetologia 1998 ; 41: 891-897.

Selman PJ, Mol JA, Rutteman GR et al - Progestin treatment in the dog 1. Effects on growth hormone, insulin-like growth factor 1 and glucose homeostasis. Eur J Endocrinol 1994 ; 131:413-421.

Simpson KW - Current concepts of the pathogenesis and pathophysiology of acute pancreatitis in the dog and cat. Compend Contin Educ Pract Vet 1993 ; 15: 247-253.

Sottiaux J - Atherosclerosis in a dog with diabetes mellitus. J Small Anim Pract 1999 ; 40: 581-584.

Spears JW, Brown TT, Sunvold GD et al - Influence of chromium on glucose metabolism and insulin sensitivity. In Reinhart GA, Carey DP (eds). Recent advances in canine and feline nutrition, volume II. 1998 Iams nutrition symposium proceedings. Wilmington, USA ; Orange Frazer Press, 1998: 103-113.

Stamler J, Vaccaro O, Neaton JD et al - Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the multiple risk factor intervention trial. Diabetes Care 1993 ; 16: 434-444.

Steiner JM, Williams DA - Development and validation of a radioimmunoassay for the measurement of canine pancreatic lipase immunoreactivity in serum of dogs. Am J Vet Res 2003 ; 64: 1237-1241.

Stenner VJ, Fleeman LM, Rand JS - Comparison of the pharmacodynamics and pharmacokinetics of subcutaneous glargine, protamine zinc, and lente insulin preparations in healthy dogs (abstract). J Vet Intern Med 2004 ; 18: 444-445.

Struble AL, Feldman EC, Nelson RW et al - Systemic hypertension and proteinuria in dogs with diabetes mellitus. J Am Vet Med Assoc 1998 ; 213: 822-825.

Sunvold GD, Bouchard GF - The glycaemic response to dietary starch. In Reinhart GA, Carey DP (eds). Recent advances in canine and feline nutrition. Vol II. Wilmington ; USA: Orange Frazer Press, 1998: 123-131.

Sunvold GD, Vickers RJ, Kelley RL et al - Effect of dietary carnitine during energy restriction in the canine (abstract). FASEB J 1999 ; 13: A268.

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus - Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 1997 ; 20: 1183-1197.

Truett AA, Borne AT, Monteiro MP et al - Composition of dietary fat affects blood pressure and insulin responses to dietary obesity in the dog. Obes Res 1998 ; 6: 137-146.

Twomey LN, Pethick DW, Rowe JB et al - The use of sorghum and corn as alternatives to rice in dog foods. J Nutr 2002 ; 132: 1704S-1705S.

Vaarala O - Gut and the induction of immune tolerance in type 1 diabetes. Diabetes Metab Res Rev 1999 ; 15: 353-361.

Villa E, Gonzalez-Albarran O, Rabano A et al - Effects of hyperinsulinemia on vascular blood flows in experimental obesity. J Steroid Biochem Mol Biol 1999 ; 69: 273-279.

Watson PJ, Herrtage ME - Use of glucagon stimulation tests to assess beta-cell function in dogs with chronic pancreatitis. J Nutr 2004 ; 134: 2081S-2083S.

Whitley NT, Drobatz KJ, Panciera DL - Insulin overdose in dogs and cats: 28 cases (1986-1993). J Am Vet Med Assoc 1997 ; 211: 326-30.

Wiberg ME, Nurmi A-K, Westermarck E - Serum trypsin like immunoreactivity measurement for the diagnosis of subclinical exocrine pancreatic insufficiency. J Vet Intern Med 1999 ; 13: 426-432.

Williams DA - Diagnosis and management of pancreatitis. J Small Anim Pract 1994 ; 35: 445-454.

Zimmet PZ, Tuomi T, Mackay IR et al - Latent autoimmune diabetes mellitus in adults (LADA): The role of antibodies to glutamic acid decarboxylase in diagnosis and prediction of insulin dependency. Diabet Med 1994; 11: 299-303.

EXAMPLES OF HOME-PREPARED THE TREATMENT OF

Example 1

COMPOSITION
(1000 g diet)

Mullet . . . . . 500 g
Pasta, wheat whole-meal . . . . . 270 g
Carrots (boiled, drained) . . . . . 155 g
Wheat bran . . . . . 50 g
Pectin . . . . . 10 g
Rapeseed oil . . . . . 15 g

Add a well-balanced mineral and vitamin supplement.

ANALYSIS		
The diet prepared in this way contains 46% dry matter and 54% water		
	% dry matter	**g/1000 kcal**
Protein	33	88
Fat	10	27
Available carbohydrate	41	109
Fiber	12	32

INDICATIVE RATIONING			
Energy value (metabolizable energy) 1710 kcal/1000 g diet prepared (3750 kcal/1000 g DM)			
Dog's weight (kg)	Daily amount (g)*	Dog's weight (kg)	Daily amount (g)*
2	130	45	1320
4	220	50	1430
6	290	55	1540
10	430	60	1640
15	580	65	1740
20	720	70	1840
25	850	75	1940
30	970	80	2030
35	1090	85	2130
40	1210	90	2220

Key Points

- **Incorporating cereals with a low glycemic index** to smooth out the postprandial hyperglycemic peak
- **Intake of soluble and insoluble fiber** to help regulate glycemia
- **Reducing the fat content** due to the risk of subclinical pancreatitis

**The number of meals must be adapted to the insulin injection protocol. Ideally, each meal must be given in such a way that the postprandial period corresponds to the maximum period of activity of the insulin.*

DIETS ADAPTED TO DIABETES MELLITUS

Example 2

COMPOSITION
(1000 g diet)

Turkey, breast without skin . . . . . 280 g
Cottage cheese * . . . . . 330 g
Rolled oats . . . . . 250 g
Carrots (boiled, drained) . . . . . 60 g
Wheat bran . . . . . 60 g
Pectin . . . . . 10 g
Rapeseed oil . . . . . 10 g
** 35% of dry matter is fat*

Add a well-balanced mineral and vitamin supplement.

INDICATIVE RATIONING

Energy value (metabolizable energy) 1675 kcal/1000 g diet prepared (3730 kcal/1000 g DM)

Dog's weight (kg)	Daily amount (g)*	Dog's weight (kg)	Daily amount (g)*
2	130	45	1350
4	220	50	1460
6	300	55	1570
10	440	60	1670
15	590	65	1780
20	730	70	1880
25	870	75	1980
30	990	80	2080
35	1120	85	2170
40	1230	90	2270

ANALYSIS

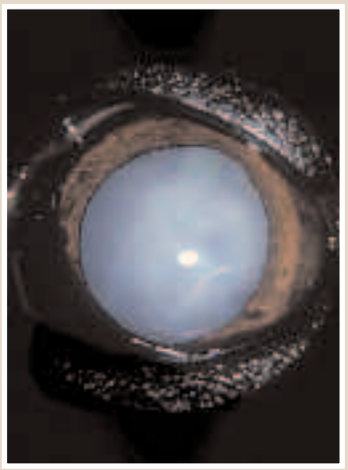
The diet prepared in this way contains 45% dry matter and 55% water

	% dry matter	g/1000 kcal
Protein	34	91
Fat	11	28
Available carbohydrate	38	102
Fiber	14	38

Contra-indications

Gestation
Lactation
Growth

Examples of home-made diets are proposed by Pr Patrick Nguyen
(Nutrition and Endocrinology Unit; Biology and Pathology Department, National veterinary School of Nantes)



Cataracts are the most common complication among diabetic dogs. The risk increases as the dog grows older. The word comes from the Greek word kataraktès (rupture) where the crystalline lens loses its transparency and the eye has a gray-blue opalescence.

Key Points
with respect to:

The role of nutrition in the treatment of diabetes mellitus in dogs

Rather than a traditional maintenance diet for adult dogs, the diet recommended for diabetic dogs and bitches presenting with diestrus-associated insulin resistance must meet the following key criteria:

- **High palatability** to guarantee regular consumption.
- **Limited starch content** (<50% carbohydrate calories): there is a correlation between the starch content and the dog's glycemic response *(Nguyen et al, 1998)*. It is easy to lower the starch content below 30% even in dry foods. If the pancreas no longer functions (which is more often the case in dogs), it is important to adjust the insulin dose to the starch intake every time the diet is changed. When the starch content of a diet is reduced, the insulin dose must also be reduced.
- High glycemic index starches such as rice and bread should be avoided in diabetic dogs. It is preferable to fed **cereals with starch that is digested more slowly**, facilitating slower, prolonged absorption of glucose. Low glycemic index cereals include corn, wheat, barley and sorghum.
- A diet with a higher fiber content compared with a standard maintenance diet for adult dogs may not be particularly beneficial for diabetic dogs. **The optimal fiber content depends on the dog's physical condition**, the level and source of the starch and the nature of the fiber used.
- Every type of fiber has its own particular properties, therefore intake of **fiber from different sources** is important

- *Insoluble, non-fermentable fiber (e.g. cellulose)* is well tolerated, even in large quantities. Varying the content of this type of fiber permits the adaptation of the energy density of a food to the dog's physical condition.

- *Soluble, non-fermentable fiber (e.g. fructo-oligosaccharides)* improves glucose tolerance.

- *Insoluble, non-fermentable fiber (e.g. psyllium)* impacts the speed of transit through the intestine and the release of glucose.

NB. Beet pulp contains both insoluble and non-fermentable fiber, and soluble and non-fermentable fiber.

- **The ideal fat content depends on the physical condition of the dog**, but diets with a high fat content should be avoided in diabetic dogs, due to the associated risk of pancreatitis. An intake of 20-35% lipid calories appears to be sufficient, unless the dog is in poor body condition. There is an inverse correlation between the dietary fat content and the postprandial glycemic and insulinemic responses *(Prudhomme et al, 1999)*. This effect is probably a consequence of deceleration of gastric emptying associated with high fat foods.

- If the food contains moderate starch, fiber and fat content, the protein will be the main source of energy. There are no negative effects associated with providing at least 30%-45% protein calories in the food. **High protein intake helps compensate for the catabolism of protein and increased gluconeogenesis in diabetic dogs**, especially when the diabetes has not been properly stabilized.

- An **L-carnitine supplement** helps maintain the lean body mass.

- Diets for diabetic dogs must contain mineral and trace-element levels similar to those for non-diabetic dogs. **Particular attention should be given to potassium** to avoid deficiencies.

- **The level of water soluble vitamins should be increased** to compensate for losses due to polyuria.

- Oxidative stress is involved in the pathophysiology of diabetes. Therefore, appropriate supplementation with a blend of antioxidants is recommended.

POINTS TO BE MONITORED BY THE OWNER OF A DIABETIC DOG

The quantities of water and food consumed by the dog	polydipsia (accompanied by polyuria), anorexia or conversely polyphagia may be signs of poor diabetic control
The dog's body weight	changes in body weight may require modification of the insulin dosage. Obesity is a risk factor contributing to insulin resistance
The dog's level of activity	regular physical activity should be included in the list of preventative measures to reduce the incidence of canine diabetes mellitus *(Hedhammar et al, 2005)*
The timing of meals	this is essential for successful treatment. Dividing the ration into two meals a day helps minimize the hyperglycemic peaks, regardless of the type of diabetes. With insulin therapy, the meals should ideally be served just after the insulin peaks, which vary according to the individual and the type of insulin administered
The composition of the meal	the appropriate food should not be changed after selection, as both the quantity and the type of carbohydrate ingested have a direct impact on the postprandial glycemic and insulinemic responses. Supplements, especially sugary treats or food rich in carbohydrates should not be given to dogs with diabetes mellitus

A few simple rules help prevent complications with diabetes mellitus in dogs.

Focus on:

THE EFFECT OF DIETARY FIBER ON GASTRO-INTESTINAL TRANSIT

Dietary fiber plays a major role in gastro-intestinal transit, although it should be noted that the action differs depending on whether it is soluble or insoluble fiber.

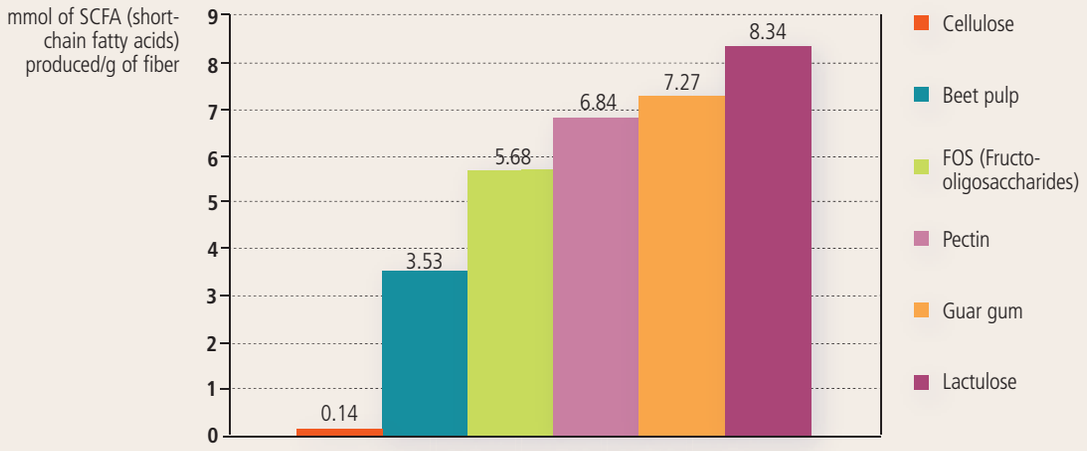
Soluble fiber

In contact with water, soluble fiber (pectins, gums, oligosaccharides, etc) forms a gel or a viscous solution. The viscosity of this type of fiber tends to slow down gastro-intestinal transit due to the simple increase in flow-through resistance *(Guilford, 1996)*.

The effect of fiber on the quality of stools varies according to its ability to be fermented by colonic bacteria. With the exception of psyllium, most types of soluble fiber are degraded by the microflora of the large intestine. The bacteria flora use the fermentable fiber as an energy source, and in the process, generate fermentation products such as short chain fatty acids and lactic acid which have a trophic effect on the colonic mucosa.

CAPACITY OF IN VITRO FERMENTATION OF SEVERAL DIETARY FIBERS

(From Sunvold et al, 1994)



The ratio that exists between fermentable and non fermentable fibers (F/nF) in the food influences the production of putrefaction by-products in the stools.
Example: if the F/nF increases from 0.15 to 0.48, the fecal concentration in amines is 50% lower, corresponding to a total dietary fiber content of 7.7% and 9.2%, respectively (Hernot et al, 2005).

However, a excess quantities of fermentable fiber in a diet is detrimental to digestive tolerance. A diet rich in fermentable fiber (pectins, guar gums) increases the water content and the volume of the feces *(Wiernusz, 1995; Silvio et al, 2000)*. Furthermore, the fermentation products may induce osmotic diarrhea by attracting free water into the intestinal lumen. These effects are mainly due to proliferation of the bacterial biomass produced.

Insoluble fiber

Insoluble fiber regulates transit, accelerating it during constipation and decelerating it during diarrhea *(Guilford, 1996)*.

Insoluble fiber is not generally degraded by the microflora of the colon. As a consequence, insoluble fiber is excreted almost fully intact in the stools. The capacity to increase the indigestible residue of feces contributes to fecal consistency as well as increasing the volume of stools *(Silvio et al, 2000)*. An excess quantity of insoluble fiber in a food is also detrimental to its good digestibility.

References

Guilford WG - Nutritional management of gastrointestinal diseases. In: Strombeck's Small Animal Gastroenterology. 3rd Ed WB Saunders Co, Philadelphia 1996: 889-910.

Hedhammar A, Sallander M, Klinkenberg H - Diabetes in dogs: feeding, exercise and weight as possible predisposing factors. Proceedings of Waltham International Nutritional Sciences Symposium, Washington 2005 ; Innovations in Companion Animal Nutrition: 30.

Hernot D, Biourge V, Dumon et al - Effect of dietary fermentable to non fermentable fiber ratio on fecal putrefactive products in dogs varying in body size. Proceedings of Waltham International Nutritional Sciences Symposium, Washington 2005 ; Innovations in Companion Animal Nutrition: 53.

Nguyen P, Dumon H, Biourge V et al - Glycemic and insulinemic responses after ingestion of commercial foods in healthy dogs: Influence of food composition. J Nutr 1998 ; 128: 2654S-2658S.

Prudhomme O, Martin L, Dumon H et al - Effects of dietary intake level and composition on glucose and insulin responses to diet in dogs. Proceedings 3rd ESVCN Congress ; Lyon 24-25 Sept 1999: 81.

Silvio J, Harmon DL, Gross KL et al - Influence of fiber fermentability on nutrient digestion in the dog. Nutrition 2000 ;16: 289-295.

Sunvold GD, Fahey GC Jr, Merchen NR et al - Fermentability of selected fibrous substrates by dog fecal microflora as influenced by diet. J Nutr 1994 ; 124: 2719S-2720S

Wiernusz CJ, Shields Jr RG, Van Vlierbergen DJ et all - Canine nutrient digestibility and stool quality evaluation of canned diets containing various soy protein supplements. Vet Clin Nutr 1995; 2: 49-56.

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Canine hyperlipidemia: causes and nutricional management

1 - Lipid metabolism 237
2 - Diagnostic approach to the hyperlipidemic patient 240
3 - Causes of hyperlipidemia 243
4 - Primary hyperlipidemia 246
5 - Effects of persistent hyperlipidemia 248
6 - Treatment of hyperlipidemia 250

Frequently asked questions: canine hyperlipidemia 254
References 255
Examples of home-prepared diets adapted to the nutritional management of hyperlipidemia 260
Royal Canin Nutritional Information 262

Canine hyperlipidemia: causes and nutritional management

Patricia SCHENCK
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Dr. Schenck received her Masters degree in Animal Science and her DVM degree from the University of Illinois in Champaign-Urbana. After owning her own small animal practice, she returned to the University of Florida where she completed her PhD in lipid biochemistry. After completing a post-doc at the USDA in Peoria Illinois, she joined the Ohio State University, where she became interested in research in calcium regulation. After working in the pet food industry for a number of years, she joined the Endocrinology section in the Diagnostic Center for Population and Animal Health at Michigan State University in 2001. Her current research interests include developing new tests for increasing diagnostic utility in calcium and lipid disorders, hyperlipidemias in the dog, idiopathic hypercalcemia in the cat, and the relationships between lipids and parathyroid hormone.

Hyperlipidemia or hyperlipemia refers to an increased cloudiness in serum due to an excess of circulating lipids. The term lipemia, the presence of lipids in serum, is often incorrectly used to describe excess circulating lipids. Hyperlipidemia and hyperlipoproteinemia are often used interchangeably, but hyperlipoproteinemia more correctly refers to an excess of circulating lipoproteins. Hypercholesterolemia and hypertriglyceridemia refer respectively to an excess of circulating cholesterol or triglyceride. Hypercholesterolemia or hypertriglyceridemia may occur alone or in combination with hyperlipoproteinemia. Normally hyperlipidemia occurs after ingesting a meal, but fasting hyperlipidemia is indicative of abnormal lipid metabolism.

1 - Lipid metabolism

Perturbations in any aspect of lipid metabolism may result in abnormal hyperlipidemia. Abnormalities may occur in lipid absorption, synthesis, esterification, lipoprotein synthesis, receptor-mediated uptake, bile formation and circulation, or reverse cholesterol transport.

► Lipid absorption

Cholesterol and triglycerides are absorbed in the small intestine. Cholesterol may be ingested in the diet (exogenous), or is derived from biliary secretion and desquamation of intestinal epithelial cells (endogenous) which may account for up to 50% of the total cholesterol present in the small intestinal lumen *(Holt, 1972)*. Absorption requires bile acids and micelle formation **(Figure 1)**. Bile salts are secreted by the liver and enter the small intestine via the bile, and most salts exist as conjugates with glycine or taurine. When the concentration of bile salts reaches a high enough level, bile salts form aggregates or micelles *(Feldman et al, 1983)*, and allow approximately 30 to 60% of available cholesterol to be absorbed. Within the lumen of the intestine, cholesteryl esters from micelles are hydrolyzed by pancreatic cholesterol esterase. Free cholesterol passively diffuses across the intestinal mucosal cell wall *(Westergaard et al, 1976)*. Within the intestinal cell, free cholesterol is re-esterified with fatty acids, a process mediated by the enzyme acyl CoA:cholesterylacyltransferase (ACAT). A combination of free cholesterol and cholesteryl esters are then secreted into chylomicron particles.

Within the intestinal lumen, triglycerides are hydrolyzed by pancreatic lipase to monoglycerides, diglycerides, and free fatty acids. In combination with cholesterol, phospholipid, and bile salts, these monoglycerides, diglycerides, and free fatty acids form mixed micelles. These micelles release monoglycerides, diglycerides, and free fatty acids at the intestinal cell wall where they are absorbed **(Figure 1)**. Within the intestinal cell, monoglycerides and diglycerides are re-esterified to form triglycerides. Triglycerides along with cholesteryl esters, free cholesterol, phospholipid, and proteins will be incorporated into chylomicron particles for release into the circulation via the lymphatic system and the thoracic duct.

► Cholesterol synthesis

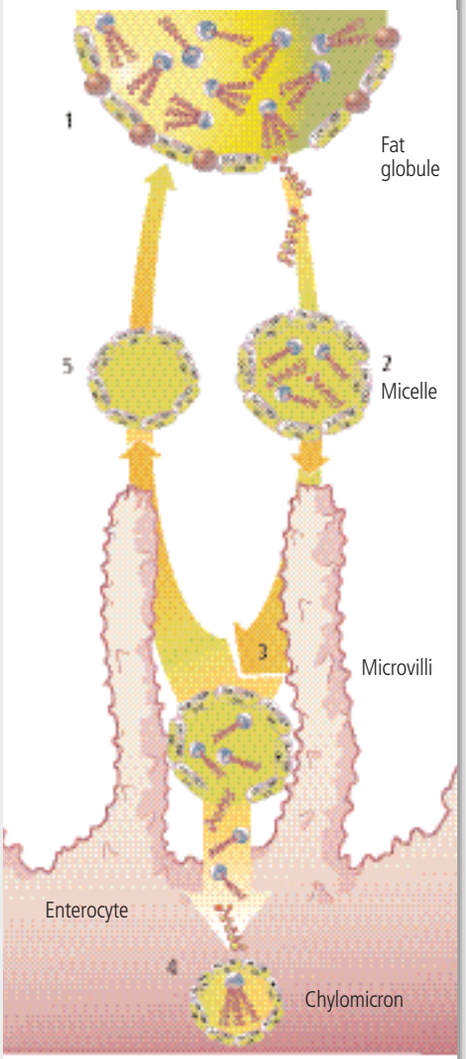
Endogenous cholesterol synthesis contributes to the total body cholesterol concentration. Cholesterol can be synthesized by almost all cells, with the highest rate of synthesis in the liver and intestine *(Turley et al, 1981)*. Approximately 1g cholesterol per day is synthesized within the body from acetyl CoA. The enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCoA reductase) is the rate-limiting enzyme in cholesterol synthesis *(Alberts, 1988)*.

► Lipoprotein production

Lipoproteins are the main carriers of triglycerides and cholesterol in the blood and are important in the delivery of cholesterol to all tissues. Circulating lipoproteins are classified by their size, density, and electrophoretic behavior *(Mahley et al, 1974a)*. Lipoproteins in humans have been well characterized *(Alaupovic et al, 1968; Assmann, 1982; Shepherd et al, 1989)*, but direct correlations cannot be made to the dog due to many differences in lipoprotein characteristics *(Mahley et al, 1974a; Mahley et al, 1974b)*.

Lipoproteins are micellar particles with a hydrophobic core containing triglycerides and cholesteryl esters, and an amphipathic outer surface containing phospholipid,

FIGURE 1 - DIGESTION AND ABSORPTION OF LIPIDS
(From Gogny, 1994)



unesterified cholesterol, and proteins *(Assmann, 1982)*. Proteins within a lipoprotein tend to be specific for that lipoprotein class.
Lipoprotein particles are not static, but are in a dynamic state of equilibrium, with transfer of components occurring between lipoproteins.

Five major classes of lipoproteins have been characterized, including:
- **chylomicrons**
- **very low density lipoproteins (VLDL)**
- **intermediate density lipoproteins (IDL)**
- **low density lipoproteins (LDL)**
- **and high density lipoproteins (HDL).**

Some mammals (such as humans and most monkeys) have a predominance of LDL and are classified as "LDL mammals" *(Chapman, 1986)*. LDL mammals are more sensitive to elevations in LDL cholesterol and the development of atherosclerosis. Dogs and most other mammals are considered "HDL mammals" due to the predominance of circulating HDL. HDL mammals are less sensitive to elevated LDL cholesterol concentrations, and are more resistant to the development of atherosclerosis **(Table 1)**.

TABLE 1 - PREDOMINANCE OF CERTAIN LIPOPROTEINS BY SPECIES

"LDL mammals"	"HDL mammals"
Humans and most Monkeys	Dogs
Rabbits	Cats
Hamsters	Horses
Guinea pigs	Ruminants
Pigs	Rats
Camels	Mice
Rhinoceros	Most other mammals

LDL: low density lipoproteins
HDL: high density lipoproteins

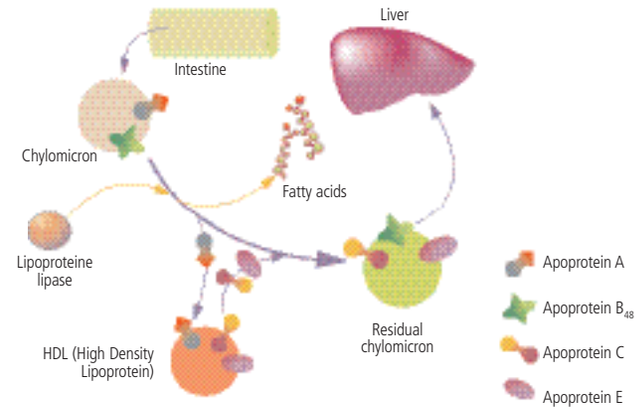
In general, the larger lipoproteins are less dense, contain less protein, and more lipid. Chylomicrons are the largest of the lipoproteins with the lowest density. HDL are the smallest and heaviest of the lipoproteins. Characteristics of the individual lipoproteins are summarized in **Table 2**.

TABLE 2 - CANINE LIPOPROTEIN CHARACTERISTICS

			APPROXIMATE COMPOSITION %					
Lipoprotein	**Hydrated Density g/mL**	**Electro-phoretic Mobility**	**Triglyceride**	**Cholesteryl Ester**	**Free Cholesterol**	**Protein**	**Phospholipid**	**Major Apoproteins**
Chylomicron	0.930	Origin	**90**	2	1	2	5	B_{48}, A, C, E
VLDL	< 1.006	β (preβ)	**60**	13	7	5	15	B_{100}, B_{48}
LDL	1.019 – 1.087	β	10	**38**	8	22	22	B_{100}
HDL	-	-	4	16	5	50	25	-
HDL1	1.025 – 1.100	α2	-	-	-	-	-	E, A, C
HDL2	1.063 – 1.100	α1	-	-	-	-	-	A, C, E
HDL3	1.100 – 1.210	α1	-	-	-	-	-	A, C

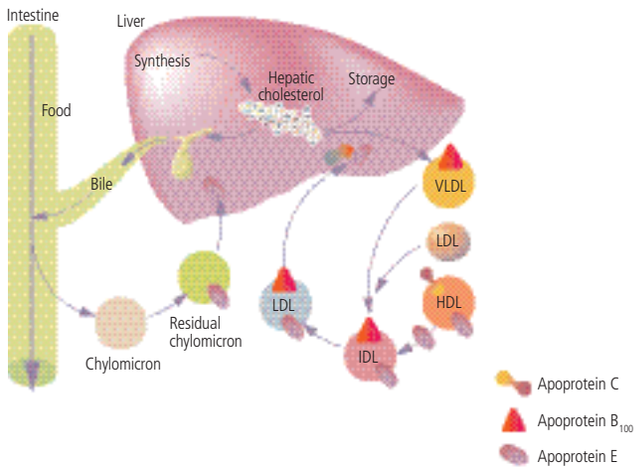
In the peripheral circulation, chylomicrons gain apoprotein C and apoprotein E from HDL **(Figure 2)**, increasing their protein content *(Capurso, 1987)*. Lipoprotein lipase activated by apoprotein C-II of chylomicrons hydrolyzes the triglyceride present in chylomicrons, creating a phospholipid-rich particle. Lipoprotein lipase is associated with endothelial cell surfaces, interacting with membrane associated heparan sulfate *(Nilsson-Ehle et al, 1980)*. Apoprotein A is transferred to HDL, and a chylomicron remnant is formed.

FIGURE 2 - CHYLOMICRON METABOLISM



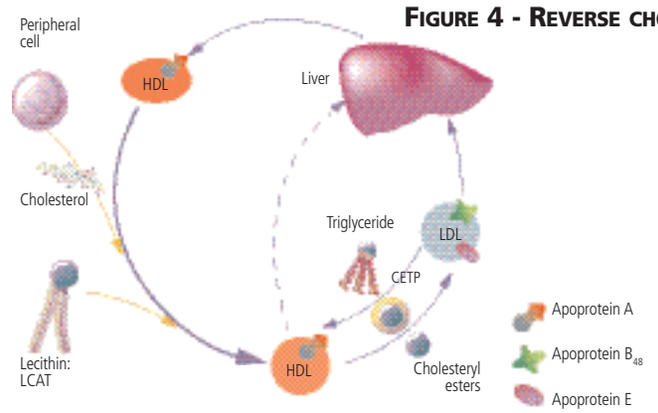
Chylomicron particles containing a high concentration of triglyceride are released from the intestinal mucosal cell into the lymphatics and to the circulation. Lipoprotein lipase hydrolysis of triglycerides within chylomicrons releases fatty acids and decreases the triglyceride content of chylomicrons, creating a chylomicron remnant. In addition, there is an exchange of apoproteins between HDL and chylomicrons. Chylomicrons contribute apoprotein A to HDL in exchange for apoproteins C and E. The chylomicron remnant formed is recognized by an apoprotein E receptor on hepatocytes and is removed from the circulation. A deficiency of lipoprotein lipase activity can result in decreased metabolism of chylomicrons to chylomicron remnants and thus a prolonged appearance of chylomicrons in the circulation.

FIGURE 3 - CHYLOMICRON, VLDL, LDL, AND LIVER CHOLESTEROL METABOLISM



Chylomicron particles containing lipids are released from the intestine into the circulation. Cholesterol-rich chylomicron remnants form and are recognized by the apoprotein E receptor on hepatocytes. Once in the hepatocyte, cholesterol can be stored as cholesteryl ester (via the action of ACAT), can be excreted into bile as cholesterol or bile acids, or secreted into VLDL particles. Synthesis of cholesterol in the hepatocyte (via HMGCoA reductase) contributes to the available cholesterol pool. Lipoprotein lipase hydrolysis of triglyceride within secreted VLDL and exchange of apoproteins create a triglyceride-depleted IDL which forms the triglyceride-poor, cholesterol-enriched LDL particle. The LDL receptor recognizes apoproteins B and E and mediates uptake and removal of LDL from the circulation. A deficiency of lipoprotein lipase activity can result in decreased metabolism of VLDL to LDL and thus a prolonged appearance of VLDL in the circulation.

FIGURE 4 - REVERSE CHOLESTEROL TRANSPORT



Discoidal HDL (nascent HDL) is secreted by the liver and obtains unesterified cholesterol from peripheral cells. LCAT in the circulation esterifies this cholesterol, resulting in a more spherical cholesteryl ester-rich particle. If cholesteryl ester transfer protein (CETP) is present, cholesteryl ester is transferred from HDL to LDL, with exchange of triglyceride from LDL to HDL. LDL carrying cholesteryl ester derived from peripheral cells returns to the liver completing reverse cholesterol transport. In dogs with little CETP, other mechanisms exist to return cholesterol to the liver via HDL directly.

Figure 5 - The appearance of normal and hyperlipidemic serum. *Normal serum should be clear, with no evidence of turbidity (left tube). Fasting serum that is turbid indicates the presence of excess lipid in the serum (right tube).*

Figure 6 - Refrigeration test of canine hyperlipidemic serum. *On the left, a fasting serum sample from a dog shows hyperlipidemia. After the refrigeration test, there is the appearance of a lactescent layer ('cream layer') floating on top of the serum. This layer is due to increased chylomicron particles present in the serum sample. Note that the serum below the top lactescent layer is also turbid, indicating the presence of other lipoproteins in excess (in addition to the excess chylomicron particles).*

Chylomicron remnant formation is necessary for hepatic clearance *(Cooper, 1977)*. Once chylomicron remnants are formed, they are rapidly removed from the circulation by the apoprotein E receptor in liver cells *(Mahley et al, 1989)*.

VLDL are synthesized by hepatocytes **(Figure 3)**, and are a major transporter of triglyceride *(Mills et al, 1971)*. VLDL binds to lipoprotein lipase, and lipoprotein lipase hydrolyzes the triglyceride present in VLDL. This process may create VLDL remnants which can be removed by the liver via receptor or non-receptor-mediated uptake *(Havel, 1984)*. HDL transfers apoprotein E to VLDL, creating an IDL particle. With further loss of triglyceride, phospholipid, and apoprotein, LDL is formed. Removal of LDL from the circulation is via the LDL receptor which binds both apoprotein B and apoprotein E *(Goldstein et al, 1984)*.

Nascent HDL is secreted by the liver **(Figure 4)**, and contains very little free cholesterol and cholesteryl ester. Free cholesterol is transferred from peripheral cells to nascent HDL, and these cholesterol-rich particles serve as substrate for lecithin:cholesterol acyltransferase (LCAT), converting free cholesterol to cholesteryl esters. With the increased concentration of cholesteryl esters, the core of HDL enlarges and becomes more spherical. Hepatic lipase may also play a role in the interconversion of HDL subfractions *(Groot et al, 1981)*. The conversion of free cholesterol to cholesteryl esters and its subsequent transfer to other lipoproteins allows additional free cholesterol to transfer from the surface of cells and other lipoproteins to HDL *(Kostner et al, 1987)*. Thus LCAT plays a key role in the transfer of free cholesterol from peripheral tissues to the liver *(Albers et al, 1986)*.

In humans, cholesteryl ester transfer protein (CETP) is responsible for cholesteryl ester and triglyceride exchange between HDL and LDL or VLDL. Cholesteryl ester derived from free cholesterol in peripheral cells is transferred to LDL, which can then return to the liver via receptor-mediated uptake (reverse cholesterol transport) *(Noel et al, 1984)*. Dogs however have low levels of CETP *(Mahley et al, 1983)*; thus there is little transfer of cholesteryl ester to LDL. Without cholesteryl ester transfer, HDL remains enriched with cholesteryl esters, and is designated HDL1, or HDLc. In the dog, reverse cholesterol transport is completed via HDL uptake by the liver. The dog is a "HDL mammal" since most of the circulating cholesterol is carried by HDL and cannot be transferred to LDL as in humans (an "LDL mammal").

2 - Diagnostic approach to the hyperlipidemic patient

When a patient exhibits serum hyperlipidemia after a 10 to 12 hour fast **(Figure 5)**, investigation into the cause is warranted **(Figure 7)**. The presumption that the dog was fasted should be verified to ensure that all food and treats have been withheld. Once fasting hyperlipidemia has been confirmed, hyperlipidemia secondary to other disorders should be investigated. If no secondary disorder resulting in hyperlipidemia can be identified, a primary lipid abnormality should be considered.

► Serum turbidity

Visual evaluation of the degree of serum turbidity can provide an estimation of serum triglyceride concentration. Normal, clear serum typically has a triglyceride concentration of less than 200 mg/dL, while hazy serum may have a triglyceride concentration of approximately 300 mg/dL. Opacity is seen when triglyceride concentration approaches 600 mg/dL, and if the serum has the appearance of skim milk, the triglyceride concentration is usually around 1000 mg/dL. Serum with the appearance of whole milk can have triglyceride concentration as high as 2500 to 4000 mg/dL.

► Refrigeration test

To ascertain the lipoprotein classes that may be present in excess, a simple refrigeration test can be performed **(Figure 6)**. The serum sample is refrigerated and left undisturbed overnight. Chylomicrons, being the least dense lipoprotein, will 'float' forming a 'cream layer' on the top of the serum sample *(Rogers, 1977)*. If the serum below is clear, only chylomicrons are present in excess, and either a non-fasted sample, or primary hyperchylomicronemia should be suspected. If the serum below the chylomicron layer is turbid, then other lipoproteins are present in excess in addition to the hyperchylomicronemia. If a 'cream layer' does not form after refrigeration, then chylomicrons are not present, and the visible hyperlipidemia is due to an excess of other lipoproteins.

FIGURE 7 - ALGORITHM TO AID IN THE DETERMINATION OF CAUSE OF SERUM HYPERLIPIDEMIA

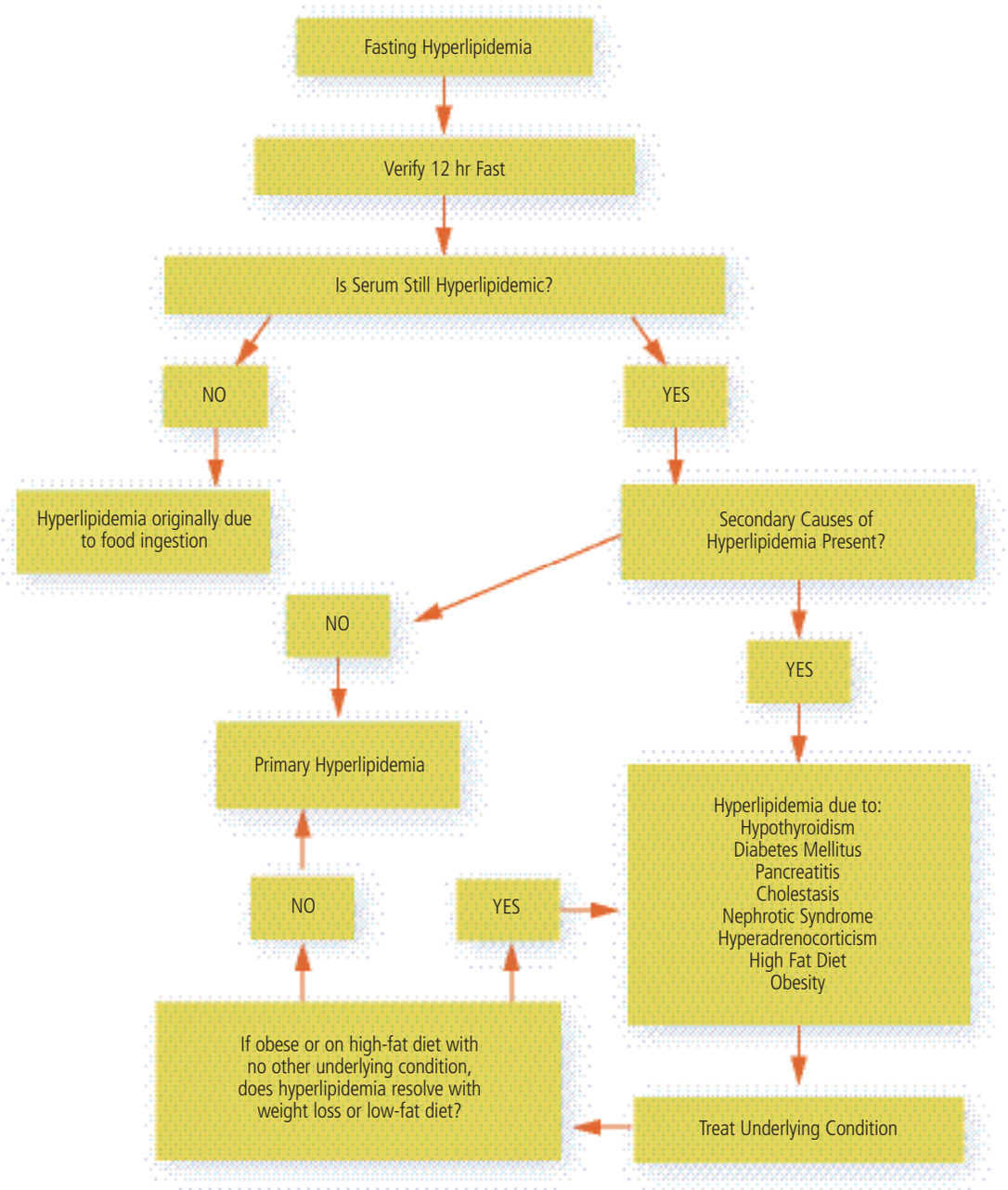
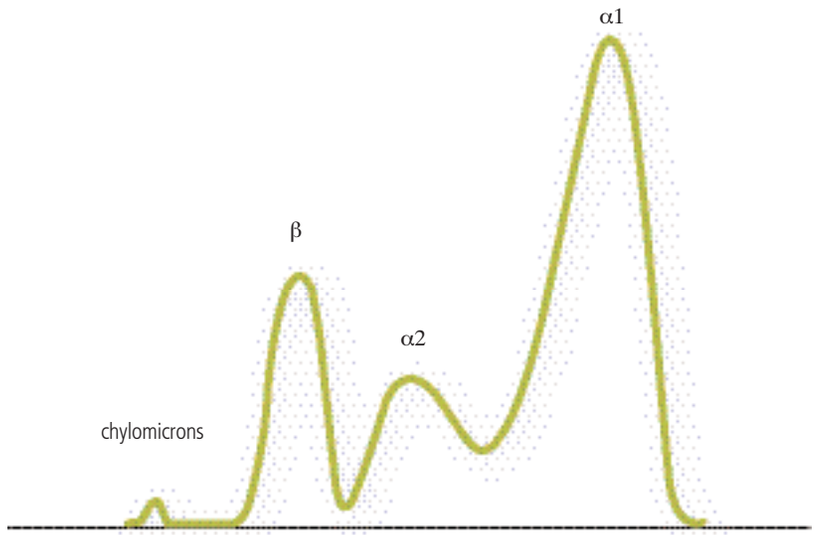


FIGURE 8 - DENSITOMETRIC TRACING OF LIPOPROTEIN ELECTROPHORETOGRAM OF A NORMAL DOG



The peaks from left to right represent the relative concentrations of chylomicrons (which have remained at the origin), β-migrating lipoproteins (VLDL/LDL), α2-migrating lipoproteins (HDL1), and α1-migrating lipoproteins (HDL2). Note the predominance of α1-migrating lipoproteins in the normal dog (a HDL mammal).

► Lipoprotein electrophoresis

Lipoprotein electrophoresis can be used to characterize lipoproteins in serum. With electrophoresis, lipoproteins separate based on their charge and mobility on agarose gel. The agarose gel is then stained and scanned using a densitometer to semi-quantify classes of lipoproteins **(Figure 8)**. Lipoprotein electrophoresis should be performed on fresh, not-previously-frozen serum, and the scan interpreted by someone knowledgeable of canine lipoprotein characteristics (i.e. not a human laboratory), since major differences exist between humans and dogs in electrophoretic pattern. Lipoprotein electrophoresis is not specific since there is some overlap in electrophoretic migration, but is useful especially for monitoring effectiveness of treatment of lipid abnormalities.

► Ultracentrifugation

Ultracentrifugation can be utilized to separate lipoproteins based on density. Ultracentrifugation is time-consuming, requires expensive equipment, and considerable skill to produce reliable results, and is rarely available except in the research setting.

► Serum interferences

Excess of other analytes present in serum may interfere with the measurement of lipids.

- Hyperbilirubinemia may cause a false lowering of cholesterol measurement.
- Hypertriglyceridemia may also result in a falsely lower cholesterol concentration *(Cobbaert et al, 1993)*.
- If cholesterol is present at a concentration of greater than 700 mg/dL, the measured triglyceride concentration may be falsely lowered *(Shephard et al, 1990)*.
- Pentobarbital may also falsely increase triglyceride measurement *(Hata et al, 1978)*, but phenobarbitone has no effect on cholesterol concentration *(Foster et al, 2000)*.

Depending on methodology utilized for analysis, hyperlipidemia may interfere with a number of assays. Hyperlipidemia may result in an approximately 2% increase in sodium, urea, glucose, chloride, and total protein measurement *(Miyada et al, 1982)*. Total calcium measurement may be slightly elevated *(Darras et al, 1992)*, and cortisol may be slightly elevated, but not clinically significant *(Lucena et al, 1998)*. Bilirubin concentration may be falsely increased *(Ng et al, 2001)*, and immunoglobulin A, immunoglobulin M, haptoglobin and ·1-antitrypsin concentration may also be falsely increased *(Bossuyt et al, 1999)*. Concentration of LDH is decreased and AST and ALT concentrations are increased *(Miyada et al, 1982)*. Hypertriglyceridemia may interfere with WBC, RBC, hemoglobin and platelet measurements *(Peng et al, 2001)*, and causes a false increase in haptoglobin concentration *(Weidmeyer et al, 1996)*. Glycated hemoglobin measurement may be falsely decreased *(Garrib et al, 2003)*, and free thyroxine measured by ELISA may be increased *(Lucena et al, 1998)*. However, triglyceride concentration up to 1000 mg/dL will not interfere with phenobarbital measurement *(Baer et al, 1987)*.

3 - Causes of hyperlipidemia

Hyperlipidemia may be the result of lipid abnormalities secondary to a number of other conditions **(Table 3)**. Conditions resulting in secondary hyperlipidemia include hypothyroidism, pancreatitis, cholestasis, hyperadrenocorticism, diabetes mellitus, nephrotic syndrome, obesity, and the feeding of very high fat diets. These conditions should be investigated and eliminated as potential causes of the hyperlipidemia before primary hyperlipidemia is considered.

TABLE 3
CAUSES OF HYPERLIPIDEMIA IN THE DOG

Postprandial
Primary
Idiopathic hyperlipoproteinemia
Idiopathic hypercholesterolemia
Idiopathic hyperchylomicronemia
Secondary
Hypothyroidism
Diabetes Mellitus
Pancreatitis
Cholestasis
Nephrotic Syndrome
Hyperadrenocorticism
High Fat Diets
Obesity

► Hypothyroidism

Hypothyroidism is the most common endocrine disease in dogs and often causes serum hyperlipidemia. In a survey of 2007 dogs with reported recurrent hyperlipidemia, 413 (21%) were diagnosed with hypothyroidism. Dogs with fasting hyperlipidemia were 3.2 times more likely to have hypothyroidism than dogs that did not have hyperlipidemia *(Schenck, 2004)*.

Increases in both serum cholesterol and triglyceride concentrations have been associated with canine hypothyroidism *(Rogers et al, 1975b; Boretti et al, 2003)*. In one study of 50 dogs with hypothyroidism, 88% exhibited hypertriglyceridemia and 78% had hypercholesterolemia *(Dixon et al, 1999)*. Congenital hypothyroidism resulted in hypercholesterolemia in 4 out of 5 Giant Schnauzers *(Greco et al, 1991)*. Cholesterol elevations are usually moderate *(Jaggy et al, 1994)*, and with adequate treatment of hypothyroidism, both cholesterol and triglyceride concentrations return to normal *(Rogers et al, 1975b; Cortese et al, 1997)*. In dogs with hypercholesterolemia and hypertriglyceridemia associated with hypothyroidism, there are increases in VLDL, LDL and HDL1 *(Mahley et al, 1974b; Rogers et al, 1975b)*, and the lipoprotein electrophoresis pattern should return to normal with thyroid replacement therapy. Cholesterol accumulation is seen in VLDL, and these cholesterol-rich particles may stimulate cholesteryl ester synthesis within tissue macrophages *(Mahley et al, 1980)*.

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11 year old Labrador bitch with hypothyroidism (only clinical sign: obesity).

In humans with hypothyroidism, mRNA for LDL receptors is decreased resulting in decreased cholesterol and chylomicron clearance *(Kovanen, 1987)*. Lipoprotein lipase activity may be increased *(Hansson et al, 1983)*, diminished *(Pykalisto et al, 1976)* or unaltered *(Franco et al, 2003)*, and there is decreased excretion of cholesterol into bile *(Gebhard et al, 1992)*. Cholesterol synthesis is also decreased, but the decrease in clearance is greater than the decrease in synthesis, leading to a net increase in cholesterol concentration *(Field et al, 1986)*.

► Pancreatitis

Pancreatitis usually results in hyperlipidemia with an increase in both serum cholesterol and triglyceride concentrations, but the lipoprotein electrophoresis pattern remains normal until 48 to 72 hours post-induction of pancreatitis *(Whitney et al, 1987)*. Free fatty acids and β-migrating lipoproteins (VLDL and LDL) increase *(Rogers et al, 1975b; Whitney et al, 1987; Chikamune et al, 1998)*, and there is a consistent decrease in α1-migrating lipoprotein (HDL2) *(Bass et al, 1976; Whitney et al, 1987)*. Changes in α2-migrating lipoproteins (HDL1) are inconsistent, and may be increased or decreased *(Whitney et al, 1987)*. In addition, there may be other differences in the lipoprotein electrophoresis pattern depending on whether the pancreatitis is naturally occurring or experimentally induced.

Within the lipoprotein structure, there are changes in lipid and protein content in pancreatitis. LDL exhibits an increase in triglyceride, total cholesterol, and phospholipid, and an increase of apoprotein B100 *(Chikamune et al, 1998)*. VLDL shows an increase in total cholesterol and phospholipid. HDL particles have decreased total cholesterol and phospholipid, with an increase in apoprotein A-IV and a decrease in apoprotein A-I *(Chikamune et al, 1998)*.

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Naturally occurring atherosclerosis has been noted in dogs with hypothyroidism. In a family of Beagles with hypothyroidism, there was evidence of moderate to severe atherosclerosis which occurred mainly in the coronary and renal arteries (Manning, 1979). Arteries were stenotic but patent, with no evidence of prior occlusion. Even with therapy for hypothyroidism, no regression of atherosclerotic plaques was seen despite a decrease in serum cholesterol concentration (DePalma et al, 1977).

In humans, there is evidence that pancreatitis is associated with decreased lipoprotein lipase activity *(Hazzard et al, 1984)*. This decreased activity of lipoprotein lipase may result in increased triglyceride concentrations with slower clearance of chylomicrons. Two dogs with pancreatitis also exhibited a moderate decrease in lipoprotein lipase activity, which returned to normal with treatment and resolution of the pancreatitis *(Schenck, unpublished observations)*.

► Diabetes mellitus

In diabetes mellitus, elevations of both serum triglyceride and cholesterol concentration are typically observed *(Rogers et al, 1975b; Renauld et al, 1998)* **(Table 4)**.

TABLE 4 - MODIFICATIONS OF LIPOPROTEIN ELECTROPHORESIS IN DIABETES MELLITUS

Increased lipoproteins
- β-migrating lipoproteins, mostly due to an increase in VLDL *(Whitney et al, 1993)*
- α2-migrating lipoprotein
- Apoprotein E *(Gleeson et al, 1990)*
- Chylomicrons *(Whitney et al, 1993)*

Decreased lipoproteins
- α_1-migrating lipoproteins (HDL_2) *(Wilson et al, 1986)*

Cholesterol concentration increases in VLDL and IDL, and decreases in HDL *(Wilson et al, 1986)*. Insulin therapy will usually decrease serum triglyceride concentration, but serum cholesterol concentration may remain elevated due to increased cholesterol synthesis *(Gleeson et al, 1990)* **(Figure 8)**.

In humans with diabetes mellitus, lipoprotein lipase activity is decreased, with an increase in free fatty acids *(Steiner et al, 1975)* and hepatic lipase activity *(Muller et al, 1985)*. Urinary mevalonate concentration is elevated approximately 6-fold, indicating an increase in whole-body cholesterol synthesis, and HMGCoA reductase activity is increased *(Kwong et al, 1991; Feingold et al, 1994)*. Intestinal cholesterol absorption may also be increased in diabetes mellitus *(Kwong et al, 1991) (Gylling et al, 1996)*. There is impaired removal of VLDL from the circulation *(Wilson et al, 1986)*, and a decrease in the number and affinity of LDL receptors *(Takeuchi, 1991)*. Prolonged retention of lipoprotein remnants may contribute to an increased delivery of cholesterol to extrahepatic tissues, and the increased concentration of HDL1 reflects a disturbance in cholesterol transport from peripheral cells back to the liver *(Wilson et al, 1986)*.

Naturally occurring atherosclerosis has been observed at necropsy in a dog with diabetes mellitus *(Sottiaux, 1999)*. Atherosclerotic plaques were noted in the terminal aorta, coronary arteries, renal arteries, and arteries of the brain, but there was no evidence of thrombosis or complete occlusion of any vessel.

► Nephrotic syndrome

Lipoprotein abnormalities have been poorly characterized in dogs with nephrotic syndrome. Dogs with nephrotic syndrome show a mild increase in serum cholesterol concentration early in the course of disease, with a mild elevation of serum triglyceride concentration occurring later. Dogs with secondary hyperparathyroidism due to chronic renal failure exhibit a decrease in lipoprotein lipase activity, resulting in impaired removal of lipid from the circulation *(Akmal et al, 1990)*.

Lipoprotein abnormalities in nephrotic syndrome and chronic renal disease have been well characterized in humans, and the progression of renal dysfunction has been shown to correlate with serum total cholesterol *(Washio et al, 1996)*. Lipoprotein lipase activity is decreased which may account for the hypertriglyceridemia due to a decrease in lipoprotein clearance *(Olbricht, 1991)*. There is decreased clearance of LDL *(Shapiro, 1991; Vaziri et al, 1996)* due to decreased LDL receptor expression *(Portman et al, 1992)*. LDL may also be increased due to an increase in synthesis *(de Sain-van der Velden et al, 1998)*. HMGCoA reductase activity is increased in the liver *(Szolkiewicz et al, 2002; Chmielewski et al, 2003)*, and the increased cholesterol does not up-regulate LDL receptors *(Liang et al, 1997)*. Reverse cholesterol transport is impaired *(Kes et al, 2002)*, and ACAT activity within the liver is increased with a decrease in LCAT activity *(Liang et al, 2002)*.

VLDL increases due to decreased catabolism *(de Sain-van der Velden et al, 1998)*, and proteinuria may also stimulate VLDL synthesis by the liver, induced by hypoalbuminemia *(D'Amico, 1991)*. Impaired clearance of VLDL may be due to deficiencies in apoprotein C-II, apoprotein C-III, and

apoprotein E, creating smaller VLDL particles that are not cleared efficiently by receptors *(Deighan et al, 2000)*. This altered structure of VLDL results in altered binding to endothelial bound lipoprotein lipase *(Shearer et al, 2001)*, and proteinuria may also be associated with the urinary loss of heparan sulfate, an important cofactor for lipoprotein lipase *(Kaysen et al, 1986)*. Synthesis of apoprotein A-I by the liver increases in response to proteinuria *(Marsh, 1996)*, and protein catabolism in peripheral tissues is increased.

► Hyperadrenocorticism

In hyperadrenocorticism, mild elevations of both serum cholesterol and triglyceride may be seen in dogs and humans *(Friedman et al, 1996)*. Lipoprotein lipase activity is decreased with an increase in hepatic lipase activity *(Berg et al, 1990)*. In addition, hypercortisolism stimulates production of VLDL by the liver *(Taskinen et al, 1983)*. Excess glucocorticoids stimulate lipolysis, and this excess fat breakdown exceeds the liver's capacity for clearance. The occurrence of steroid hepatopathy in hyperadrenocorticism may lead to biliary stasis resulting in further lipid abnormalities.

In hyperadrenocorticism, mild elevations of both serum cholesterol and triglyceride may be seen *(Ling et al, 1979; Reusch et al, 1991)*.
In dogs, concentration of β-migrating lipoproteins (VLDL and LDL) are typically increased *(Bilzer, 1991)*.

► Cholestasis

In cholestasis, there is typically moderate hypercholesterolemia, and there may be a mild hypertriglyceridemia *(Chuang et al, 1995)*. Concentration of LDL increases, and HDL1 concentration decreases *(Danielsson et al, 1977)*. In LDL, phospholipid content increases and triglyceride concentration decreases, but there is no change in composition of HDL. Both plasma cholesteryl ester and LCAT activity increases *(Blomhoff et al, 1978)*.

► Obesity

Some obese dogs show an increase in serum triglyceride concentration *(Bailhache et al, 2003)*, and a mild increase in serum cholesterol *(Chikamune et al, 1995)*. Free fatty acids are increased, triglyceride concentration is increased in both VLDL and HDL, and HDL cholesterol may be decreased *(Bailhache et al, 2003)*. Phospholipid concentration is increased in both VLDL and LDL, and is decreased in HDL2 *(Chikamune et al, 1995)*. There is a moderate decrease in lipoprotein lipase activity in some obese dogs, and activity increases with weight loss (Schenck, unpublished observation). Lipid abnormalities observed in obese dogs may however be secondary to insulin resistance *(Bailhache et al, 2003)*.

English Bulldog.
Obesity may result in hyperlipidemia in a small percentage of dogs.

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► High fat diets

The feeding of high fat diets may result in hyperlipidemia and moderate elevation in serum cholesterol concentration. As serum cholesterol concentration increases, the majority of cholesterol is carried by HDLc (HDL1); thus an increase in α2-migrating lipoprotein is observed *(Mahley et al, 1974b)*. A substantial portion of the HDL observed in response to cholesterol feeding is formed in the periphery *(Sloop et al, 1983)*. Once this HDL reaches the plasma, it is converted to HDLc via the action of LCAT, which exhibits increased activity *(Bauer, 2003)*. LDL and IDL concentrations increase, and the concentration of HDL2 decreases. Hypercholesterolemia results in the appearance of α-migrating VLDL, and cholesterol-enrichment also occurs in LDL, IDL and HDLc *(Mahley et al, 1974b)*. Diets very high in fats (above 50%) may additionally cause an elevation in triglyceride *(Reynolds et al, 1994)* with a marked increase in circulating LDL and other abnormalities.

4 - Primary hyperlipidemia

Once it is verified that hyperlipidemia occurs after a 10- to 12-hour fast, and all possible causes of secondary hyperlipidemia have been ruled out, a presumptive diagnosis of primary hyperlipidemia is made. Primary hyperlipidemias are usually genetically determined. In the dog, several different types of primary hyperlipidemia have been observed, including idiopathic hyperchylomicronemia, idiopathic hypercholesterolemia, and idiopathic hyperlipoproteinemia; however etiologies of these conditions have not been well established. It is likely that with further research, many different primary syndromes with subtle differences in etiology will be identified in dogs as in humans.

► Idiopathic hyperchylomicronemia

A pure hyperchylomicronemia has been reported in a 28 day old mixed-breed puppy *(Baum et al, 1969)*. This puppy was the smallest in a litter of three, was irritable and weak, with a palpably enlarged liver. Blood had the appearance of "cream-of-tomato" soup, and after cold centrifugation, a lactescent upper layer was observed with a triglyceride concentration of 830 mg/dL, and cholesterol concentration of 312 mg/dL. The administration of heparin sulfate did not clear the plasma from this puppy, and a presumptive diagnosis of lipoprotein lipase deficiency was made. There was no evidence of diabetes mellitus, but other causes of secondary hyperlipemia were not ruled out. The puppy died of pneumonia at 33 days of age. At necropsy, the liver was enlarged, yellow in color, with marked accumulation of lipid within hepatocytes.

► Idiopathic hypercholesterolemia

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In the Briard, idiopathic hypercholesterolemia may be related to the development of retinal pigment epithelial dystrophy.

In 15 clinically healthy Briards with unexplained fasting hypercholesterolemia, serum was not hyperlipemic, and serum triglyceride concentrations were normal in all dogs *(Watson et al, 1993)*. Causes of secondary hyperlipidemia were ruled out. Lipoprotein electrophoresis revealed a marked increase in α2-migrating lipoproteins (HDL1) with no other abnormalities. This abnormality is unlike those reported in dogs with idiopathic hyperlipoproteinemia where serum cholesterol and triglyceride concentrations are both increased.

Idiopathic hypercholesterolemia has also been noted in a miniature Bull Terrier (Schenck, unpublished observation). This dog was clinically healthy with unexplained fasting hypercholesterolemia and normal serum triglyceride concentration. Serum was not hyperlipemic, and the only abnormality seen on lipoprotein electrophoresis was an accumulation in α2-migrating lipoprotein (HDL1).

► Idiopathic or primary hyperlipoproteinemia

Primary hyperlipoproteinemia with similar characteristics has been observed in a number of dog breeds including the miniature Schnauzer, Shetland sheepdog, Beagle, miniature Poodle, Cocker Spaniel, English Cocker Spaniel, and mixed-breed dog. Miniature Schnauzers appear to have a higher incidence of primary hyperlipoproteinemia, however any breed of dog may be affected. Clinical signs associated with primary hyperlipoproteinemia may include abdominal pain (presumptively due to pancreatitis) and seizures *(Rogers et al, 1975a)*, but many dogs exhibit no obvious clinical signs.

In a study of 5 miniature Schnauzers diagnosed with idiopathic hyperlipoproteinemia, all dogs had moderately increased serum cholesterol concentrations, and moderate to marked increase in serum triglyceride concentration *(Rogers et al, 1975a)*. Increases in β-migrating and α2-migrating lipoproteins on lipoprotein electrophoresis were the most consistent findings. Two of 5 dogs had an increase in chylomicrons. Injection of heparin caused shifting of lipoproteins in two dogs, but only cleared the serum of one dog.

In another study of 6 healthy miniature Schnauzers diagnosed with idiopathic hyperlipoproteinemia, 4 of 6 had a history of recurrent episodes of hyperlipidemia *(Whitney et al, 1993)*. On lipoprotein electrophoresis all 6 dogs had increased β-migrating lipoproteins, predominantly due to an increase in VLDL as determined by density gradient ultracentrifugation. Four of 6 had an increase in chylomicrons at the origin.

Two related Beagles with idiopathic hyperlipoproteinemia also exhibited an increase in β-migrating and α2-migrating lipoproteins on lipoprotein electrophoresis *(Wada et al, 1977)*. Both dogs were clinically normal, showed increased serum cholesterol and triglyceride concentrations, and had a common sire.

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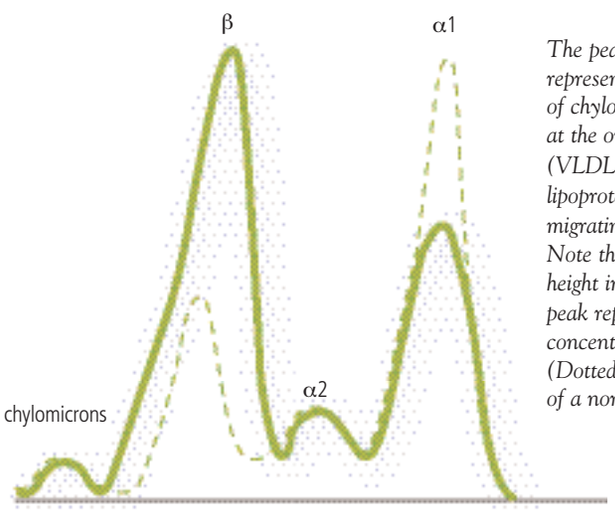
Miniature Schnauzers appear to present a high incidence of primary hyperlipoproteinemia, although no breed is safe.

Potentially two different abnormalities may exist in a study of 62 Shetland sheepdogs with hypercholesterolemia *(Sato et al, 2000)*. Both mean plasma cholesterol and triglyceride concentrations were increased in these dogs, though no correlation between cholesterol and triglyceride was observed. In Shetland sheepdogs with plasma cholesterol concentrations greater than 250 mg/dL, an increase in α2-migrating lipoproteins was noted, similar to that seen in Briards. In dogs with plasma cholesterol concentrations greater than 500 mg/dL, an increase in β-migrating lipoprotein, mostly due to LDL was also observed. The plasma triglyceride concentration in the group of dogs with plasma cholesterol concentration greater than 500 mg/dL was not reported.

In 10 clinically healthy dogs of various breeds diagnosed with primary hyperlipoproteinemia, mean serum cholesterol concentration was 532 ± 256 mg/dL, and mean serum triglyceride concentration was 1955 ± 2193 mg/dL *(Schenck, 2002)*. A group of healthy, non-hyperlipidemic control dogs had mean serum cholesterol and triglyceride concentrations of 153 ± 17 mg/dL and 56 ± 13 mg/dL respectively. On lipoprotein electrophoresis the most consistent finding was an increase in β-migrating lipoproteins, and percentages of chylomicrons and α2-migrating lipoproteins were similar in both groups **(Figure 9)**. Lipoprotein lipase activity was significantly decreased in dogs with primary hyperlipoproteinemia, with a mean of 35±8 nmol free fatty acids released/min/mL compared to 110 ± 10 nmol free fatty acid released/min/mL in the control dogs. Hepatic lipase activity was significantly increased in dogs with primary hyperlipoproteinemia, with a mean of

FIGURE 9 - DENSITOMETRIC TRACING OF LIPOPROTEIN ELECTROPHORETOGRAM OF A DOG WITH PRIMARY HYPERLIPOPROTEINEMIA



The peaks from left to right represent the relative concentrations of chylomicrons (which have remained at the origin), β-migrating lipoproteins (VLDL/LDL), α2-migrating lipoproteins (HDL1), and α1-migrating lipoproteins (HDL2). Note the broadening and increased height in the β-migrating lipoprotein peak representing an increased concentration of VLDL and/or LDL. (Dotted line: electrophoretogram of a normal dog.)

37±10 nmol free fatty acid released/min/mL compared to 28 ± 5 nmol free fatty acid released/min/mL in the control dogs. This study presents the first potential etiology for 'idiopathic' hyperlipoproteinemia. Decreased activity of lipoprotein lipase leads to decreased clearance of VLDL and chylomicrons, and hepatic lipase may be increased in a compensatory role. A decrease in lipoprotein lipase activity in 8 miniature Schnauzers with primary hyperlipoproteinemia was also observed in a subsequent study *(Jaeger, 2003)*.

5 - Effects of persistent hyperlipidemia

Long-term effects of hyperlipidemia in dogs are unknown. Dogs are resistant to the development of atherosclerosis as compared to humans, due to differences in lipoprotein metabolism between the species *(Mahley et al, 1977)*. For atherosclerosis to develop in the dog, serum cholesterol concentrations greater than 750 mg/dL must be maintained for more than 6 months *(Mahley et al, 1974b)*.

Arteriosclerosis is often confused with atherosclerosis. Arteriosclerosis is a chronic hardening of the arteries, with loss of elasticity, and luminal narrowing. Lipid and cholesterol accumulation in arterial tunica intima and tunica media is not a feature of arteriosclerosis as opposed to atherosclerosis. Arteriosclerosis may be more common in the dog, but has not been associated with chronic hyperlipidemia.

► Hyperlipidemia and atherosclerosis in dogs

Atherosclerosis is a specific type of arteriosclerosis with deposition of lipid and cholesterol in arterial tunica intima and tunica media *(Liu et al, 1986)*. The dog has been used as an experimental model for atherosclerosis lesions for more than 40 years, with experimental induction of atherosclerosis resulting from hypothyroid dogs fed high levels of cholesterol, fat, taurocholic acid and/or coconut oil *(Duncan et al, 1960; Mahley et al, 1974b)*. However, naturally occurring atherosclerosis in the dog has also been reported.

> Atherosclerosis and Hypothyroidism

An association of atherosclerosis and hypothyroidism in dogs was noted over 30 years ago *(Manning, 1979)*. In a family of Beagles, moderate to severe atherosclerosis occurred in the coronary and renal arteries with no evidence of occlusion. Hyperlipidemia was present, even when feeding a diet low in fat and cholesterol. Treatment of hypothyroidism with thyroxine resulted in a decrease in serum cholesterol concentrations. However, dogs that have developed atherosclerosis do not have any regression of atherosclerotic lesions even with lowering cholesterol concentrations *(DePalma et al, 1977)*.

Cerebrovascular atherosclerosis associated with hypothyroidism was observed in a 6 year old Doberman pinscher *(Patterson et al, 1985)*. This dog presented with seizures, ataxia, circling and head tilt. At necropsy, severe generalized atherosclerosis and cerebrocortical necrosis were noted. Necrosis was due to tissue hypoxia secondary to cerebrovascular atherosclerosis.

Twenty one cases of atherosclerosis in dogs over a 14 year period were associated with hypothyroidism *(Liu et al, 1986)*. Clinical signs included lethargy, anorexia, weakness, dyspnea, collapse and vomiting. Necropsy revealed myocardial fibrosis and infarction in the myocardium. Affected arteries included coronary, myocardial, renal, carotid, thyroidal, intestinal, pancreatic, splenic, gastric, prostatic, cerebral, and mesenteric. Arteries were thick and nodular with narrow lumens, and walls contained foamy cells or vacuoles, and mineralized material.

> Atherosclerosis and diabetes mellitus

Atherosclerosis in the canine has also been associated with diabetes mellitus *(Sottiaux, 1999)*. A 7 year old Pomeranian initially presented with poorly controlled insulin-dependent diabetes mellitus and anterior uveitis with lipid deposition in the anterior chamber of the eye. Both hypertri-

Aging German Shepherd
Lipid accumulation may be age-related, and deposition of modified LDL may be a critical step in the development of atherosclerosis in the canine (Kagawa et al, 1998).

glyceridemia and hypercholesterolemia were present, with increases in chylomicrons and β-migrating lipoproteins. One year later the dog died from ketoacidosis. Atherosclerosis was observed in the abdominal aorta, coronary, renal, arcuate, and carotid arteries. Thyroid histology appeared normal with no evidence of atrophy.

Thirty dogs with atherosclerosis confirmed at necropsy were retrospectively evaluated for the presence of hypothyroidism, diabetes mellitus, or hyperadrenocorticism *(Hess et al, 2003)*. Dogs with atherosclerosis were 53 times more likely to have diabetes mellitus, and 51 times more likely to have hypothyroidism compared to dogs without atherosclerosis. An increased incidence of hyperadrenocorticism was not noted in dogs with atherosclerosis.

► Pathogenesis of atherosclerosis in dogs

Recently, apoprotein B_{100} has been localized to the accumulation of lipids seen in the splenic arteries of aged dogs *(Sako et al, 2001)*. Chlamydial antigens have also been noted in canine atherosclerotic lesions *(Sako et al, 2002)*, and the Chlamydial organism may play a role in the pathogenesis of canine atherosclerosis. The ratio of apoprotein B_{100} to apoprotein A-I is increased in dogs with systemic atherosclerosis and hyperlipidemia, and this ratio could be important in the diagnosis of atherosclerosis in dogs *(Miyoshi et al, 2000)*.

► Hyperlipidemia and pancreatitis in dogs

There is also evidence that persistent hyperlipidemia may lead to pancreatitis *(Dominguez-Munoz et al, 1991)*, and pancreatitis often occurs in humans with familial hyperchylomicronemia *(Heaney et al, 1999)*. A burst of free radical activity in pancreatic acinar cells disrupts glutathione homeostasis and may be the initiating event in pancreatitis *(Guyan et al, 1990)*. Increased free radical activity may relate to pancreatic ischemia resulting from sluggish pancreatic microcirculation due to

high concentrations of chylomicrons *(Sanfey et al, 1984)*. Free radical damage causes leakage of lipase into the pancreatic microcirculation. Lipase causes hydrolysis of triglyceride present in excess chylomicrons or VLDL resulting in release of free fatty acids which are intensely inflammatory. Free fatty acids can also cause activation of Hageman factor, or may bind calcium leading to microthrombi and capillary damage. Phospholipid present in chylomicrons and VLDL are also susceptible to free radical attack leading to lipid peroxidation, intensifying inflammation. This results in an increase in release of pancreatic lipase and further lipolysis, leading to pancreatitis *(Havel, 1969)*.

► Hyperlipidemia and diabetes mellitus in dogs

Persistent hyperlipidemia may also cause diabetes mellitus *(Sane et al, 1993)*. Increased triglyceride and free fatty acids may lead to insulin resistance due to inhibition of glucose oxidation and glycogen synthesis *(Boden, 1997)*. Free fatty acids may stimulate glyconeogenesis which contributes to inappropriate glucose production *(Rebrin et al, 1995)*. Increased free fatty acids early on act to stimulate insulin production even with low glucose concentrations. In the long term, increased free fatty acids modulate β-cell gene expression and inhibit insulin secretion *(Prentki et al, 1996)*. By multiple mechanisms, increased serum triglyceride and free fatty acids can lead to hyperglycemia and diabetes mellitus. If hyperlipidemia is corrected, diabetes mellitus caused by hyperlipidemia can be reversed *(Mingrone et al, 1999)*.

The effects of persistent hyperlipidemia in the canine on other organ systems have not been studied. In rats with nephrotic syndrome, persistent hyperlipidemia contributes to progressive renal injury *(Hirano et al, 1992)*, and progression of renal dysfunction correlates to serum cholesterol concentration *(Washio et al, 1996)*.

6 - Treatment of hyperlipidemia

Because of the potential risks associated with persistent hyperlipidemia, hyperlipidemia should be treated aggressively. The underlying disorder in secondary hyperlipidemias should be treated, but there is no specific therapeutic regimen for dogs with idiopathic hyperlipoproteinemias. Unfortunately since little is known regarding the mechanisms of primary hyperlipidemia, and multiple syndromes most likely exist, no single treatment regimen has been effective in all cases.

Caution must be exercised when considering dietary fat content on only a percentage basis. For example, a diet containing 10% fat with an ME of 4000 kcal/kg provides only 25 g fat/1000 kcal, whereas a diet containing 8% fat with an ME of 2700 kcal/kg provides 30 g fat/1000 kcal.

► Nutritional treatment of hyperlipidemia

> A fat-restricted diet

Initial treatment of primary hyperlipidemia involves a switch to a low-fat diet (<25 g/1000 kcal) with moderate protein content (generally greater than 18%, or 60 g protein/1000 kcal). Diets low in protein may cause an increase in serum cholesterol concentration *(Polzin et al, 1983; Hansen et al, 1992)* and are therefore not recommended unless the presence of other conditions warrant their use. Numerous nutritionally complete, low-fat canine diets are commercially available, but one must be careful to choose a diet that is low in fat based on a metabolizable energy (ME), and not strictly on the percent fat present in the diet. Most diets with a fat content less than 8% will provide less than 25g fat/1000 kcal. However, some diets appear low in fat on a percentage basis (<8%), but actually provide substantially more than 25 g fat/1000 kcal when the amount of fiber in the diet and metabolizable energy are taken into account, and thus are not low-fat diets.

After feeding a low-fat diet for 6 to 8 weeks, the presence of hyperlipidemia should be re-evaluated. Low-fat diets alone may not cause resolution of hyperlipidemia, especially when there is a high concentration of endogenous triglyceride (VLDL-TG) *(Bauer, 1995)*.

> Omega-3 fatty acid supplementation

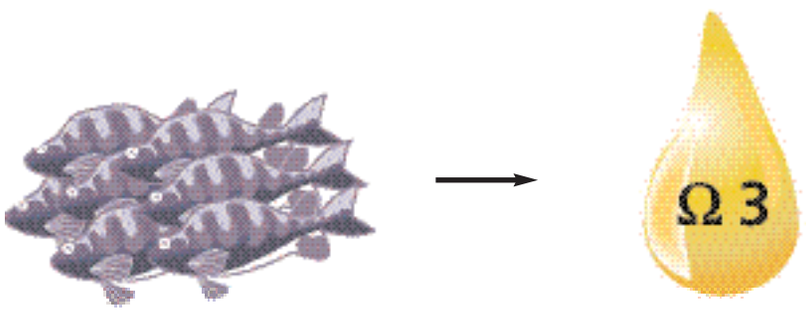
If hyperlipidemia is still present after 6 to 8 weeks, then fish oil at a dose of 220 mg/ kg of body weight (BW) once daily should be added to the treatment regimen. Fish oil capsules may be obtained over-the-counter, but labels should be read carefully to ensure that the dog receives 220 mg/kg BW of a combination of alpha-linolenic acid, and the long chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Some products claim to be 'omega-3 supplements,' but contain a high percentage of other non-omega-3 fatty acids.

In the author's experience the only side effect noted with this level of fish oil supplementation is that the dog may have a noticeable 'fishy' odor which may be objectionable to some owners. If hyperlipidemia resolves with this level of fish oil supplementation and the owner complains about the fishy odor, a half-dose (110 mg fish oil/kg BW/day) can be evaluated. A few dogs can be managed at this dose; however, most will require a minimum of 170 mg fish oil/kg BW/day to maintain the absence of hyperlipidemia. In one particular case in the author's experience, a 6 year-old Shetland Sheepdog with idiopathic hyperlipoproteinemia and multiple lipomas showed complete resolution of serum hyperlipidemia, hypertriglyceridemia, and hypercholesterolemia after 4 weeks on a low-fat diet and 220 mg fish oil/kg BW/day. In addition, most of the lipomas resolved. Due to the dog's fishy odor, the dosage of fish oil was dropped to 110 mg/kg BW/day, with a return of hyperlipidemia. A dosage of 170 mg fish oil/kg BW/day in combination with a low-fat diet has maintained the absence of hyperlipidemia for over one year.

The use of fish oil and EPA & DHA in the treatment of hyperlipidemia and atherosclerosis has been extensively studied in a number of species.

- EPA supplementation resulted in a 31% decrease in serum triglyceride in human patients *(Okumura et al, 2002)*.
- Rats fed diets containing EPA and DHA exhibited a decrease in serum cholesterol and triglyceride and the development of atherosclerosis was prevented *(Adan et al, 1999)*.
- Fish oil supplementation decreased serum triglyceride, total cholesterol, VLDL-triglyceride and VLDL-cholesterol in chicks *(Castillo et al, 2000)*.
- In dogs with renal insufficiency, fish oil supplementation resulted in a decrease in serum cholesterol concentration *(Brown et al, 2000)*.
- Watanabe heritable hyperlipidemia (WHHL) rabbits exhibited a decrease in serum triglyceride and cholesterol with a decrease in VLDL-triglyceride *(Mortensen et al, 1998)*.

Fish oil and omega-3 fatty acids



Synthesis of triglyceride and VLDL in the liver is decreased by omega-3 fatty acids (Harris et al, 1990; Connor et al, 1993), and the effectiveness of fish oils in dogs with hyperlipidemia suggests that the hypertriglyceridemia may be partly due to overproduction of VLDL (Bauer, 1995).

Fish oils may exert a beneficial effect on hyperlipidemia by stimulating lipoprotein lipase activity *(Levy et al, 1993)*, decreasing the intestinal absorption of glucose and lipid *(Thomson et al, 1993)*, increasing cholesterol secretion into bile *(Smit et al, 1991)* and by decreasing cholesterol absorption *(Thompson et al, 1989)*. Fish oils also decrease serum concentration of free fatty acids *(Singer et al, 1990)* which may be important in the prevention of pancreatitis and diabetes mellitus. Development of atherosclerosis may be prevented by fish oil due to an inhibition of mitogen-induced smooth muscle cell proliferation *(Pakala et al, 2000)*.

Unfortunately there are no long-term studies to verify the safety and efficacy of any lipid-lowering agent in dogs, and any therapy should be used with caution. One concern with fish oil therapy is that fish oil increases the concentration of lipoperoxides in LDL *(Puiggros et al, 2002)*. The addition of vitamin E to the fish oil therapy regimen may enhance beneficial effects by increasing glutathione reductase activity and decreasing peroxide levels *(Hsu et al, 2001)*.

In severe cases of lipoprotein lipase deficiency in human patients, fish oil and other dietary therapies result in some improvement, but serum lipids may remain elevated *(Richter et al, 1992)*.

> Interest of medium chain triglycerides

In human patients, in addition to fish oil therapy, medium chain triglycerides (MCT) in combination with low-fat diets cause a decrease in hypertriglyceridemia *(Rouis et al, 1997; Chou et al, 2002; Nagasaka et al, 2003)*. MCT administration results in increased lipoprotein lipase activity *(Shirai et al, 1992)* and may prevent hyperlipidemia associated pancreatitis *(Mizushima et al, 1998)*. MCT administration does not lower, and may even elevate serum cholesterol concentration *(Asakura et al, 2000)*. Therefore, MCT therapy should only be used in cases where there is elevation of serum triglyceride concentration without a high elevation in serum cholesterol. Unfortunately, MCT oil is not very palatable, limiting its use.

> Fermentable fiber intake

The presence of a blend of fructooligosaccharides and beet pulp in the diet may also be desirable, since this blend can decrease serum triglyceride and cholesterol concentrations in the dog *(Diez et al, 1997)*.

> Antioxidant treatment

Since the pathogenesis for idiopathic hyperlipoproteinemia has been at least partly determined *(Schenck, 2002)*, treatments that have been effective in human patients with lipoprotein lipase deficiency may be worthy of investigation.

Several humans with familial lipoprotein lipase deficiency treated with a combination of oral antioxidant therapy (OAT) showed prevention of recurrent pancreatitis even though there was no effect on circulating lipids *(Heaney et al, 1999)*. Antioxidant therapy consisted of a combination of α-tocopherol, β-carotene, vitamin C, selenium, and methionine.

► Medical treatment of hyperlipidemia

Other treatment regimens have been attempted with variable results.

Gemfibrozil has been used to stimulate lipoprotein lipase activity and decrease VLDL secretion *(Santamarina-Fojo et al, 1994)*.

Niacin therapy has also been used in a few dogs; however, adverse effects have been noted in both dogs *(Bauer, 1995)*, and humans *(Kashyap et al, 2002)*.

Dextrothyroxine administration significantly decreased serum lipids in dogs with induced hyperlipidemia and atherosclerosis *(Nandan et al, 1975)*, though these effects may have been due to contamination of dextrothyroxine with L-thyroxine *(Young et al, 1984)*. Dextrothyroxine administration in humans results in an approximately 18% decrease in serum total cholesterol *(Brun et al, 1980)*, but is not vastly utilized as a treatment for hyperlipidemia due to a concurrent lowering of HDL cholesterol *(Bantle et al, 1984)*. A major mechanism of cholesterol-lowering by thyroxine in humans is an increase in cholesteryl ester transfer protein *(Berti et al, 2001)*; however, since dogs have little cholesteryl ester transfer protein, thyroxine may not be as effective. Thyroxine does have other lipid-lowering mechanisms, including an increase in hepatic lipase activity and increased conversion of IDL to LDL *(Asami et al, 1999)*, and is effective in lowering lipid concentrations in hypothyroid dogs *(Rogers et al, 1975b; Cortese et al, 1997)*. Since thyroxine is fairly well tolerated in the dog, an investigation of lipid-lowering properties in euthyroid dogs with primary hyperlipoproteinemia may be warranted.

Gene therapy has been effective in mice *(Zsigmond et al, 1997)* and may become a clinical reality in the future for patients with severe dyslipidemias *(Rader et al, 1999)*.

TABLE 5 - LIPOPROTEIN CHANGES IN CANINE HYPERLIPIDEMIAS

Condition	Cholesterol	Triglyceride	Chylomicron	LDL/VLDL	HDL_2	HDL_1	LPL_a
Idiopathic hyperlipoproteinemia	↑	↑↑	±	↑		±	↓
Idiopathic hypercholesterolemia	↑	N	N	N	N	↑	N
Idiopathic hyperchylomicronemia	↑	↑↑	↑↑	–	–		↓[b]
Hypothyroidism	↑	↑	–	↑↑	–	↑	–
Hyperadrenocorticism	↑	↑	–	↑	–	–	–
Diabetes mellitus	↑	↑	–	↑↑	–	↑	↓[c]
Nephrotic syndrome	↑ Early	↑ Later	±	↑↑	–	–	↓
Cholestasis	↑	–	–	↑		↓	
Pancreatitis	↑	↑	–	↑	↓	±	↓
High fat diets	↑	–	–	↑	–	↑	–
Ultra high fat diets	↑	↑	–	↑	–	↑	–
Obesity	±	–	±	↑	–	–	↓

[a] *Lipoprotein lipase activity*
[b] *Presumptive decrease based on literature report and human findings*
[c] *Presumptive decrease based on human findings*

N: normal values
–: no specific data

Conclusion

Many conditions may cause hyperlipidemia in the dog. Postprandial hyperlipidemia should always be verified, and secondary causes of hyperlipidemia must be ruled out before a diagnosis of primary hyperlipidemia can be made. Hyperlipidemias are characterized by a number of different changes in lipoprotein concentrations, depending on cause **(Table 5)**. Treatment of the underlying cause of hyperlipidemia is usually effective at resolving the secondary hyperlipidemia. Primary hyperlipidemias should be aggressively treated because of the potential complications of persistent hyperlipidemia.

Frequently asked questions: canine hyperlipidemia

Q	A
What causes serum to be turbid?	Elevated serum triglyceride carried by lipoproteins causes serum to appear turbid. Opacity is seen when triglyceride concentration approaches 600 mg/dL. Serum may have the appearance of whole milk when triglyceride concentrations reach 2500-4000 mg/dL. 
What conditions cause hyperlipidemia?	The most common cause is a non-fasted animal. If fasting for greater than 12 hours is confirmed, then primary hyperlipidemia, or secondary hyperlipidemia due to hypothyroidism, pancreatitis, diabetes mellitus, hyperadrenocorticism, cholestasis, or nephrotic syndrome may be present.
Is primary hyperlipoproteinemia hereditary?	Since hyperlipoproteinemias appear to be more common in certain breeds, some defects in lipid metabolism may be hereditary. However, it is likely that primary hyperlipoproteinemia may represent a number of different lipid metabolic defects which may or may not be hereditary in nature.
Are high fat diets harmful to dogs?	Not usually. Lipid metabolism in dogs is very different from that in humans. Dogs carry most of their cholesterol in HDL, and are very resistant to the development of atherosclerosis. However, if certain other diseases are present such as hypothyroidism or diabetes mellitus, high fat diets could result in further lipid abnormalities.
What causes a 'cream layer' to separate in some turbid serum samples?	The 'cream layer' which floats to the top of serum is due to the presence of chylomicrons. This is normal in a non-fasted animal, but represents an abnormality if the animal has been fasted for greater than 12 hours. 
Do dogs develop atherosclerosis?	Unlike humans, dogs rarely develop atherosclerosis due to differences in lipid metabolism. Atherosclerosis may develop in some dogs that have another concurrent disease that causes chronic hyperlipidemia.
Should persistent fasting hyperlipidemia be treated	**Yes**. If the hyperlipidemia is due to a secondary cause, then treatment of the underlying condition may resolve the hyperlipidemia. There is evidence suggesting that chronic hyperlipidemia may lead to the development of pancreatitis, insulin resistance, diabetes mellitus, or atherosclerosis in some dogs.

References

Adan Y, Shibata K, Sato M et al - Effects of docosahexaenoic and eicosapentaenoic acid on lipid metabolism, eicosanoid production, platelet aggregation and atherosclerosis in hypercholesterolemic rats. Biosci Biotechnol Biochem 1999; 63(1): 111-9.

Akmal M, Kasim SE, Soliman AR et al - Excess parathyroid hormone adversely affects lipid metabolism in chronic renal failure. Kidney Int 1990; 37(3): 854-8.

Alaupovic P, Furman RH, Falor WH et al - Isolation and characterization of human chyle chylomicrons and lipoproteins. Ann N Y Acad Sci 1968; 149(2): 791-807.

Albers JJ, Chen CH & Lacko AG - Isolation, characterization, and assay of lecithin-cholesterol acyltransferase. Methods Enzymol 1986; 129: 763-83.

Alberts AW - HMG-CoA reductase inhibitors - the development. Atherosclerosis Review. J. Stokes, III, (1988) & Mancini, M. New York, Raven Press, Ltd. 18: 123-131.

Asakura L, Lottenberg AM, Neves MQ et al - Dietary medium-chain triacylglycerol prevents the postprandial rise of plasma triacylglycerols but induces hypercholesterolemia in primary hypertriglyceridemic subjects. Am J Clin Nutr 2000; 71(3): 701-5.

Asami T, Ciomartan T, Uchiyama M - Thyroxine inversely regulates serum intermediate density lipoprotein levels in children with congenital hypothyroidism. Pediatr Int 1999; 41(3): 266-9.

Assmann G - Lipid Metabolism and Atherosclerosis (1982 Ed.). Stuttgart, Germany, F.K. Schattauer Verlag GmbH.

Baer DM, Paulson RA - The effect of hyperlipidemia on therapeutic drug assays. Ther Drug Monit 1987; 9(1): 72-7.

Bailhache E, Nguyen P, Krempf M et al - Lipoproteins abnormalities in obese insulin-resistant dogs. Metabolism 2003; 52(5): 559-64.

Bantle JP, Hunninghake DB, Frantz ID et al - Comparison of effectiveness of thyrotropin-suppressive doses of D- and L-thyroxine in treatment of hypercholesterolemia. Am J Med 1984; 77(3): 475-81.

Bass VD, Hoffmann WE, Dorner JL - Normal canine lipid profiles and effects of experimentally induced pancreatitis and hepatic necrosis on lipids. Am J Vet Res 1976; 37(11): 1355-7.

Bauer JE - Evaluation and dietary considerations in idiopathic hyperlipidemia in dogs. J Am Vet Med Assoc 1995; 206(11): 1684-8.

Bauer JE - Comparative lipid and lipoprotein metabolism. Vet Clin Pathol 1996;25(2): 49-56.

Bauer JE - Comparative lipoprotein metabolism and lipid abnormalities in dogs and cat - Part II. Diagnostic approach to hyperlipemia and hyperlipoproteinemia. American College of Veterinary Internal Medicine, 2003.

Baum D, Schweid AI, Porte D Jr et al - Congenital lipoprotein lipase deficiency and hyperlipemia in the young puppy. Proc Soc Exp Biol Med 1969; 131(1): 183-5.

Berg AL, Hansson P, Nilsson-Ehle P - Salt resistant lipase activity in human adrenal gland is increased in Cushing's disease. J Intern Med 1990; 228(3): 257-60.

Berti JA, Amaral ME, Boschero AC et al - Thyroid hormone increases plasma cholesteryl ester transfer protein activity and plasma high-density lipoprotein removal rate in transgenic mice. Metabolism 2001; 50(5): 530-6.

Bilzer T - Tumors of the hypophysis as the cause of both Cushing's syndrome and diabetes insipidus in dogs. Tierarztl Prax 1991; 19(3): 276-81.

Blomhoff JP, Holme R, Ostrem T - Plasma cholesterol esterification and plasma lipoproteins in bile-duct-ligated dogs. Scand J Gastroenterol 1978; 13(6): 693-702.

Boden G - Role of fatty acids in the pathogenesis of insulin resistance and NIDDM. Diabetes 1997; 46(1): 3-10.

Boretti FS, Breyer-Haube I, Kaspers B et al - Clinical, hematological, biochemical and endocrinological aspects of 32 dogs with hypothyroidism. Schweiz Arch Tierheilkd 2003; 145(4): 149-56, 158-9.

Bossuyt X, Blanckaert N - Evaluation of interferences in rate and fixed-time nephelometric assays of specific serum proteins. Clin Chem 1999; 45(1): 62-7.

Brown SA, Brown CA, Crowell WA et al - Effects of dietary polyunsaturated fatty acid supplementation in early renal insufficiency in dogs. J Lab Clin Med 2000; 135(3): 275-86.

Brun LD, Gagne C, Coulombe P et al - Effects of dextrothyroxine on the pituitary-thyroid axis in hypercholesterolemic children and goitrous adults. J Clin Endocrinol Metab 1980;51(6): 1306-10.

Capurso A, Catapano AL, Mills GL et al - Formation of HDL-like particles following chylomicron lipolysis. High-Density Lipoproteins: Physiopathological Aspects and Clinical Significance; Atherosclerosis Review (1987). Catapano A, Salvioli G, Vergani C. New York, Raven Press. 16: 19-38.

Castillo M, Amalik F, Linares A et al - Fish oil reduces cholesterol and arachidonic acid levels in plasma and lipoproteins from hypercholesterolemic chicks. Mol Cell Biochem 2000; 210(1-2): 121-30.

Chapman MJ - Comparative analysis of mammalian plasma lipoproteins. Methods Enzymol 1986; 128: 70-143.

Chikamune T, Katamoto H, Nomura K et al - Lipoprotein profile in canine pancreatitis induced with oleic acid. J Vet Med Sci 1998; 60(4): 413-21.

Chikamune T, Katamoto H, Ohashi F et al - Serum lipid and lipoprotein concentrations in obese dogs. J Vet Med Sci 1995; 57(4): 595-8.

Chmielewski M, Sucajtys E, Swierczynski J et al - Contribution of increased HMG-CoA reductase gene expression to hypercholesterolemia in experimental chronic renal failure. Mol Cell Biochem 2003; 246(1-2): 187-91.

Chou TS, Liu HY, Hsiao PJ et al - Hypertriglyceridemia in a 5-day-old newborn-a case report. Kaohsiung J Med Sci 2002; 18(3): 141-5.

Chuang JH, Shieh CS, Chang NK et al - Metabolic effect of parenteral nutrition in dogs with obstructive jaundice. J Am Coll Nutr 1995; 14(2): 197-201.

Cobbaert C, Tricarico A - Different effect of Intralipid and triacylglycerol rich lipoproteins on the Kodak Ektachem serum cholesterol determination. Eur J Clin Chem Clin Biochem 1993; 31(2): 107-9.

Connor WE, DeFrancesco CA, Connor SL - N-3 fatty acids from fish oil. Effects on plasma lipoproteins and hypertriglyceridemic patients. Ann N Y Acad Sci 1993; 683: 16-34.

Cooper AD - The metabolism of chylomicron remnants by isolated perfused rat liver. Biochim Biophys Acta 1977; 488(3): 464-74.

Cortese L, Oliva G, Verstegen J et al - Hyperprolactinaemia and galactorrhoea associated with primary hypothyroidism in a bitch. J Small Anim Pract 1997; 38(12): 572-5.

D'Amico G - Lipid changes in the nephrotic syndrome: new insights into pathomechanisms and treatment. Klin Wochenschr 1991; 69(13): 618-22.

Danielsson B, Ekman R, Johansson BG et al - Plasma lipoprotein changes in experimental cholestasis in the dog. Clin Chim Acta 1977; 80(1): 157-70.

Darras C, Brivet F, Chalas J et al - Factitious acute hypercalcemia biological interference between calcium and lipids. Intensive Care Med 1992; 18(2): 131-2.

De Sain-van der Velden MG, Kaysen GA, Barrett HA et al - Increased VLDL in nephrotic patients results from a decreased catabolism while increased LDL results from increased synthesis. Kidney Int 1998; 53(4): 994-1001.

Deighan CJ, Caslake MJ, McConnell M et al - Patients with nephrotic-range proteinuria have apolipoprotein C and E deficient VLDL1. Kidney Int 2000; 58(3): 1238-46.

DePalma RG, Koletsky S, Bellon EM et al - Failure of regression of atherosclerosis in dogs with moderate cholesterolemia. Atherosclerosis 1977; 27(3): 297-310.

Diez M, Hornick JL, Baldwin P et al - Influence of a blend of fructo-oligosaccharides and sugar beet fiber on nutrient digestibility and plasma metabolite concentrations in healthy beagles. Am J Vet Res 1997; 58(11): 1238-42.

Dixon RM, Reid SW, Mooney CT - Epidemiological, clinical, haematological and biochemical characteristics of canine hypothyroidism. Vet Rec 1999; 145(17): 481-7.

Dominguez-Munoz JE, Malfertheiner P, Ditschuneit HH et al - Hyperlipidemia in acute pancreatitis. Relationship with etiology, onset, and severity of the disease. Int J Pancreatol 1991; 10(3-4): 261-7.

Duncan LE, Jr Buck K - Quantitative analysis of the development of experimental atherosclerosis in the dog. Circ Res 1960; 8: 1023-7.

Feingold KR, Wilson DE, Wood LC et al - Diabetes increases hepatic hydroxymethyl glutaryl coenzyme A reductase protein and mRNA levels in the small intestine. Metabolism 1994; 43(4): 450-4.

Feldman EB, Russell BS, Chen R et al - Dietary saturated fatty acid content affects lymph lipoproteins: studies in the rat. J Lipid Res 1983; 24(8): 967-76.

Field FJ, Albright E, Mathur SN - The effect of hypothyroidism and thyroxine replacement on hepatic and intestinal HMG-CoA reductase and ACAT activities and biliary lipids in the rat. Metabolism 1986; 35(12): 1085-9.

Foster SF, Church DB, Watson AD - Effects of phenobarbitone on serum biochemical tests in dogs. Aust Vet J 2000; 78(1): 23-6.

Franco M, Castro G, Romero L et al - Decreased activity of lecithin:cholesterol acyltransferase and hepatic lipase in chronic hypothyroid rats: implications for reverse cholesterol transport. Mol Cell Biochem 2003; 246(1-2): 51-6.

Friedman TC, Mastorakos G, Newman TD et al - Carbohydrate and lipid metabolism in endogenous hypercortisolism: shared features with metabolic syndrome X and NIDDM. Endocr J 1996; 43(6): 645-55.

Garrib A, Griffiths W, Eldridge P et al - Artifactually low glycated haemoglobin in a patient with severe hypertriglyceridaemia. J Clin Pathol 2003; 56(5): 394-5.

Gebhard RL, Prigge WF - Thyroid hormone differentially augments biliary sterol secretion in the rat. II. The chronic bile fistula model. J Lipid Res 1992; 33(10): 1467-73.

Gleeson JM, Hejazi JS, Kwong L et al - Plasma apolipoprotein E, high density lipoprotein1 (HDL1) and urinary mevalonate excretion in pancreatectomized diabetic dogs: effects of insulin and lovastatin. Atherosclerosis 1990; 84(1): 1-12.

Gogny M - Structure et fonctions de l'intestin. In: Encyclopédie Médico-Chirurgicale Vétérinaire, Paris, 1994; Gastro-Entérologie 1300: 1-8.

Goldstein JL, Brown MS - Progress in understanding the LDL receptor and HMG-CoA reductase, two membrane proteins that regulate the plasma cholesterol. J Lipid Res 1984; 25(13): 1450-61.

Greco DS, Feldman EC, Peterson ME et al - Congenital hypothyroid dwarfism in a family of giant schnauzers. J Vet Intern Med 1991;5(2): 57-65.

Groot PH, Jansen H, Van Tol A - Selective degradation of the high density lipoprotein-2 subfraction by heparin-releasable liver lipase. FEBS Lett 1981; 129(2): 269-72.

Guyan PM, Uden S, Braganza JM - Heightened free radical activity in pancreatitis. Free Radic Biol Med 1990; 8(4): 347-54.

Gylling H, Miettinen TA - Cholesterol absorption and lipoprotein metabolism in type II diabetes mellitus with and without coronary artery disease. Atherosclerosis 1996; 126(2): 325-32.

Hansen B, DiBartola SP, Chew DJ et al - Clinical and metabolic findings in dogs with chronic renal failure fed two diets. Am J Vet Res 1992; 53(3): 326-34.

Hansson P, Nordin G, Nilsson-Ehle P - Influence of nutritional state on lipoprotein lipase activities in the hypothyroid rat. Biochim Biophys Acta 1983; 753(3): 364-71.

Harris WS, Connor WE, Illingworth DR et al - Effects of fish oil on VLDL triglyceride kinetics in humans. J Lipid Res 1990; 31(9): 1549-58.

Hata Y, Shigematsu H, Tonomo Y et al - Interference of an anesthetic preparation with plasma triglyceride determinations. Jpn Circ J 1978; 42(6): 689-94.

Havel RJ - Pathogenesis, differentiation and management of hypertriglyceridemia. Adv Intern Med 1969;15: 117-54.

Havel RJ - The formation of LDL: mechanisms and regulation. J Lipid Res 1984;25(13): 1570-6.

Hazzard WR, Kushwaha RS, Applebaum-Bowden D et al - Chylomicron and very low-density lipoprotein apolipoprotein B metabolism: mechanism of the response to stanozolol in a patient with severe hypertriglyceridemia. Metabolism 1984; 33(10): 873-81.

Heaney AP, Sharer N, Rameh B et al - Prevention of recurrent pancreatitis in familial lipoprotein lipase deficiency with high-dose antioxidant therapy. J Clin Endocrinol Metab 1999; 84(4): 1203-5.

Hess RS, Kass PH, Van Winkle TJ - Association between diabetes mellitus, hypothyroidism or hyperadrenocorticism, and atherosclerosis in dogs. J Vet Intern Med 2003; 17(4): 489-94.

Hirano T, Morohoshi T - Treatment of hyperlipidemia with probucol suppresses the development of focal and segmental glomerulosclerosis in chronic aminonucleoside nephrosis. Nephron 1992; 60(4): 443-7.

Holt PR - The roles of bile acids during the process of normal fat and cholesterol absorption. Arch Intern Med 1972;130(4): 574-83.

Hsu HC, Lee YT, Chen MF - Effects of fish oil and vitamin E on the antioxidant defense system in diet-induced hypercholesterolemic rabbits. Prostaglandins Other Lipid Mediat 2001; 66(2): 99-108.

Jaeger JQ, Johnson S, Hinchcliff KW et al - Characterization of biochemical abnormalities in idiopathic hyperlipidemia of miniature Schnauzer dogs. ACVIM, Charlotte, NC, 2003.

Jaggy A, Oliver JE, Ferguson DC et al - Neurological manifestations of hypothyroidism: a retrospective study of 29 dogs. J Vet Intern Med 1994; 8(5): 328-36.

Kagawa Y, Uchida E, Yokota H et al - Immunohistochemical localization of apolipoprotein B-100 (ApoB-100) and expression of glutathione peroxidase (GSH-PO) in canine atherosclerotic lesions. Vet Pathol 1998; 35(3): 227-9.

Kashyap ML, McGovern ME, Berra K et al - Long-term safety and efficacy of a once-daily niacin/lovastatin formulation for patients with dyslipidemia. Am J Cardiol 2002; 89(6): 672-8.

Kaysen GA, Myers BD, Couser WG et al - Mechanisms and consequences of proteinuria. Lab Invest 1986; 54(5): 479-98.

Kes P, Reiner Z, Brunetta B - Lipoprotein disorders in chronic kidney failure, nephrotic syndrome and dialysis. Lijec Vjesn 2002; 124(11-12): 372-7.

Kostner GM, Knipping G, Groener JE et al - The role of LCAT and cholesteryl ester transfer proteins for the HDL and LDL structure and metabolism. Adv Exp Med Biol 1987; 210: 79-86.

Kovanen PT - Regulation of plasma cholesterol by hepatic low-density lipoprotein receptors. Am Heart J 1987; 113(2 Pt 2): 464-9.

Kwong LK, Feingold KR, Peric-Golia L et al - Intestinal and hepatic cholesterogenesis in hypercholesterolemic dyslipidemia of experimental diabetes in dogs. Diabetes 1991; 40(12): 1630-9.

Levy E, Thibault L, Turgeon J et al - Beneficial effects of fish-oil supplements on lipids, lipoproteins, and lipoprotein lipase in patients with glycogen storage disease type I. Am J Clin Nutr 1993; 57(6): 922-9.

Liang K, Vaziri ND - Gene expression of LDL receptor, HMG-CoA reductase, and cholesterol-7 alpha-hydroxylase in chronic renal failure. Nephrol Dial Transplant 1997; 12(7): 1381-6.

Liang K, Vaziri ND - Upregulation of acyl-CoA: cholesterol acyltransferase in chronic renal failure. Am J Physiol Endocrinol Metab 2002; 283(4): E676-81.

Ling GV, Stabenfeldt GH, Comer KM et al - Canine hyperadrenocorticism: pretreatment clinical and laboratory evaluation of 117 cases. J Am Vet Med Assoc 1979; 174(11): 1211-5.

Liu SK, Tilley LP, Tappe JP et al - Clinical and pathologic findings in dogs with atherosclerosis: 21 cases (1970-1983). J Am Vet Med Assoc 1986; 189(2): 227-32.

Lucena R, Moreno P, Perez-Rico A et al - Effects of haemolysis, lipaemia and bilirubinaemia on an enzyme-linked immunosorbent assay for cortisol and free thyroxine in serum samples from dogs. Vet J 1998; 156(2): 127-31.

Mahley RW, Hui DY, Innerarity TL et al - Chylomicron remnant metabolism. Role of hepatic lipoprotein receptors in mediating uptake. Arteriosclerosis 1989; 9(1 Suppl): I14-8.

Mahley RW, Innerarity TL - Lipoprotein receptors and cholesterol homeostasis. Biochim Biophys Acta 1983; 737(2): 197-222.

Mahley RW, Innerarity TL, Brown MS et al - Cholesteryl ester synthesis in macrophages: stimulation by beta-very low density lipoproteins from cholesterol-fed animals of several species. J Lipid Res 1980; 21(8): 970-80.

Mahley RW, Innerarity TL, Weisgraber KH, et al - Canine hyperlipoproteinemia and atherosclerosis. Accumulation of lipid by aortic medial cells in vivo and in vitro. Am J Pathol 1977;87(1): 205-25.

Mahley RW, Weisgraber KH - Canine lipoproteins and atherosclerosis. I. Isolation and characterization of plasma lipoproteins from control dogs. Circ Res 1974a; 35(5): 713-21.

Mahley RW, Weisgraber KH, Innerarity T - Canine lipoproteins and atherosclerosis. II. Characterization of the plasma lipoproteins associated with atherogenic and nonatherogenic hyperlipidemia. Circ Res 1974b; 35(5): 722-33.

Manning PJ - Thyroid gland and arterial lesions of Beagles with familial hypothyroidism and hyperlipoproteinemia. Am J Vet Res 1979; 40(6): 820-8.

Marsh JB - Lipoprotein metabolism in experimental nephrosis. Proc Soc Exp Biol Med 1996; 213(2): 178-86.

Mills GL, Taylaur CE - The distribution and composition of serum lipoproteins in eighteen animals. Comp Biochem Physiol B 1971; 40(2): 489-501.

Mingrone G, Henriksen FL, Greco AV et al - Triglyceride-induced diabetes associated with familial lipoprotein lipase deficiency. Diabetes 1999; 48(6): 1258-63.

Miyada D, Tipper P, Jantsch D et al - The effect of hyperlipidemia on Technicon SMAC measurements. Clin Biochem 1982; 15(4): 185-8.

Miyoshi K, Uchida E, Niiyama M - Enzyme-linked immunosorbent assays of canine apolipoproteins B-100 and A-I. J Vet Med Sci 2000; 62(12): 1269-74.

Mizushima T, Ochi K, Matsumura N et al - Prevention of hyperlipidemic acute pancreatitis during pregnancy with medium-chain triglyceride nutritional support. Int J Pancreatol 1998; 23(3): 187-92.

Mortensen A, Hansen BF, Hansen JF et al - Comparison of the effects of fish oil and olive oil on blood lipids and aortic atherosclerosis in Watanabe heritable hyperlipidaemic rabbits. Br J Nutr 1998; 80(6): 565-73.

Muller DL, Saudek CD, Applebaum-Bowden D - Hepatic triglyceride lipase in diabetic dogs. Metabolism 1985; 34(3): 251-4.

Nagasaka H, Kikuta H, Chiba H et al - Two cases with transient lipoprotein lipase (LPL) activity impairment: evidence for the possible involvement of an LPL inhibitor. Eur J Pediatr 2003; 162(3): 132-8.

Nandan R, Fisher JD, Towery EP et al - Effects of dextrothyroxine on hyperlipidemia and experimental atherosclerosis in beagle dogs. Atherosclerosis 1975; 22(2): 299-311.

Ng PC, Lam CW, Fok TF et al - Deceptive hyperbilirubinaemia in a newborn with familial lipoprotein lipase deficiency. J Paediatr Child Health 2001; 37(3): 314-6.

Nilsson-Ehle P, Garfinkel AS, Schotz MC - Lipolytic enzymes and plasma lipoprotein metabolism. Annu Rev Biochem 1980; 49: 667-93.

Noel SP, Dupras R, Vezina C et al - Comparison of very-low-density lipoproteins isolated from rat liver perfusate, rat serum and human plasma as acceptors for cholesteryl ester transfer. Biochim Biophys Acta 1984; 796(3): 277-84.

Okumura T, Fujioka Y, Morimoto S et al - Eicosapentaenoic acid improves endothelial function in hypertriglyceridemic subjects despite increased lipid oxidizability. Am J Med Sci 2002; 324(5): 247-53.

Olbricht CJ - Pathophysiology and therapy of lipid metabolism disorders in kidney diseases. Klin Wochenschr 1991; 69(11): 455-62.

Pakala R, Sheng WL, Benedict CR - Vascular smooth muscle cells preloaded with eicosapentaenoic acid and docosahexaenoic acid fail to respond to serotonin stimulation. Atherosclerosis 2000; 153(1): 47-57.

Patterson JS, Rusley MS, Zachary JF - Neurologic manifestations of cerebrovascular atherosclerosis associated with primary hypothyroidism in a dog. J Am Vet Med Assoc 1985; 186(5): 499-503.

Peng L, Gao X, Jiang H et al - Laboratory evaluation of the Sysmex SE-9500 automated haematology analyser. Clin Lab Haematol 2001; 23(4): 237-42.

Polzin DJ, Osborne CA, Hayden DW et al - Effects of modified protein diets in dogs with chronic renal failure. J Am Vet Med Assoc 1983; 183(9): 980-6.

Portman RJ, Scott RC 3rd, Rogers DD et al - Decreased low-density lipoprotein receptor function and mRNA levels in lymphocytes from uremic patients. Kidney Int 1992; 42(5): 1238-46.

Prentki M, Corkey BE - Are the beta-cell signaling molecules malonyl-CoA and cystolic long-chain acyl-CoA implicated in multiple tissue defects of obesity and NIDDM? Diabetes 1996; 45(3): 273-83.

Puiggros C, Chacon P, Armadans LI et al - Effects of oleic-rich and omega-3-rich diets on serum lipid pattern and lipid oxidation in mildly hypercholesterolemic patients. Clin Nutr 2002; 21(1): 79-87.

Pykalisto O, Goldberg AP, Brunzell JD - Reversal of decreased human adipose tissue lipoprotein lipase and hypertriglyceridemia after treatment of hypothyroidism. J Clin Endocrinol Metab 1976; 43(3): 591-600.

Rader DJ, Tietge UJ - Gene therapy for dyslipidemia: clinical prospects. Curr Atheroscler Rep 1999; 1(1): 58-69.

Rebrin K, Steil GM, Getty L et al - Free fatty acid as a link in the regulation of hepatic glucose output by peripheral insulin. Diabetes 1995; 44(9): 1038-45.

Renauld A, Gomez NV, Scaramal JD et al - Natural estrous cycle in normal and diabetic bitches. Basal serum total lipids and cholesterol. Serum triglycerides profiles during glucose and insulin tests. Acta Physiol Pharmacol Ther Latinoam 1998; 48(1): 41-51.

Reusch C, Hahnle B - Laboratory parameters for the control of the course of therapy of canine Cushing's syndrome.]. Tierarztl Prax 1991; 19(1): 102-6.

Reynolds AJ, Fuhrer L, Dunlap HL et al - Lipid metabolite responses to diet and training in sled dogs. J Nutr 1994; 124(12 Suppl): 2754S-2759S.

Richter WO, Jacob BG, Ritter MM et al - Treatment of primary chylomicronemia due to familial hypertriglyceridemia by omega-3 fatty acids. Metabolism 1992; 41(10): 1100-5.

Rogers WA - Lipemia in the dog. Vet Clin North Am 1977; 7(3): 637-47.

Rogers WA, Donovan EF, Kociba GJ - Idiopathic hyperlipoproteinemia in dogs. J Am Vet Med Assoc 1975a; 166(11): 1087-91.

Rogers WA, Donovan EF, Kociba GJ - Lipids and lipoproteins in normal dogs and in dogs with secondary hyperlipoproteinemia. J Am Vet Med Assoc 1975b; 166(11): 1092-1100.

Rouis M, Dugi KA, Previato L et al - Therapeutic response to medium-chain triglycerides and omega-3 fatty acids in a patient with the familial chylomicronemia syndrome. Arterioscler Thromb Vasc Biol 1997; 17(7): 1400-6.

Sako T, Takahashi T, Takehana K et al - Chlamydial infection in canine atherosclerotic lesions. Atherosclerosis 2002; 162(2): 253-9.

Sako T, Uchida E, Kagawa Y et al - Immunohistochemical detection of apolipoprotein B-100 and immunoglobulins (IgA, IgM, IgG) in the splenic arteries of aging dogs. Vet Pathol 2001; 38(4): 407-13.

Sane T, Taskinen MR - Does familial hypertriglyceridemia predispose to NIDDM? Diabetes Care 1993; 16(11): 1494-501.

Sanfey H, Bulkley GB, Cameron JL - The role of oxygen-derived free radicals in the pathogenesis of acute pancreatitis. Ann Surg 1984; 200(4): 405-13.

Santamarina-Fojo S, Dugi KA - Structure, function and role of lipoprotein lipase in lipoprotein metabolism. Curr Opin Lipidol 1994; 5(2): 117-25.

Sato K, Agoh H, Kaneshige T et al - Hypercholesterolemia in Shetland sheepdogs. J Vet Med Sci 2000; 62(12): 1297-301.

Schenck PA - Lipoprotein lipase and hepatic lipase activity in dogs with primary hyperlipoproteinemia. J Vet Intern Med 2002; 16(3): 386.

Schenk PA, Donovan D , Refsal K et al – Incidence of hypothyroidism in dogs with chronic hyperlipidemia, American College of Veterinary Medicine, Minneapolis, MN, 2004.

Shapiro RJ - Impaired binding of low density lipoprotein to hepatic membranes from uremic guinea pigs. Biochem Cell Biol 1991; 69(8): 544-50.

Shearer GC, Kaysen GA - Proteinuria and plasma compositional changes contribute to defective lipoprotein catabolism in the nephrotic syndrome by separate mechanisms. Am J Kidney Dis 2001; 37(1 Suppl 2): S119-22.

Shephard MD, Whiting MJ - Falsely low estimation of triglycerides in lipemic plasma by the enzymatic triglyceride method with modified Trinder's chromogen. Clin Chem 1990; 36(2): 325-9.

Shepherd J, Packard CJ - Lipoprotein metabolism in familial hypercholesterolemia. Arteriosclerosis 1989; 9(1 Suppl): I39-42.

Shirai K, Kobayashi J, Inadera H et al - Type I hyperlipoproteinemia caused by lipoprotein lipase defect in lipid-interface recognition was relieved by administration of medium-chain triglyceride. Metabolism 1992; 41(11): 1161-4.

Singer P, Berger I, Moritz V et al - N-6 and N-3 PUFA in liver lipids, thromboxane formation and blood pressure from SHR during diets supplemented with evening primrose, sunflowerseed or fish oil. Prostaglandins Leukot Essent Fatty Acids 1990; 39(3): 207-11.

Sloop CH, Dory L, Hamilton R et al - Characterization of dog peripheral lymph lipoproteins: the presence of a disc-shaped "nascent" high density lipoprotein. J Lipid Res 1983; 24(11): 1429-40.

Smit MJ, Temmerman AM, Wolters H et al - Dietary fish oil-induced changes in intrahepatic cholesterol transport and bile acid synthesis in rats. J Clin Invest 1991; 88(3): 943-51.

Sottiaux J - Atherosclerosis in a dog with diabetes mellitus. J Small Anim Pract 1999; 40(12): 581-4.

Steiner G, Poapst M, Davidson JK - Production of chylomicron-like lipoproteins from endogenous lipid by the intestine and liver of diabetic dogs. Diabetes 1975;24(3): 263-71.

Szolkiewicz M, Sucajtys E, Chmielewski M et al - Increased rate of cholesterologenesis--a possible cause of hypercholesterolemia in experimental chronic renal failure in rats. Horm Metab Res 2002; 34(5): 234-7.

Takeuchi N - Metabolic disorders of lipoproteins-influences of compositional changes of lipoproteins upon their metabolic behavior. Rinsho Byori 1991; 39(6): 565-73.

Taskinen MR, Nikkila EA, Pelkonen R et al - Plasma lipoproteins, lipolytic enzymes, and very low density lipoprotein triglyceride turnover in Cushing's syndrome. J Clin Endocrinol Metab 1983; 57(3): 619-26.

Thompson JC, Johnstone AC, Jones BR et al - The ultrastructural pathology of five lipoprotein lipase-deficient cats. J Comp Pathol 1989; 101(3): 251-62.

Thomson AB, Keelan M, Lam T et al - Fish oil modifies effect of high cholesterol diet on intestinal absorption in diabetic rats. Diabetes Res 1993; 22(4): 171-83.

Turley SD, Dietschy JM - The contribution of newly synthesized cholesterol to biliary cholesterol in the rat. J Biol Chem 1981; 256(5): 2438-46.

Vaziri ND, Liang KH - Down-regulation of hepatic LDL receptor expression in experimental nephrosis. Kidney Int 1996; 50(3): 887-93.

Wada M, Minamisono T, Ehrhart LA et al - Familial hyperlipoproteinemia in beagles. Life Sci 1977; 20(6): 999-1008.

Washio M, Okuda S, Ikeda M et al - Hypercholesterolemia and the progression of the renal dysfunction in chronic renal failure patients. J Epidemiol 1996; 6(4): 172-7.

Watson P, Simpson KW, Bedford PG - Hypercholesterolaemia in briards in the United Kingdom. Res Vet Sci 1993; 54(1): 80-5.

Weidmeyer CE, Solter PF - Validation of human haptoglobin immunoturbidimetric assay for detection of haptoglobin in equine and canine serum and plasma. Vet Clin Pathol 1996; 25(4): 141-146.

Westergaard H, Dietschy JM - The mechanism whereby bile acid micelles increase the rate of fatty acid and cholesterol uptake into the intestinal mucosal cell. J Clin Invest 1976; 58(1): 97-108.

Whitney MS, Boon GD, Rebar AH et al - Effects of acute pancreatitis on circulating lipids in dogs. Am J Vet Res 1987; 48(10): 1492-7.

Whitney MS, Boon GD, Rebar AH et al - Ultracentrifugal and electrophoretic characteristics of the plasma lipoproteins of miniature schnauzer dogs with idiopathic hyperlipoproteinemia. J Vet Intern Med 1993; 7(4): 253-60.

Wilson DE, Chan IF, Elstad NL et al - Apolipoprotein E-containing lipoproteins and lipoprotein remnants in experimental canine diabetes. Diabetes 1986; 35(8): 933-42.

Young WF, Jr, Gorman CA, Jiang NS et al - L-thyroxine contamination of pharmaceutical D-thyroxine: probable cause of therapeutic effect. Clin Pharmacol Ther 1984; 36(6): 781-7.

Zsigmond E, Kobayashi K, Tzung KW et al - Adenovirus-mediated gene transfer of human lipoprotein lipase ameliorates the hyperlipidemias associated with apolipoprotein E and LDL receptor deficiencies in mice. Hum Gene Ther 1997; 8(16): 1921-33

EXAMPLES OF HOME-PREPARED
THE NUTRITIONAL MANAGEMENT

Example 1

COMPOSITION
(1000 g diet)

Halibut . . . . . 460 g
Rice, cooked . . . . . 500 g
Wheat bran . . . . . 30 g
Rapeseed oil . . . . . 10 g

Add a well-balanced mineral and vitamin supplement.

ANALYSIS		
The diet prepared in this way contains 29% dry matter and 71% water		
	% dry matter	**g/1000 kcal**
Protein	37	92
Fat	7	17
Available carbohydrate	46	116
Fiber	5	14

INDICATIVE RATIONING			
Energy value (metabolizable energy) 1180 kcal/1000 g of diet prepared (4000 kcal/1000 g DM)			
Dog's weight (kg)*	Daily amount (g)**	Dog's weight (kg)*	Daily amount (g)**
2	190	45	1910
4	310	50	2070
6	420	55	2230
10	620	60	2380
15	840	65	2520
20	1040	70	2670
25	1230	75	2810
30	1410	80	2950
35	1590	85	3080
40	1750	90	3220

Key Points

- **Restrict fat** to combat hyperlipidemia and any obesity
- **Ensure low fiber content and high digestibility** to promote the good absorption of essential nutrients

**The diet is offered in accordance with the dog's healthy weight. In obese dogs, the diet must be prescribed in accordance with the ideal weight and not the real weight of the dog.*
***Dividing the daily amount over two or three meals is recommended to promote good digestion.*

DIETS ADAPTED TO OF HYPERLIPIDEMIA

Example 2

COMPOSITION
(1000 g diet)

Beef, minced meat, 5% fat ..... 350 g
Potato, cooked, with skin ..... 630 g
Wheat bran ..... 15 g
Rapeseed oil ..... 5 g

Add a well-balanced mineral and vitamin supplement.

INDICATIVE RATIONING

Energy value (metabolizable energy) 895 kcal/1000 g of diet prepared (3590 kcal/1000 g DM)

Dog's weight (kg)*	Daily amount (g)**	Dog's weight (kg)*	Daily amount (g)**
2	240	45	2520
4	410	50	2730
6	560	55	2930
10	820	60	3130
15	1110	65	3330
20	1370	70	3520
25	1620	75	3700
30	1860	80	3890
35	2090	85	4070
40	2310	90	4240

ANALYSIS

The diet prepared in this way contains 25% dry matter and 75% water

	% dry matter	g/1000 kcal
Protein	37	103
Fat	7	19
Available carbohydrate	40	112
Fiber	7	19

Contra-indications

Gestation
Lactation
Growth
Cachexia

Examples of home-made diets are proposed by Pr Patrick Nguyen
(Nutrition and Endocrinology Unit; Biology and Pathology Department, National veterinary School of Nantes)

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The Collie (and the German Shepherd) may suffer primary disorders of lipoprotein metabolism, leading to hypercholesterolemia. The disease may lead to corneal lipidosis where the cholesterol and phospholipid vacuoles are present in the superficial stroma of the cornea.

Key Points
to remember:

In the nutritional management of hyperlipidemia

• **Achieve weight loss in the dog** if the body condition demands it. There is a correlation between obesity and the plasma indicators of hyperlipidemia (lipoproteins, leptin, insulin and ghrelin) *(Jeusette et al, 2005)*.

• **Give the dog a low-fat diet**: < 25 g/1000 kcal, or less than 9% fat in a 3500 kcal/kg diet. Controlling the energy ingested is the best way of controlling hyperlipidemia in obese dogs.

• During the low fat diet, simply controlling the hyperlipidemia is not enough. It may be necessary to prescribe a **fish oil supplement** (220 mg/kg) to provide EPA and DHA (long-chain omega 3 fatty acids), which have a lipopenic action.

• High levels of poly-unsaturated omega-3 fatty acids may increase the risk of oxidation of lipid membranes. The **administration of biological antioxidants** (e.g. vitamin E, vitamin C and beta-carotene) may be necessary to prevent oxidative reactions.

• Supplementation with **fermentable fiber** in association with a low-calorie diet may help to regress corneal lipidosis. In practice, this supplementation can be achieved by the inclusion of 1-2% fructo-oligosaccharides (FOS) or the gradual addition of guar gum in the same proportions *(Jeusette et al, 2004)*. Interestingly, the effect of the FOS on hypercholesterolemia is in consistent.

• The patient should be re-evaluated every month for the first three months. Once the hyperlipidemia has been controlled re-evaluation every six months will be sufficient.

References

Jeusette IC, Grauwels M, Cuvelier C et al - Hypercholesterolaemia in a family of rough collie dogs. J Small Anim Pract. 2004 ; 45(6) : 319-24

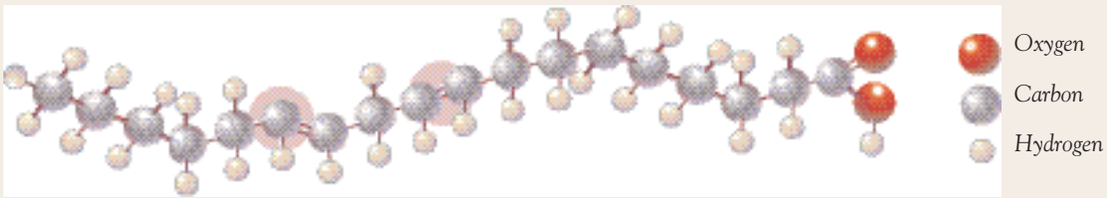
Jeusette IC, Lhoest ET, Istasse LP et al - Influence of obesity on plasma lipid and lipoprotein concentrations in dogs. Am J Vet Res. 2005 ; 66 (1) : 81-6.

Focus on:

LONG-CHAIN OMEGA 3 FATTY ACIDS (EPA-DHA)

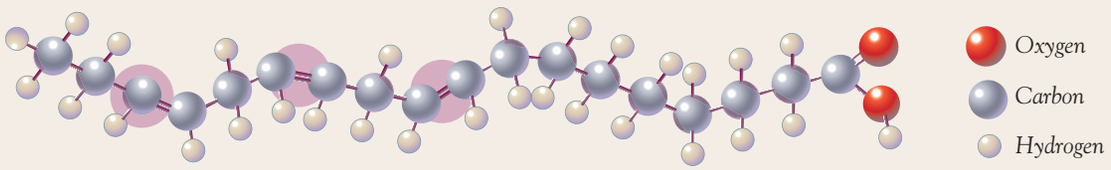
Omega 3 fatty acids constitute a specific family within polyunsaturated fatty acids (PUFA). Their precursor is alpha linolenic acid (C18:3, n-3), the chemical structure of which distinguishes it from linoleic acid (C18:2, n-6), which is the precursor of the omega 6 family of fatty acids. Both are essential fatty acids in dogs, because the dog lacks the appropriate enzymes to synthesize them hence, the dog depends on adequate dietary intake to meet its needs.

LINOLEIC ACID: $C_{18:2}$ (N-6); OMEGA 6 FATTY ACID PRECURSOR



Omega 6 fatty acids are characterized by the first double bond between the sixth and seventh carbon atoms, counting from the omega carbon (i.e. the carbon atom located opposite the carboxyl – COOH group).

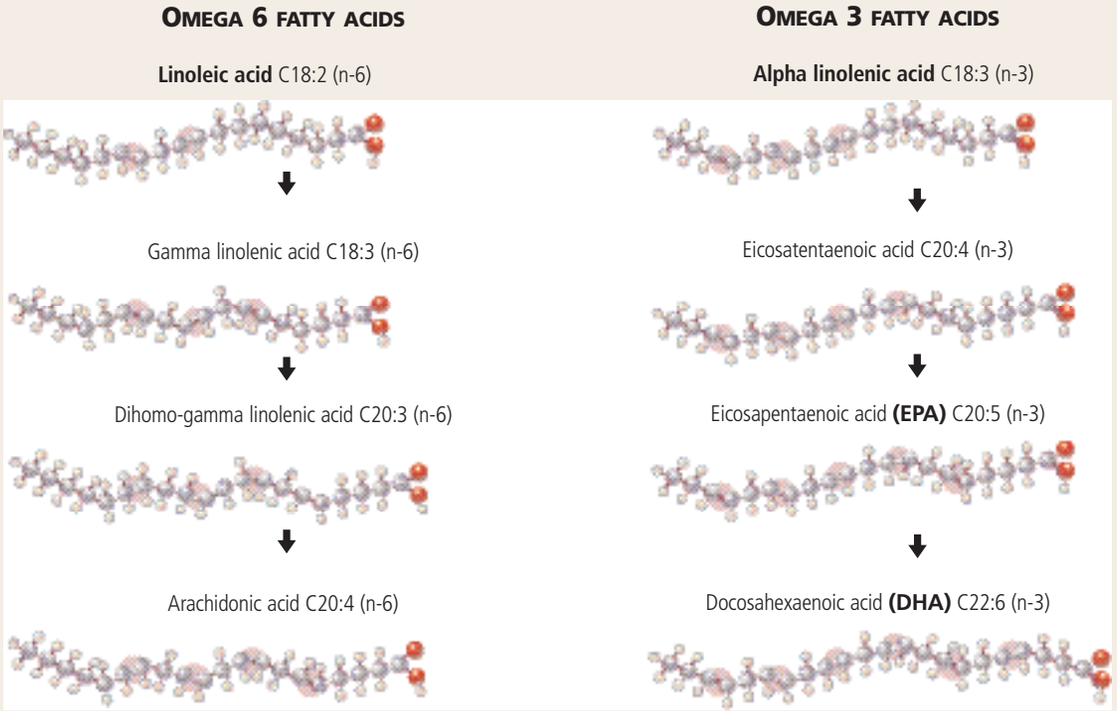
ALPHA LINOLENIC ACID: $C_{18:3}$ (N-3) ; OMEGA 3 FATTY ACID PRECURSOR



In the omega 3 fatty acid family the first double bond is between the third and fourth carbon atom.

The synthesis of long-chain fatty acids is due to the action of hepatic enzymes (desaturases and elongases), which attach to the carbon atoms and the unsaturated double bonds. These are the same enzymes that act in the synthesis of omega 3 and omega 6, which is the reason for competition between the two families.

Hepatic synthesis of long-chain omega 3 and omega 6 fatty acids from their respective precursors



Sources of omega 3 fatty acids

Fish oils (especially fish from cold water, like salmon, mackerel, halibut and herring) may contain more than 30% EPA-DHA. They are by far, the most abundant sources. Marine PUFA are synthesized in the chloroplasts of phytoplankton or microalgae consumed by fish. Higher in the food chain, some fish incorporate omega 3 PUFA and transform them into fatty acids with 20-22 carbon atoms. EPA and DHA are especially concentrated in the fat tissue of fish.

Some vegetable oils contain a significant quantity of alpha linolenic acid, which is an EPA-DHA precursor. These include soybean oil and especially linseed oil. The efficiency of transformation to long-chain fatty acids is strongly dependent on the animal's age and health, and on the general dietary context. Fish oil is the best available source of EPA-DHA fatty acids.

Comparative intake of omega 3 fatty acids in different oils

Omega 3 fatty acids (% dry matter)	Soybean oil	Linseed oil	Fish oil
Alpha linolenic acid	6	51	<1
EPA + DHA	-	-	17-34

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Chronic renal disease: the importance of nutrition

1 - Classification and etiology 269
2 - Pathophysiology 270
3 - Clinical consequences of uremia 271
4 - Clinical presentation 275
5 - Diagnostic evaluation 275
6 - Treatment 276
7 - Nutritional management 282
8 - Feeding strategy 288

Frequently asked questions: Chronic Renal Failure 291
References 292
Examples home-prepared diets adapted
to the dietetic treatment of chronic renal disease 294
Royal Canin Nutritional Information 296

Chronic renal disease: the importance of nutrition

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Denise Elliott graduated from the University of Melbourne with a Bachelor in Veterinary Science with Honors in 1991. After completing an internship in Small Animal Medicine and Surgery at the University of Pennsylvania, Denise moved to the University of California-Davis where she completed a residency in Small Animal Medicine, a fellowship in Renal Medicine and Hemodialysis, and a residency in Small Animal Clinical Nutrition. Denise received board certification with the American College of Veterinary Internal Medicine in 1996 and with the American College of Veterinary Nutrition in 2001. The University of California-Davis awarded a PhD in Nutrition in 2001 for her work on Multifrequency Bioelectrical Impedance Analysis in Healthy Cats and Dogs. Denise is currently the Director of Scientific Communications for Royal Canin USA.

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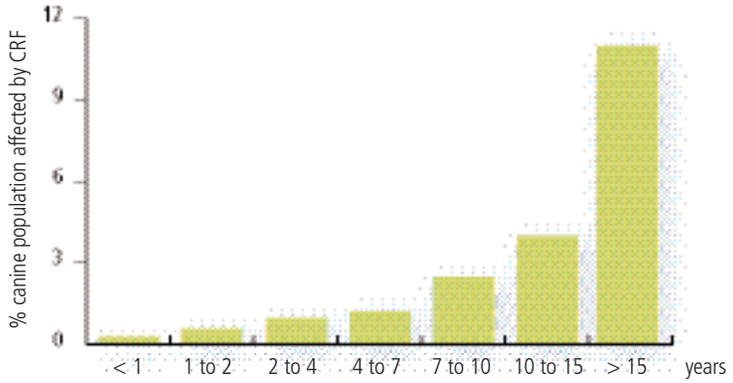
Chronic renal failure (CRF) ensues from the irreversible loss of the metabolic, endocrine and excretory capacities of the kidney. It is a common clinical problem occurring in 2-5% of dogs *(Bronson, 1982; Lund et al, 1999)****. Chronic renal failure is considered a leading cause of death in older patients (Figure 1). The 1997 Morris Animal Foundation Animal Health Survey of 2,000 pet owners identified kidney disease as the third leading cause of death in dogs. The mean age of diagnosis in dogs is 6.5 years, with 45% of cases reported over 10 years of age*** *(Polzin, 1989; Polzin et al 2000)****. The onset of renal failure tends to be insidious as renal function generally declines over a period of months to years. The uremic syndrome manifests when the residual renal mass is generally less than 25% of normal and compensatory changes fail to meet the metabolic and excretory needs of the body for homeostasis.***

FIGURE 1 - THE PREVALENCE OF CHRONIC RENAL IN DOGS AS A FUNCTION OF AGE
(Adams, 1995)



Although chronic renal failure is a relatively common disorder in elderly dogs, it can occur at any age.

1 - Classification and etiology

Chronic renal failure is caused by replacement of functional nephrons by non-functional scar tissue and inflammatory infiltrates. The precise etiology is however multifactorial: it may be congenital or familial in origin or occur secondary to acquired disease processes that injure the renal glomeruli, tubules, interstitium or vasculature **(Table 1)**. Damage to the glomeruli, tubules, interstitium or vasculature results in entire nephron destruction with ultimate replacement by fibrous scar tissue **(Figure 2)**.

TABLE 1 - POTENTIAL CAUSES OF CHRONIC RENAL FAILURE

Immunological disorders	Polycystic Disease
- Systemic lupus erythromatosus	Idiopathic
- Glomerulonephritis	Familial
- Vasculitis	- Lhasa Apsos
Neoplastic disorders	- Shih Tzus
- Primary	- Norwegian Elkhounds
- Metastatic	- Sharpeis
Amyloidosis	- Dobermans
Nephrotoxic agents	- Samoyeds
Renal Ischemia	- Wheaten Terriers
Inflammatory disorders	- Cocker Spaniels
Infectious disorders	- Beagles
- Leptospirosis	- Keeshonds
- Pyelonephritis	- Bedlington Terriers
Renal Calculi	- Cairn Terriers
Urinary outflow obstructions	- Basenjis
Hereditary/Congenital	

The congenital and familial causes of chronic renal failure can be considered based on breed, family history and the date on which the renal disease commenced.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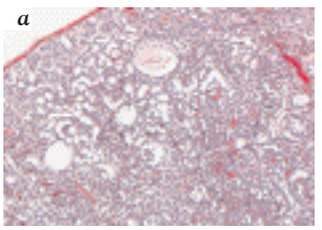

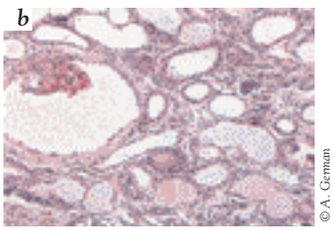

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Figure 2 - Histopathological images of renal parenchyma in a Cocker Spaniel diagnosed with familial nephropathy
(a: x100 magnification) (b: x400 magnification); HE stain. The Bowman spaces are dilated and empty; some of them contain glomerular vascular components and protein deposits, some scattered tubules also contain protein material. Multifocal calcification of Bowman capsules, the tubule basement membrane and the glomeruli are observed.

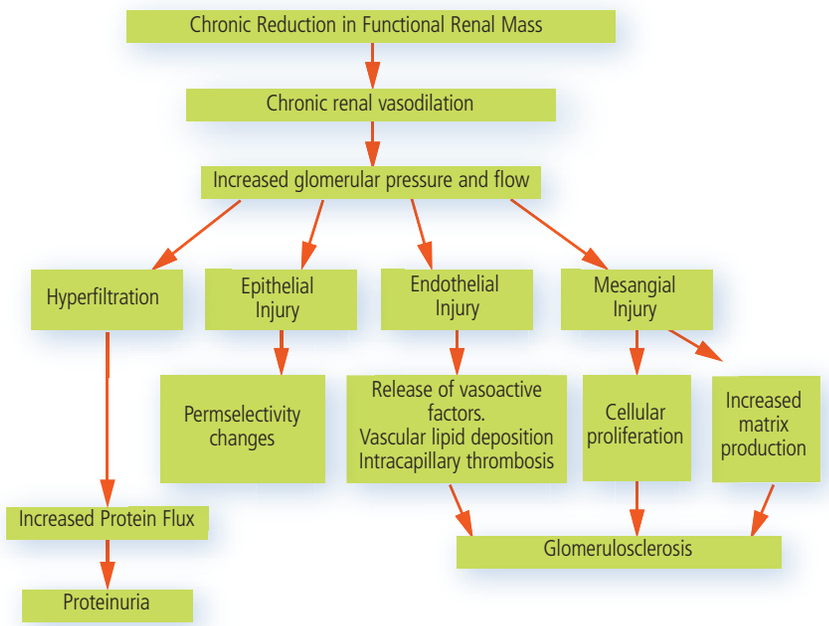
2 - Pathophysiology

Most of the nephrons of the diseased kidney fall into one of two categories. They are either non-functioning nephrons, as a result of destruction of any portion of their structures, or they are intact nephrons that function normally. Changes in renal function occur as a result of a reduction in the number of functioning nephrons. As the number of functioning nephrons diminishes, there are adaptations that occur in a regular sequence. When nephrons are damaged and essentially rendered non functional, the remaining "healthy" nephrons increase their size and their work load to compensate for nephron loss. This is referred to as the hyperfiltration theory **(Figure 3)**. Nephron hypertrophy and hyperfiltration is an adaptative mechanism to compensate for reduced nephron number.

Nevertheless the chronic increase in glomerular capillary pressure and/or glomerular plasma flow rate damages the endothelium, mesangium and epithelium. Mesangial matrix production, glomerular deposition of circulating lipid, and capillary thrombosis promote structural injury to the glomerulus. Tubulointerstitial damage, increased tubular ammoniagenesis, and soft tissue mineralization contribute to nephron injury and ultimately lead to nephron sclerosis. Continued nephron destruction initiates further compensation, promoting a self-perpetuating cycle of adaptation and injuries **(Figure 4)**.

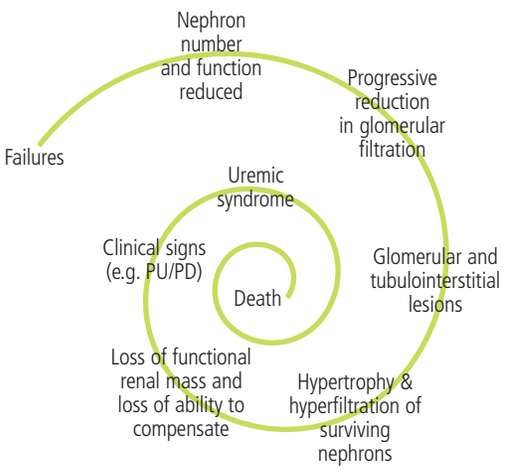
The progression of CRF has been described as occurring in four stages that are not sharply demarcated but rather, are phases in a continuing degenerative process with loss of more and more functioning nephrons **(Table 2)**.

FIGURE 3 - CENTRAL ROLE OF GLOMERULAR HYPERTENSION IN THE INITIATION AND PROGRESSION OF NEPHRON INJURY



Increase in single nephron glomerular filtration rate is mainly due to the vasoconstricting action of angiotensin II on the efferent arteriole, which consequently increases the filtration pressure. This leads to an increased glomerular capillary plasma flow and increased trans-capillary hydraulic pressure so that more plasma is filtered by each surviving nephron.

FIGURE 4 - ILLUSTRATION OF THE RELATIONSHIP BETWEEN RENAL INJURY, LOSS OF NEPHRONS, RENAL COMPENSATORY ADAPTATIONS, AND THE ULTIMATE PROGRESSION OF RENAL FAILURE



The compensatory changes maintain clinically stable disease until structural and functional damage exceeds a threshold beyond which progression of renal function and clinical signs of uremia occur. Chronic renal disease typically progresses to end-stage renal disease after a critical number of nephrons have been damaged.

Table 2 - International Renal Interest Society (IRIS) Classification of stages of renal disease and chronic renal failure in dogs

Stages	I	II	III	IV
Plasma Creatinine				
µmol/L	< 125	125 to 180	181 to 440	> 440
mg/dL	< 1.4	1.4 to 2.0	2.1 to 5.0	> 5.0

The four phases are:
(1) decreased renal reserve,
(2) renal insufficiency
(3) renal failure
(4) uremic syndrome.

Given the large reserve capacity of the kidney at least 60-70% of normal renal function must be lost before azotemia increases, although there may be some nephron hypertrophy during the first phase of decreased renal reserve. At this stage, the patient does not have any clinical symptoms although decreased urine concentrating ability may be noted. In renal insufficiency, up to 75% of the nephrons may be lost. There is mild azotemia, loss of urine concentrating ability and the patient becomes more susceptible to the effects of stresses such as large changes in fluid intake, protein and electrolytes. The patient may remain symptom-free if no overwhelming metabolic stress occurs.

In renal failure nephron loss may reach 90%. There is moderate to severe azotemia, anemia, decreased urine concentration ability and impaired ability to maintain electrolyte and acid base balance.

The pathogenesis of the uremic syndrome is complex and not fully understood. Many toxins are involved and no single compound is likely to explain the diversity of the uremic symptoms. Nitrogenous waste products of protein digestion and catabolism (e.g. urea, creatinine, ammonia, middle molecules, guanidine and its derivatives) accumulate when renal function is reduced and some of them contribute to many of the clinical consequences of uremic intoxication associate with chronic renal failure **(Table 3)**.

Table 3 - Examples of toxins implicated in the uremic syndrome

Oxalic acid	Dimethyl arginine
Parathyroid hormone	Amines
β-2 microglobulin	Phenols
Methylguanidine	Indoles
Guanidinosuccinic acid	Pseudouridine

3 - Clinical consequences of uremia

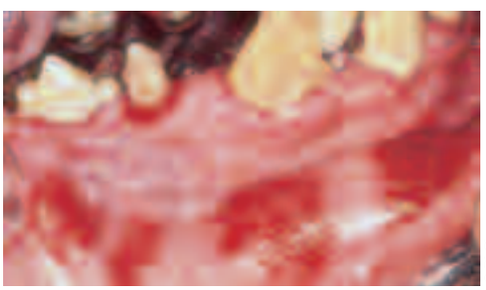
► Gastrointestinal consequences

Gastrointestinal intoxications including anorexia, nausea, vomiting, fetid breath, stomatitis, oral ulcerations **(Figure 5)**, tongue tip necrosis, gastritis, gastrointestinal ulcers, hematemesis, enterocolitis, diarrhea, intussusception and ileus are the most common and prominent clinical signs of uremia. These lesions and dysfunctions act singularly or in concert to induce gastrointestinal pathology.

Excess urea secreted in salivary and gastric juices is converted by urease producing bacteria to ammonia that directly damages the mucosa. Uremic toxins also injure the gastric mucus, mucosa, submucosa or vasculature, thereby reducing the protection afforded by the gastric mucosal barrier. Reduced renal clearance of gastrin leads to hypergastrinemia and stimulation of gastric acid production.

Increased diffusion of acid into the gastric wall induces inflammation, ulceration, and hemorrhage, in addition to perpetuating uremic toxin induced gastric injury. Vomiting occurs secondary to gastritis in addition to the direct effect of uremic toxins on the chemoreceptor trigger zone.

Figure 5 - *Oral lesions in uremic stomatitis/gingivitis*



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The Doppler technique and oscillometry are very common methods for detecting hypertension. Doppler is the recommended technique for cats. The oscillometric measurements in dogs can be unreliable due to differences in conformation, obesity or a thick coat (Stepien, 2001). The animal's adaptation to the environment is critical to the interpretation of arterial pressure measurements, as stress can induce erroneous results. Six to ten measurements are recommended.

► Neuromuscular consequences

The two major neurologic complications of uremia are uremic encephalopathy and neuropathy. Uremic encephalopathy is a term that reflects diffuse and non specific alterations of the cerebral cortex. The severity and progression of the neurological signs is generally correlated with the magnitude and progression of the azotemia. Typical signs include a progressive decline in alertness and awareness, dullness, lethargy, impaired mentation, altered behavior, confusion, stupor, tremors, ataxia, muscular cramps, fatigue, muscle weakness, seizures and coma. The neurological signs are due to the effects of uremic toxins, hyperparathyroidism, hypocalcemia, hypokalemia and hypertension.

► Cardiopulmonary consequences

Cardiopulmonary complications include hypertension, uremic cardiomyopathy, uremic pericarditis, pulmonary edema and uremic pneumonitis. Abnormalities in fluid, electrolyte and acid base balance may contribute to alterations in cardiac contractility and excitability. Azotemia and overhydration play a role in pericarditis, uremic cardiomyopathy and pulmonary edema. Hypertension arises secondary to a combination of activation of the renin-angiotensin aldosterone system, sodium retention, plasma volume expansion, activation of the sympathetic nervous system, decreased activity of vasodilatory substances, increased cardiac output, increased total peripheral vascular resistance and secondary hyperparathyroidism. Systemic hypertension predominately targets the kidneys (glomerulosclerosis), heart (left ventricular hypertrophy, myocardial ischemia), eyes (retinal detachment, hyphema, retinal hemorrhage) and brain (hypertensive encephalopathy, dementia, cerebrovascular hemorrhage). Uremic pneumonitis refers to the formation of a high protein pulmonary edema which is presumably a consequence of uremic toxins damaging alveoli and increasing capillary permeability.

► Ocular consequences

Common manifestations of advanced uremia include scleral and conjunctival injection and ocular pathology secondary to systemic hypertension. Opthalmoscopic findings include reduced pupillary light reflexes, papilledema, retinal arterial tortuosity, retinal hemorrhage, retinal detachment, hyphema, anterior uveitis and glaucoma. Ischemia and retinal degeneration result from sustained retinal arteriolar vasoconstriction which is an attempt to auto-regulate local blood flow in the face of sustained chronic hypertension.

► Metabolic and endocrine consequences

The kidney is responsible for the degradation of many peptide hormones and loss of this catabolic function can result in metabolic derangements caused by hormone excess. Deranged insulin metabolism may also contribute to hyperlipidemia. Other hormonal alterations include increased concentrations of gastrin, glucagon, growth hormone, prolactin and luteinizing hormone. Serum T4 concentrations are low and there is impairment in the conversion of T4 to T3 (euthyroid sick syndrome).

► Fluid, electrolyte and acid-base consequences

Metabolic acidosis is a frequent finding in renal disease and results primarily from the inability of the kidney to excrete hydrogen ions and regenerate bicarbonate. Chronic acidosis causes progressive bone demineralization, urinary calcium loss, hypokalemia and increases skeletal muscle protein catabolism which exacerbates azotemia.

Hyperphosphatemia is one of the most common regulatory derangements of CRF that arises secondary to reduced glomerular filtration of phosphorus. Hyperphosphatemia contributes to renal secondary hyperparathyroidism (see below), reduced calcitriol levels, soft tissue calcification, renal

osteodystrophy and hypocalcemia. Soft tissue mineralization develops as the calcium x phosphate product exceeds 60 (concentrations are expressed in mg/dL).The most commonly targeted organs include the gastric mucosa, bronchial walls, myocardium, endocardium, renal interstitium, glomeruli, lungs, and intercostal muscles. Renal mineralization will promote interstitial inflammation, fibrosis and progression of renal failure.

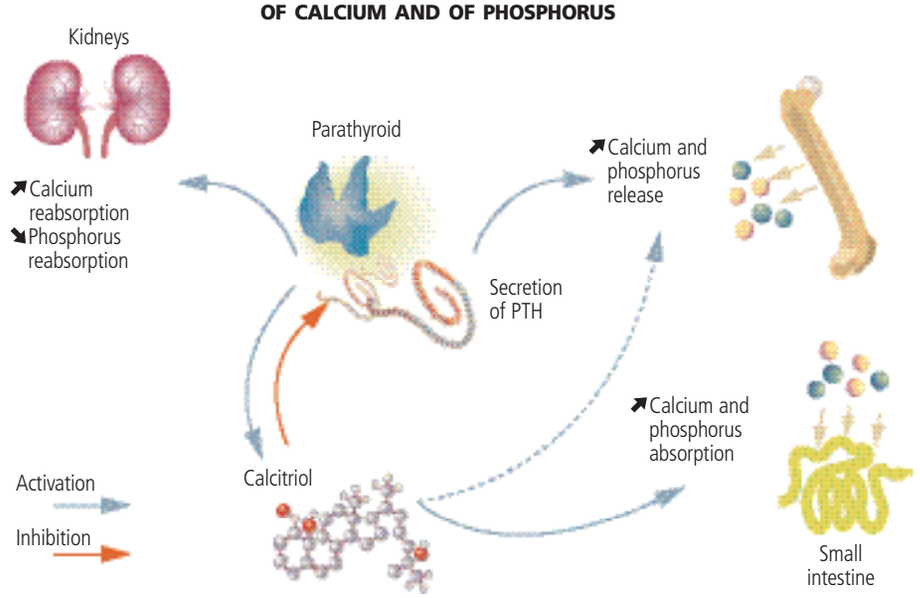
Hypokalemia is a common abnormality associated with chronic renal failure. The mechanism is unclear and includes excessive urinary potassium loss, inadequate dietary potassium intake, and acidifying diets. Hypokalemia causes generalized muscle weakness and pain which may present as cervical ventroflexion and a stiff, stilted gait. Hypokalemia also impairs protein synthesis, promotes weight loss, a poor hair coat and contributes to polyuria by decreasing the renal responsiveness to ADH. Chronic potassium depletion may indeed impair renal function by inducing a reversible, functional decline in GFR in addition to promoting renal injury by enhancing ammoniagenesis.

► Renal secondary hyperparathyroidism

Renal secondary hyperparathyroidism is a clinical syndrome that is characterized by increased secretion of parathyroid hormone (PTH). PTH secretion is stimulated by hypocalcemia and decreased plasma calcitriol concentrations. Hypocalcemia is a mass action (i.e. calcium x phosphate remains constant) consequence of renal retention of phosphate.

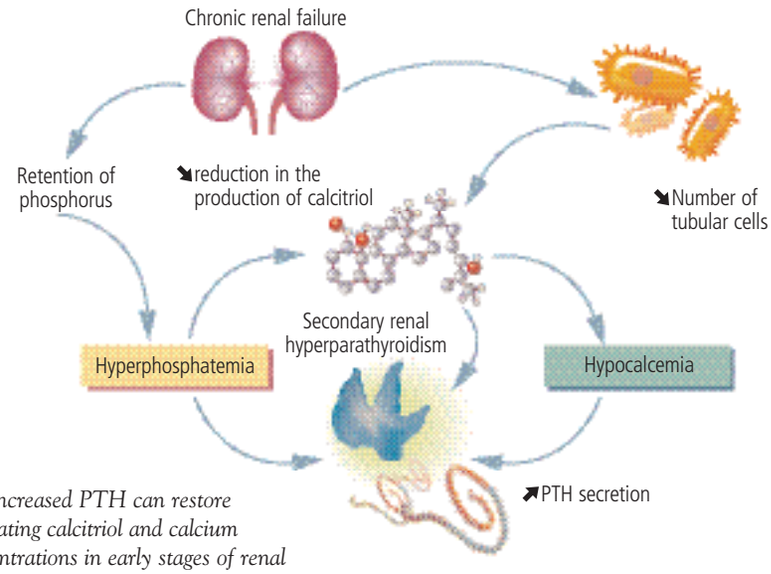
Calcitriol production is regulated at the level of the 1-α-hydroxylase enzyme in the kidney. Phosphate in excess and loss of functional renal mass result in a decrease in 1-α-hydroxylase activity and reduces the conversion of 25-dihydroxyvitamin D3 to 1,25-dihydroxyvitamin D3 (calcitriol). Calcitriol deficiency reduces the intestinal absorption of calcium, reduces the release of calcium and phosphate from bone, reduces renal reabsorption of calcium and phosphate and increases the synthesis and release of PTH (**Figures 6A and 6B**).

FIGURE 6A - INFLUENCE OF PTH ON THE METABOLISM OF CALCIUM AND OF PHOSPHORUS



This diagram emphasizes the role of calcitriol deficiency (due predominantly to phosphorus inhibition of calcitriol synthesis and to the loss of renal functional mass) in initiating and perpetuating excess levels of parathyroid hormone (PTH).

FIGURE 6B - MECHANISM OF DEVELOPMENT OF RENAL SECONDARY HYPERTHYROIDISM IN CRF



The increased PTH can restore circulating calcitriol and calcium concentrations in early stages of renal failure when enough proximal tubular cells remain to synthesize calcitriol.

Initially the increased PTH concentration activates the remaining 1-alpha hydroxylase enzyme with a compensatory increased in calcitriol concentrations. However, with disease progression stimulation of 1-α-hydroxylase becomes ineffectual and calcitriol concentrations remain low. Complications of renal secondary hyperparathyroidism include osteodystrophy, soft tissue calcification, skeletal decalcification, cystic bone lesions, bone pain and growth retardation. Osteodystrophy most commonly occurs in immature patients and is recognized by demineralization of the bones. The teeth become movable and the jaw can be bent or twisted without fracturing (rubber jaw). Facial distortion may occur secondary to connective tissue proliferation. PTH has also been implicated as a uremic toxin and may contribute to the progression of renal failure.

► Hematologic consequences

Normocytic normochromic non-regenerative anemia is the most common abnormality in uremia. The pathogenesis is multifactorial and includes inadequate production of erythropoietin by the diseased kidneys, reduced life span of red cells, nutritional deficiencies, uremic toxin induced inhibition of erythropoiesis and blood loss with consequent iron deficiency. Anemia will contribute to the clinical signs of lethargy and inappetance. Neutrophil function and cell mediated immunity is impaired in uremia, predisposing the uremic patient to infection. The specific causes of renal failure associated immunocompromise is not completely understood, although malnutrition, uremic toxins, PTH and vitamin D concentrations may be involved.

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The hydration state is evaluated by clinical examination, the measurement of hematocrit and total plasma proteins.

► Hemostatic consequences

Uremia is characterized by abnormal hemostasis manifested as petechiae, ecchymoses, bruising, bleeding from gum margins or venipuncture sites, epistaxis and gastrointestinal bleeding. The major hemostatic abnormality is a qualitative defect in platelet function which is manifest by prolongation of the bleeding time (indirectly allows evaluation of vascular contractility, platelet numbers, platelet function, and factor VIII complex function).

4 - Clinical presentation

The onset and spectrum of clinical and pathological events occurring in patients with CRF will vary depending on the nature, severity, duration and rate of progression of the renal disease in addition to the presence or absence of coexisting disease. Historical findings include anorexia, depression, weakness, lethargy, weight loss, halitosis, nausea, vomiting, diarrhea, melena, polyuria and polydipsia. Pale mucous membranes, dehydration, hypothermia, stomatitis, oral ulceration, dull dry hair coat and poor body condition may be noted on physical examination. Abdominal palpation reveals small irregular kidneys. Congenital and familial causes of CRF should be suspected on the basis of breed, family history, and age of onset of the renal disease **(Table 1)**. Some patients will present with polydipsia/polyuria as the only historical sign, while other patients may be recognized by isothenuria noted on routine geriatric or pre-anesthetic laboratory screening.

5 - Diagnostic evaluation

A thorough initial evaluation including complete blood count (CBC), biochemical profile, urine analysis, urine culture and blood pressure measurement is indicated to plan the appropriate conservative management. Abdominal radiographs and or abdominal ultrasound will complement the initial laboratory data base.

Laboratory findings consistent with renal failure include azotemia (increase in BUN, creatinine), hyperphosphatemia, mild to severe metabolic acidosis, hypo or hyperkalemia, hypo or hypercalcemia, anemia, hyperlipidemia, bleeding tendencies, isothenuria, proteinuria and hypertension **(Table 4)**. These biological signs are not necessarily present in a single dog.

TABLE 4 - LABORATORY FINDINGS IN CRF

- Azotemia
- Abnormal urine specific gravity
- Hyperphosphatemia
- Non-regenerative anemia (normochromic, normocytic)
- Hypokalemia
- Hypocalcemia (sometimes hypercalcemia)
- Hyperamylasemia
- Hyperlipasemia

► Azotemia

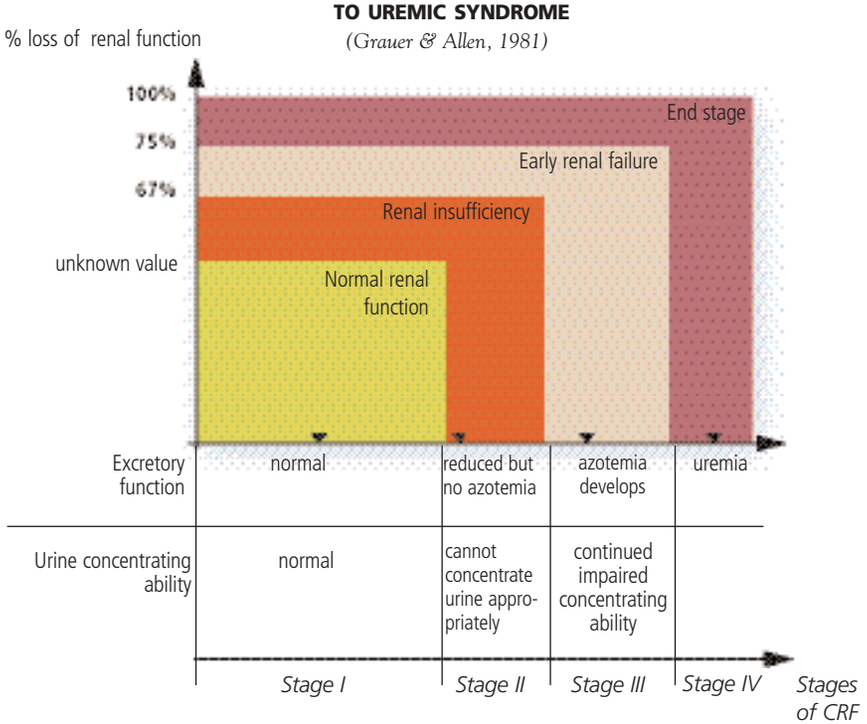
The identification of azotemia requires delineation of pre-renal azotemia, pre-renal azotemia complicating chronic renal failure, acute renal failure, acute renal failure complicating chronic renal failure, post renal azotemia and post renal azotemia complicating chronic renal failure from uncomplicated chronic end-stage renal disease. Each of these disparate azotemic conditions may appear clinically quite similar, but rapid identification is required to formulate a therapeutic plan and guide prognosis **(Figure 7)**.

► Proteinuria

Dogs with CRF may or may not have proteinuria. Urine strip or stick tests used to screen for proteinuria detect mainly albumin (lower limit of detection ~50 mg/L) and not globulin. False positive results can occur if samples are very alkaline or contaminated by quaternary ammonium compounds.

FIGURE 7 - CONSEQUENCES OF RENAL DISEASE AND ITS PROGRESSION TO UREMIC SYNDROME

(Grauer & Allen, 1981)



The diagnosis of chronic renal failure is relatively straightforward. It is, however, more difficult to identify early renal disease prior to the development of clinical signs or laboratory abnormalities.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The semi quantitative results from dipstick tests must also be compared with the urinary concentration.

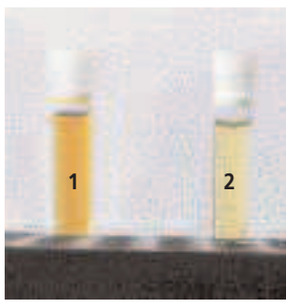
2+ proteinuria represents a more substantial protein loss if urine is dilute (USG 1.010) than if it is 4 times more concentrated (USG 1.040) **(Figure 8)**. The same principle lies behind use of urine protein to creatinine ratio (UPCR) to evaluate severity of proteinuria.

Sustained, severe proteinuria (typically 3 or 4+) strongly suggests glomerular damage, but only if hematuria and urinogenital inflammation are excluded by the absence of erythrocytes and leukocytes in urine sediment. If glomerular protein loss is suspected, proteinuria should be confirmed using the semiquantitative sulphosalicylic acid turbidometric test, which is simple enough to do in the practice laboratory, or urine protein should be quantified by a more precise method in an external laboratory. Not all proteinurias are pathological and pathological proteinurias can arise from non-renal lesions, so caution is advisable before attributing proteinuria to renal disease.

► Microalbuminuria

Microalbuminuria (i.e. urine albumin concentration < 1 mg/dL) has been suggested to be an early indicator of renal disease. However, recent studies have suggested that 56% of dogs that are microalbuminuric have systemic inflammatory, infectious or neoplastic disease. Therefore, the specificity of microalbuminuria for the diagnosis of early renal disease is not fully known.

FIGURE 8 - INTERPRETATION OF PROTEINURIA BASED ON URINARY DENSITY



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Sample	1	2
USG	1.040	1.010
Proteinuria	++	++
Conclusion	uncertain	meaningful

If urine specific gravity is low, proteinuria is more significant.

► Glomerular filtration rate

The best indicator of renal function is the glomerular filtration rate (GFR). GFR is assessed by calculating the clearance of a solute by the kidney. Urinary inulin clearance is considered the gold standard reference method for measuring GFR. Unfortunately the technique of inulin clearance is labor intensive and best utilized in a research setting. The plasma exogenous creatinine clearance test (PECCT) involves a single injection of creatinine with timed plasma samples to detect plasma clearance of creatinine **(Figure 9)**. The test has been validated in the dog and provides a clinically useful tool to assess renal function *(Watson & al, 2002)*.

6 - Treatment

Tailored supportive medical therapy has been the mainstay of management for chronic renal failure for decades. The goals of medical management are to:
(1) reduce the renal work load
(2) alleviate the clinical signs and biological consequences of the uremic intoxications
(3) minimize disturbances in fluid, electrolyte, vitamin, mineral and acid base balance
(4) slow progression of the disease.

Therapy should not necessarily be expected to reverse or eliminate the renal lesions responsible for the CRF. However, when CRF progresses due to an evolving disease (pyelonephritis, chronic urinary obstruction, nephrolithiasis, renal lymphoma, some immune-mediated diseases), rapid identification and appropriate treatment of the disorder may halt or slow progression of the renal disease.

Chronic renal failure is progressive and dynamic, hence, serial clinical and laboratory assessment of the patient and modification of the therapy in response to changes in the patient's condition

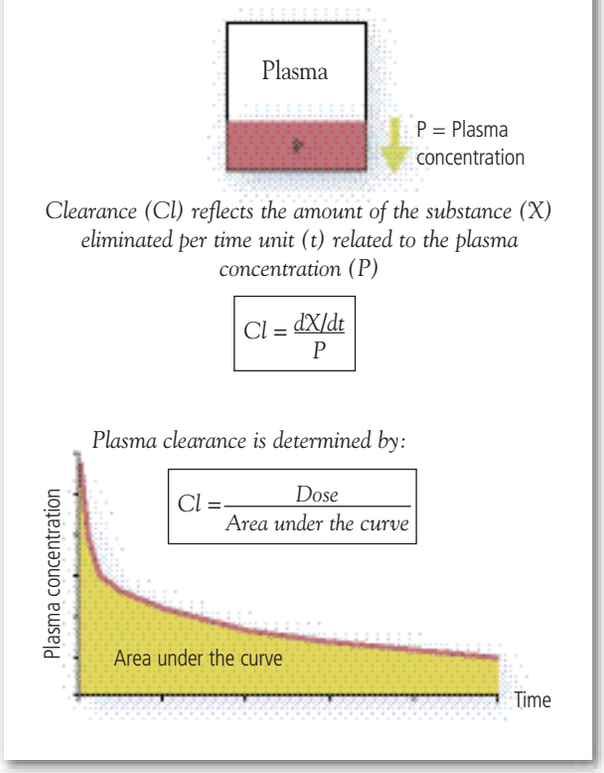
is integral to successful therapy. Select therapeutic agents used in the management of chronic renal failure are listed in **Table 5**.

Many renal failure patients are exquisitely sensitive to the gastrointestinal side-effects of prescribed drugs. The clinician also needs to consider the potential adverse effects of "poly pharmacy" and drug interactions. Furthermore, many medications undergo renal excretion and the dosages will need to be modified to account for delayed clearance and the longer half life the drug. Ideally dosage adjustments should be made according to changes in drug clearance which may be estimated by measuring creatinine clearance. The drug dose is then adjusted according to the percent reduction in creatinine clearance (i.e. the ratio of the patients' creatinine clearance to normal creatinine clearance). For example if the normal dose is 10 mg/kg q 8 hrs and the creatinine clearance is 25% of normal, the dose should be altered to 2.5 mg/kg q 8 hrs or 10 mg/kg q 32 hours. For the owner's compliance, decreasing the dose is often better accepted than stretching the administration interval (although it might be necessary for specific drugs, i.e. concentration-dependent antibiotics). The dosage regimen should be adjusted for drugs mainly excreted (>80%) unchanged by the kidney, and for drugs which are not totally excreted by the kidney and have a low therapeutic index. e.g.:

- Gentamicin: renal excretion and low therapeutic index; prescription not recommended but sometimes necessary in case of multiresistant infections
- Carboplatin: antineoplastic agent with a very low therapeutic index and renal excretion.

Although the relationship between serum creatinine concentration and creatinine clearance is not linear, creatinine clearance evolution can be estimated by the modifications of the serum creatinine concentration measured in standardized conditions for stages I and II of CRF.

FIGURE 9 - PRINCIPLE OF PLASMA CLEARANCE



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Recommendations regarding dietary therapy and other components of conservative medical management need to be individualized to patient needs based on clinical and laboratory findings.

► Anemia

Treatment of anemia encompasses administration of androgens, blood transfusions or erythropoietin replacement therapy with recombinant human erythropoietin. In addition, every attempt should be made to minimize blood loss by venipuncture, gastrointestinal ulcerations, gastrointestinal parasites and uremic bleeding. Androgen therapy is not particularly effective in increasing the hematocrit, although improvements in lean body mass and attitude have been reported *(Cowan et al, 1997)*. Blood transfusions will temporarily correct the anemia and are useful when rapid correction of the anemia is required prior to anesthesia or surgery. Repeated transfusions have been used to support the anemia of chronic renal failure but they are not recommended due to the increased risk of transfusion reaction.

Effective erythropoiesis is readily obtained by the administration of recombinant human erythropoietin *(Cowgill et al, 1995; 1998)*. A dose dependent response in hematocrit can be seen within the first week of therapy, however 2 to 8 weeks of therapy is generally required to normalize the hematocrit. Erythropoietin therapy is initiated at 100 U/kg subcutaneously three times weekly with weekly monitoring of the hematocrit. Once the hematocrit is 35-40%, the dosing interval is decreased to twice weekly therapy. The lowest dose/frequency that maintains the hematocrit in the normal range should be identified by monitoring the hematocrit. Side effects of erythropoietin therapy include polycythemia, vomiting, seizures, pain at the injection site, fever and hypertension.

Table 5 - Therapeutic agents used in the management of chronic renal failure*

Uremic Complication		Conventional Dose
Gastrointestinal	Chlorhexidine (solution 0.1-0.2%) Cimetidine† Ranitidine† Famotidine† Omeprazole Sucralfate† Misoprostol Metoclopramide† Chlorpromazine Acepromazine Cisapride	Oral rinse q6-8h 5-10 mg/kg PO, IM, IV q 6-8h 0.5-2.0 mg/kg PO, IV q8-12h 0.5-1.0 mg/kg PO, IM, IV q12-24h 0.5-1.0 mg/kg PO q24h 0.5-1 g PO q6-8h 1-5 mg/kg PO q6-12h 0.1-0.5 mg/kg PO, IM, SC q6-8h 0.2-0.5 mg/kg PO, IM, SC q6-8h 0.01-0.05 mg/kg PO IM, SC q8-12h 0.1-0.5 mg/kg PO q8-12h
Anemia	Erythropoietin Ferrous sulfate Stanozolol	100 U/kg SC 1-3 times per week 100-300 mg/day PO 1-4 mg PO q4h
Metabolic Acidosis	Sodium Bicarbonate Potassium Citrate	8-12 mg/kg PO q8-12h 40-60 mg/kg PO q8-12h
Hypokalemia	Potassium Gluconate Potassium Citrate	0.5 mEq/kg PO q12-24h 40-60 mg/kg PO q8-12h
Hyperphosphatemia	Aluminium hydroxide/carbonate/oxide Calcium acetate Calcium carbonate	30-90 mg/kg PO q12-24h 60-90 mg/kg PO q12-24h 90-150 mg/kg PO q12-24h
Renal Osteodystrophy	Calcitriol	1.5-6.0 ng/kg PO q24h
Hypertension	Amlodipine Benazepril Enalapril Imidapril Ramipril Propranolol It is recommended that treatment with antihypertensive agents be commenced with the lowest dose and increased gradually	0.05-0.3 mg/kg PO q12-24 h 0.25-0.50 mg/kg PO q 24 h 0.5 mg/kg PO q12-24 h 0.25 mg/kg PO q24 h 0.125-0.250 mg/kg PO q24 h 0.1-1 mg/kg PO q8-12 h
Proteinuria	Angiotensin conversion enzyme inhibitors (Benazepril, Enalapril, Imidapril and Ramipril)	Regimen: see Hypertension

** Most of these drugs have not been approved for use in the dog.*
† Agent undergoes renal excretion and the dosage must be adjusted accordingly to prevent toxicity.

Some dogs will develop erythropoietin antibodies that effectively neutralize endogenous and exogenous erythropoietin. These patients are identified by either refractory anemia or the development of anemia weeks to months following institution of therapy. Diagnosis requires elimination of other causes of anemia and bone marrow assessment of myeloid to erythroid ratios (M:E ratio > 10). Treatment requires cessation of recombinant erythropoietin therapy. After therapy is stopped, the antibody concentrations will decline and the pretreatment levels of endogenous erythropoietin and hematocrit will be obtained. Blood transfusions may be required until the hematocrit stabilizes. The future availability of canine recombinant erythropoietin will eliminate the development of antibodies to human recombinant erythropoietin *(Randolph et al, 2004)*.

A risk-benefit assessment is necessary prior to institution of human recombinant erythropoietin. Erythropoietin therapy is generally recommended when the packed cell volume is less than 25%. At this stage, the benefits of improved clinical status with increases in appetite, body weight, energy level and sociability appear to out weigh the risks of antibody formation. Iron deficiency secondary to gastrointestinal blood loss generally accompanies CRF. Iron status can be assessed by serum iron, transferrin, ferritin, or total iron binding capacity (TIBC). Oral supplementation with iron sulfate (100 to 300 mg/day) is recommended, particularly in patients starting erythropoietin replacement therapy. Intramuscular iron dextrans can be used, however, the risk of iron overload is increased. Side effects of iron therapy include gastrointestinal disturbances (diarrhea).

Two to eight weeks are generally needed to normalize the hematocrit during erythropoietin replacement therapy.

► Acidosis

Alkalinizing agents (potassium citrate, sodium bicarbonate, calcium carbonate) should be initiated when the TCO_2 or bicarbonate concentration is less than 18 mmol/L. Alkalinization therapy will improve the clinical signs of anorexia, lethargy, nausea, vomiting, muscle weakness and weight loss in addition to preventing the catabolic effects of metabolic acidosis on protein metabolism.

Sodium bicarbonate is the most commonly utilized alkalinizing agent but it will contribute to the sodium load of the patient and may need to be avoided in patients with hypertension or cardiac insufficiency. Calcium carbonate should be used with caution in hyperphosphatemic patients as the increased dietary calcium may precipitate soft tissue mineralization. Potassium citrate provides the additional advantage of supplying potassium and may be attractive for patients with both hypokalemia and metabolic acidosis. The dose of alkalinizing agent needs to be individualized for each patient and requires routine monitoring of acid base status.

► Fluid balance

Compensatory polydipsia balances excessive fluid loss associated with polyuria, however, some patients will fail to consume sufficient water to prevent volume depletion. In these cases, cautious fluid supplementation should be used to prevent dehydration and attendant vascular depletion. Maintenance fluids (eg plasmalyte 56, plasmalyte M, Normosol M) can be administered subcutaneously. Chronic administration of lactated ringers 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.

► Hypokalemia

Potassium supplementation is indicated when the serum potassium concentration is less than 4 mmol/L and may be achieved by oral potassium gluconate or potassium citrate supplementation. Muscle weakness typically resolves within five days of institution of therapy. Side effects include gastrointestinal irritation, ulceration, nausea and vomiting. Potassium dosage should be adjusted by monitoring the serum potassium concentration and response to supplementation.

► Antihypertensive therapy

Antihypertensive therapy is indicated upon the repeatable demonstration of systemic hypertension. The clinical diagnosis of hypertension should never be made on the basis of a single blood pressure measurement.

IRIS *(http://www.iris-kidney.com/)* considers that an animal with CRF is hypertensive when its systolic blood pressure exceeds 180 mm Hg. If the systolic blood pressure is between 150 and 179 mm Hg, and if there is some extrarenal evidence of hypertension (eg. retinopathy, left ventricular hypertrophy), the animal is also considered hypertensive. Otherwise, the case is borderline and re-evaluation of blood pressure is recommended within 2 months.

The goal of antihypertensive therapy is to lower the blood pressure to the normal range. The initial selection of antihypertensive agent will be guided by the presence or absence of clinical signs of hypertension, i.e. signs of retinal detachment and hemorrhage dictate a more aggressive therapeutic approach to lower systemic blood pressure and restore vision in a timely fashion. Repeated blood pressure determinations will be required to modify and guide a step wide selection of antihypertensive drugs.

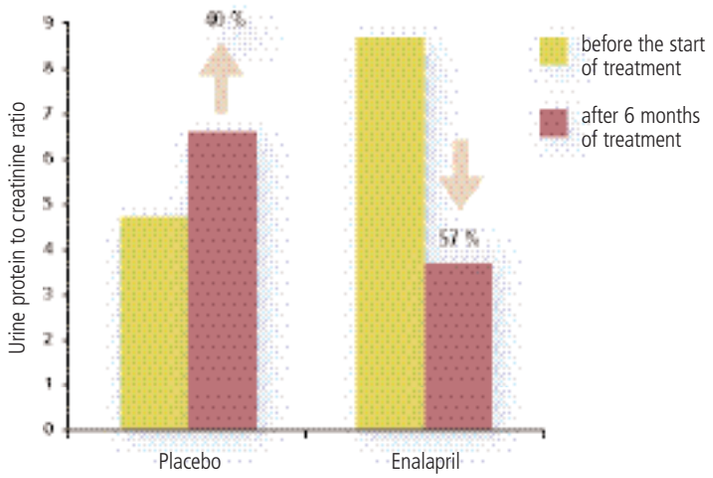
Antihypertensive drugs include diuretics, adrenergic antagonists (propanolol), ACE-inhibitors, calcium channel blockers (amlodipine), and vasodilators. Selection of the appropriate therapeutic agent should be made on the basis of appropriate hypertensive control, expense, and side-effects. The most commonly recommanded treatment relies on the association between ACE-inhibitors and amlodipine. With ACE-inhibitors alone, blood pressure can be decreased by 30 mm Hg.

The blood pressure should be rechecked within 2 weeks following institution of therapy. If there has been no response consider:
(1) increasing the dose of the current drug
(2) change to a different class of drug
(3) adding an additional drug to the therapeutic regime.

Long term monitoring of blood pressure is required as frequent dosage adjustments may be required and some patients will become refractory to the initial therapy necessitating therapeutic modification.

ACE inhibitors have been used in normotensive dogs with glomerular disease. Enalapril has been shown to significantly reduce proteinuria and improve the clinical signs in dogs with naturally occurring glomerulonephritis **(Figure 10)** *(Grauer & al, 2000)*. Proteinuria is not only a biological sign of renal injury, but also an aggravation factor of CRF. Reducing proteinuria is hence a therapeutic goal. Only the ACE inhibitors have a demonstrable antiproteinuria effect in dogs. Ace inhibitors can also slow down the progression of CRF *(Lefebre & Toutain, 2004)*.

FIGURE 10 - MEAN VALUE OF URINE PROTEIN TO CREATININE RATIO IN DOGS TREATED WITH PLACEBO OR ENALAPRIL
(Grauer et al, 2000)



Proteinuria increased in dogs receiving the placebo, whereas it decreased in dogs receiving enalapril.

► Hyperphosphatemia

Minimizing hyperphosphatemia will limit renal secondary hyperparathyroidism, renal osteodystrophy, soft tissue calcification and the progression of renal failure. The restriction of dietary intake and oral administration of intestinal phosphorus binding agents **(Table 6)** normalizes serum phosphate concentrations. 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.

TABLE 6 - SUMMARY OF PHOSPHATE BINDING AGENTS CLASSIFICATION

Products containing aluminum: - aluminum hydroxide - aluminum carbonate - aluminum oxide	Prolonged use of products containing aluminum can predispose to aluminum toxicity (although not reported in dogs)
Products based on calcium: - acetate - carbonate - citrate*	Products based on calcium may favor hypercalcemia and are contra-indicated in dogs with serum concentrations in excess of the reference range
Sevelamer	Polymer used in humans as an intestinal phosphate binding agent. It is not absorbed and does not predispose to hypercalcemia. Nevertheless, there are no data on its use in dogs

* *Calcium citrate increases aluminum absorption in the intestine and must not be used in conjunction with phosphate binding agents containing aluminum.*

► Calcitriol replacement therapy

Calcitriol replacement therapy can limit renal secondary hyperparathyroidism. However supplementation is required for life *(Nagode et al, 1996)*. Therapy mandates serial measurement of serum calcium and phosphorus levels to avoid hypercalcemia and soft tissue mineralization. The risk of hypercalcemia is heightened by the concurrent administration of calcium based intestinal phosphate binding agents. Calcitriol should not be given with meals because it enhances intestinal calcium and phosphate absorption. In addition, the serum phosphorus concentration must be within the normal range prior to initiating therapy to minimize the risk of soft tissue calcification. The serum PTH concentration should return to normal or almost normal within 1 to 2 weeks of initiating therapy.

A recent study *(Gerber et al, 2003)* indicated that calcitriol concentration was within reference range for most dogs with renal failure. These results suggest that calcitriol replacement would not be required in such patients.

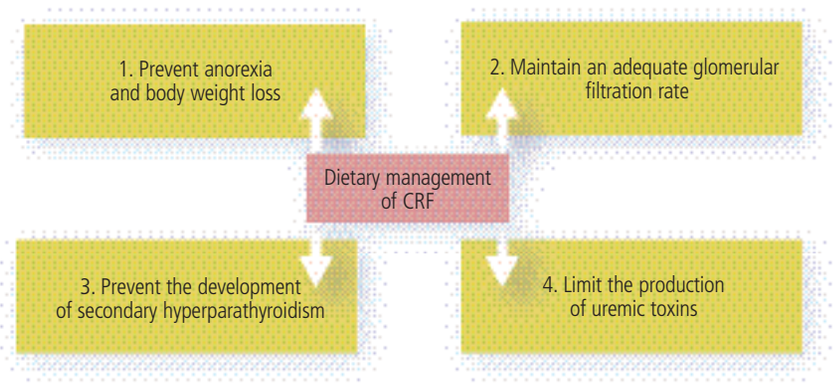
► Gastrointestinal disorders

Antiemetics such as metoclopramide or phenothiazine derivatives can be used to suppress central vomiting centers. Histamine receptor blocking drugs (cimetidine, ranitidine, famotidine) or proton pump blockers (omeprazole) in combination with gastrointestinal protectorant agents such as sucralfate or misoprostol may be used to prevent gastrointestinal ulceration.

7 - Nutritional management

Dietary therapy has remained the cornerstone of management of chronic renal failure for decades. The goals of dietary modification are to (1) meet the patient's nutrient and energy requirements, (2) alleviate clinical signs and consequences of the uremic intoxication, (3) minimize disturbances in fluid, electrolyte, vitamin, mineral and acid base balance, and (4) slow progression of the renal failure **(Figure 11)**.

FIGURE 11 - DIETARY MANAGEMENT OF CRF: 4 MAIN GOALS



► Energy

Sufficient energy needs to be provided to prevent endogenous protein catabolism which will result in malnutrition and exacerbation of azotemia. Although the energy requirements of dogs with chronic renal failure are unknown, they are presumed to be similar to healthy dogs. Dogs should be fed 132 kcal x body weight $(kg)^{0.75}$ per day. Determination of caloric requirements may vary by as much as 25%. Hence energy intake should be individualized to the patient needs based on serial determinations of body weight and body condition score. Carbohydrate and fat provide the non-protein sources of energy in the diet. Diets designed for the management of chronic renal failure are typically formulated with a high fat content because fat provides approximately twice the energy per gram of carbohydrate. Therefore fat increases the energy density of the diet which allows the patient to obtain its nutritional requirements from a smaller volume of food. A smaller volume of food minimizes gastric distention, which reduces the likelihood of nausea and vomiting.

► Protein

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 *(Polzin et al, 1983)*, while protein malnutrition is strongly correlated with morbidity and mortality.

The rationale for formulating a diet that contains a reduced quantity of high quality protein is based on the premise that controlled reduction of non essential amino-acids results in decreased production of nitrogenous wastes with consequent amelioration or elimination of clinical signs, even though renal function remain essentially unchanged. Indeed, studies have shown that modifying dietary protein intake can reduce blood urea nitrogen and provide clinical benefits to dogs with chronic renal failure *(Polzin et al, 1983; Finco et al, 1985; Polzin & Osborne, 1988; Polzin et al, 1983; Leibetseder & Neufeld, 1991; Jacob et al, 2002)*. Modified protein diets also moderate the magnitude of polyuria and polydipsia because less solute is delivered to the kidneys in the form of nitrogenous waste products. The magnitude of anemia may also be reduced, as nitrogenous waste

products are incriminated in hemolysis, shortened red blood cell survival and blood loss by gastrointestinal ulcerations and impaired platelet function.

Protein restriction has been demonstrated to slow the rate of progression of renal disease in rats and people. It is less certain if protein restriction alters progression of renal failure in dogs *(Finco et al, 1985; 1992a; 1992b; 1994; 1999; Robertson et al, 1986; Polzin et al, 1988)*. 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 & al, 1990; 1991a)*. Although protein moderation has been clearly demonstrated to improve the clinical status of the uremic patient, it is less clear what effect protein moderation has on progression of renal disease.

The goal of dietary protein restriction is to reduce the plasma urea as much as possible whilst avoiding protein malnutrition. Although urea is not a major uremic toxin it is regarded as an index for all nitrogenous wastes, hence therapies designed to reduce urea concentration are presumed to reduce other uremic toxins and usually correlate with clinical improvement (*Leibetseder & Neufeld, 1991; Hansen et al, 1992; Jacob et al, 2002)*. Urea concentration may be influenced by dietary protein intake, dehydration, catabolism, gastrointestinal bleeding, sepsis, and drug administration (glucocorticoids, tetracyclines). Most pets have minimal clinical signs when the urea is less than 28 mmol/L or 1.7 g/L (BUN < 80 mg/dL) **(Table 7)**.

TABLE 7 - CONVERSION TABLE BETWEEN BUN AND PLASMA UREA

BUN* (mg/dL)	10	20	30	40	50	60	80	100	120	140
Plasma urea (mmol/L)	3.6	7.1	10.7	14.2	17.8	21.4	28.5	35.6	42.7	65.1
Plasma urea (g/L)	0.2	0.4	0.6	0.8	1.0	1.2	1.7	2.1	2.5	3.9

**BUN is largely used in the US, while urea is generally used in Europe.*
BUN x 0.356 = plasma urea (mmol/L) and 1 mmol urea = 60 mg urea.

The minimal dietary protein requirements for dogs with chronic renal failure are not known, but are presumed to be similar to the minimal protein requirements of normal dogs, i.e. 1.33 g/kg/day (2.62 g/kg $BW^{0.75}$ or 20 g/1000 kcal ME according to NRC 2006). However, this degree of restriction is necessary only in animals with profound renal failure, and more liberal prescriptions can be fed to dogs with greater renal function. Every patient symptomatic for chronic renal failure should benefit from a protein restricted diet. Most renal dry diets contain between 12 and 18% proteins, i.e. 30-45 g/1000 kcal).

The dietary protein should be adjusted to minimize excesses in azotemia while simultaneously avoiding excessive restriction of dietary protein because of the risk of protein malnutrition. If evidence of protein malnutrition occurs (hypoalbuminemia, anemia, weight loss or loss of body tissue 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.

Owner dietary compliance can be checked by calculating the BUN:Creatinine ratio (BUN and creatinine are expressed in mg/dl). On a normal diet it will be around 25 whereas on a restricted protein diet it will be around 10. A BUN:Creatinine ratio greater than 30 is usually associated with gastrointestinal bleeding, dehydration or sepsis.

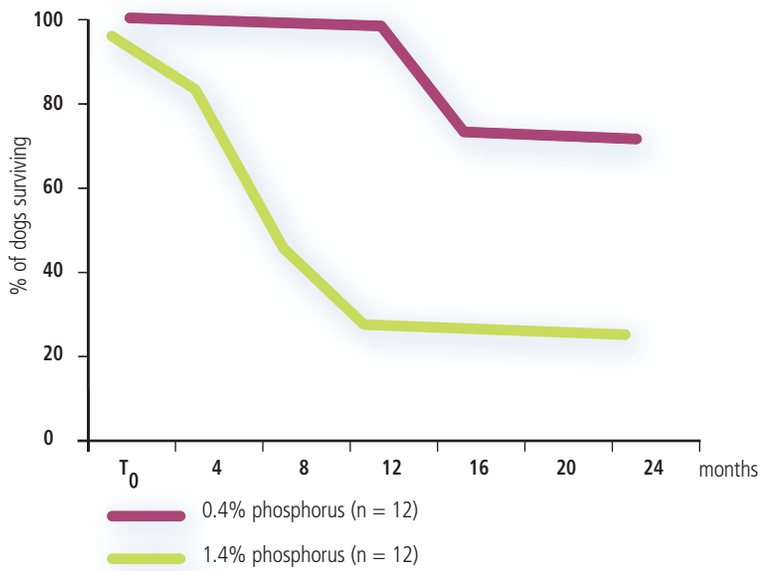
► Vitamins, minerals and electrolytes

> Phosphorus

Phosphate retention and hyperphosphatemia occur early in the course of renal disease and play a primary role in the genesis and progression of renal secondary hyperparathyroidism, renal osteodystrophy, relative or absolute deficiency of 1,25-dihydroxyvitamin D, and soft tissue calcification. By minimizing hyperphosphatemia, secondary hyperparathyroidism and its sequellae can be prevented. In addition, dietary phosphorus restriction has been shown to slow the progression of renal failure in dogs *(Brown et al, 1991b)*.

FIGURE 12 - INFLUENCE OF DIETARY PHOSPHORUS RESTRICTION ON LIFE EXPECTANCY OF DOGS WITH CHRONIC RENAL FAILURE

(Finco et al, 1992a)



After 2 years, 75% of the dogs receiving the low phosphorus diet were still alive, but only 33% in the group receiving the high-phosphorus diet were alive.

In one study of dogs with surgically induced reduced renal function, dogs fed a low phosphorus diet (0.44% DM) had a 75% survival versus a 33% survival in dogs fed a high phosphorus diet (1.44% DM) *(Finco et al, 1991b)*. Renal function also deteriorated more rapidly in the high phosphorus group **(Figure 12)**.

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 or prevention of secondary hyperparathyroidism.

The goal of therapy is to normalize serum phosphate concentration. This may be achieved by limiting dietary phosphate intake. If normophosphatemia can not been accomplished within 2-4 weeks of implementing dietary phosphate restriction, intestinal phosphate binders should be added to the treatment plan. These agents should be administered with the diet.

> Calcium

Dietary calcium is less important than phosphate in chronic renal failure and hypo, normo, or hypercalcemia may be observed. It has been recommended that the total calcium x phosphorus (expressed in mg/dL) product should not exceed 60. This may promote further soft tissue calcification and lead to progression of renal damage. For example, if the calcium concentration is 12 mg/dL and the phosphate concentration is 8 mg/dL, then the calcium x phosphate product is 12x8 = 96, which exceeds 60. Hence calcium supplementation needs to be individualized and adjusted according to response in terms of measured total blood calcium.

> Sodium

Hypertension is common in dogs with CRF *(Jacob et al, 2003)*. Furthermore, hypertension has been implicated as a factor that contributes to the progression of renal failure. Dogs with naturally occurring chronic renal 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 et al, 2003)*. Furthermore, the risk of developing a uremic crisis and of dying increased significantly as systolic blood pressure increased.

Sodium restriction has been recommended to alleviate hypertension associated with failure of the kidneys to excrete sodium. However, altering sodium intake from 0.5 to 3.25 g Na/1000 kcal did not influence development of hypertension or affect glomerular filtration rate in dogs with surgically induced renal reduction *(Greco et al, 1994a; 1994b)*. Therefore the ideal dietary sodium concentrations for dogs with chronic renal failure are not yet clearly defined. Current recommendations are normal to mildly restricted sodium diets. The capacity to adjust sodium excretion rapidly in response to changes in intake becomes severely impaired as renal failure progresses. If sodium intake is rapidly reduced, dehydration and volume contraction may occur with the potential of precipitating a renal crisis. Hence, a gradual change from the pet's previous diet to the salt restricted diet is recommended.

When an ACE-inhibitor is prescribed in a dog receiving a low sodium diet, it is recommended to check the arterial pressure and the renal function during the first few days of treatment.

> Potassium

Potassium deficiency has been identified in some dogs with chronic renal failure. Potassium status should be monitored and intake adjusted accordingly with oral potassium gluconate on an individual basis.

> Vitamins

Water-soluble vitamins are excreted in urine and deficiency may develop due to polyuria associated with chronic renal failure. These losses may be a contributing cause of anorexia and replacement of the losses may be beneficial in correcting or preventing anorexia. Commercially available renal failure diets contain additional amounts of water-soluble vitamins and further supplementation is not required.

Renal excretion of vitamin A is reduced in people with chronic renal failure. A recent study reported that dogs with naturally occurring renal disease had higher plasma concentrations of retinol compared to healthy dogs *(Raila et al, 2003)*. Therefore, it appears prudent to avoid supplements containing vitamin A.

► Acid base balance

The kidneys are central to the maintenance of acid base balance. As renal function declines, the capacity to excrete hydrogen ions and reabsorb bicarbonate ions is reduced and metabolic acidosis ensues. Metabolic acidosis increases renal ammoniagenesis which induces tubular inflammation and lesions due to complement activation, contributing to the progression of renal failure.

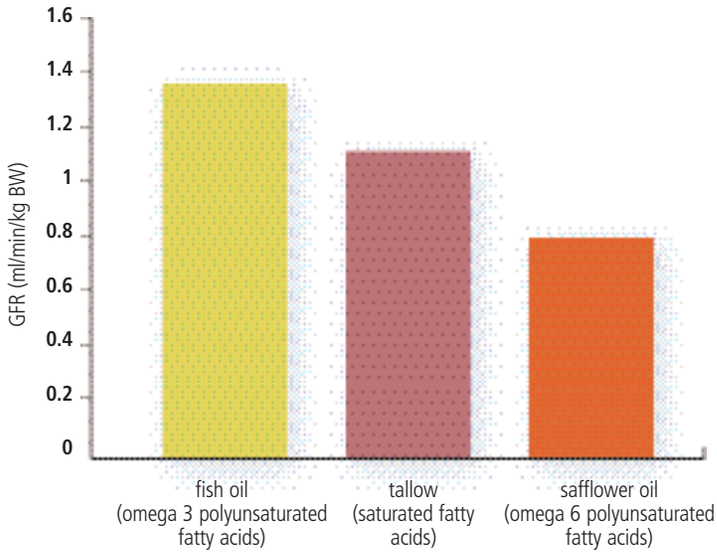
In addition, metabolic acidosis increases catabolism and degradation of skeletal muscle protein, disrupts intracellular metabolism, promotes dissolution of bone mineral exacerbating azotemia, loss of lean body mass and renal osteodystrophy. Dietary protein restriction results in the consumption of reduce quantities of protein-derived acid precursors, however, supplementation with additional alkalinizing agents such as sodium bicarbonate, calcium carbonate or potassium citrate may be required.

► Omega 3 & 6 fatty acids

Long chain ω-3 fatty acids (EPA-DHA) compete with arachidonic acid and alter eicosanoid, thromboxane and leukotriene production *(Bauer et al, 1999)*. Remnant kidney studies in dogs have reported that long chain ω-3 fatty acid supplementation (menhaden fish oil) reduces inflammation, lowers systemic arterial pressure, alters plasma lipid concentrations and preserves renal function **(Figure 13)** *(Brown et al, 1996; 1998a; 1998b; 2000)*. The efficacy of shorter chain ω-3 fatty acids such as those found in linseed oil, are not yet known.

FIGURE 13 - INFLUENCE OF FEEDING DIFFERENT DIETARY FATTY ACIDS OVER 20 MONTHS ON GLOMERULAR FILTRATION RATE IN 3 GROUPS OF DOGS SUFFERING FROM CRF

(Brown et al, 1996)



Compared to a diet consisting of mostly omega 6 fatty acids, a diet with a high fish oil content appears to improve GFR in the long term whilst minimizing the development of glomerulosclerosis

Omega 6 fatty acids (safflower oil) appear to be detrimental in dogs with naturally occurring renal disease by acutely increasing glomerular filtration rate *(Bauer et al 1997)*.

Some commercially available diets have an adjusted ω-6: ω-3 ratio however, rather than focusing on ratios, the absolute concentrations of specific omega-3 fatty acids would be more appropriate. Such studies have not yet been reported.

► Fiber

Fermentable fiber is a recent addition to the nutritional management of CRF. It is hypothesized that the fermentable fiber provides a source of carbohydrate for gastrointestinal bacteria which consequently utilize blood urea as a source of nitrogen for growth. The increase in bacterial cell mass increases fecal nitrogen excretion and has been suggested to decrease the blood urea nitrogen concentration and reduce the need for protein restriction. However, the major concern with this concept is that unlike BUN, the classical uremic toxins (middle-molecules) are too large in molecular size to readily cross membrane barriers. As a consequence, it is highly unlikely that these toxins are reduced by bacterial utilization of ammonia. Furthermore, studies to document these changes have not yet been reported. As a consequence, widespread application of fermentable fiber as a nitrogen trap cannot be recommended at this time.

However, even moderate renal disease alters duodenojejunal motility and decreases colonic transit time in dogs *(Lefebvre et al, 2001)*. Therefore, dietary fiber may be beneficial for improving gastrointestinal health and motility.

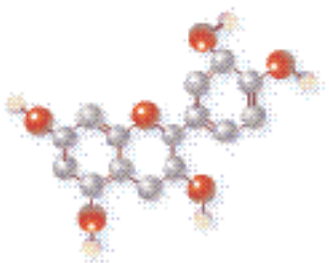
► Antioxidants

Endogenous oxidative damage to proteins, lipids and DNA is thought to play an important role in the progression of renal disease in humans *(Locatelli et al, 2003; Cochrane et al, 2003)*.

Nutrients such as **vitamin E, vitamin C, taurine, carotenoids and flavanols** are effective antioxidants that trap free radical species. Humans with chronic renal disease have been shown to have lower concentrations of vitamin E and vitamin C, and high concentrations of markers of lipid peroxidation *(Jackson et al, 1995)*. These studies suggest that humans with chronic renal disease have oxidative stress. Studies in rats have suggested that supplementation with vitamin E may modulate tubulointerstitial injury and glomerulosclerosis, suggesting that vitamin E may slow progression of renal damage *(Hahn et al, 1998; 1999)*. One study in children with focal segmental glomerulosclerosis reported that vitamin E supplementation decreased proteinuria *(Tahzib et al, 1999)*. There have not been any studies evaluating oxidative stress or antioxidant status in dogs with renal disease.

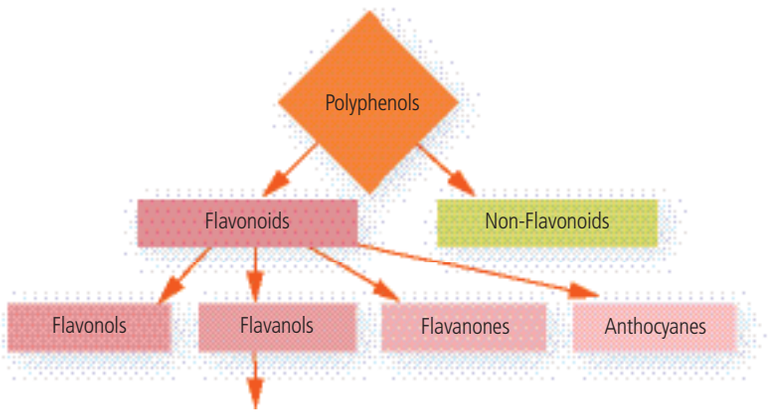
Flavanols, a subclass of flavonoids, are polyphenolic antioxidants which are found in a variety of plants. **(Figure 14)**. Epigallocatechin gallate is recognized as one of the most active flavanols in protection against oxidation **(Figure 15)**. Within plants, flavanols are powerful antioxidants that protect the integrity of the cell membrane and genetic material. Flavanols also chelate metal ions such as iron and copper, which may contribute to their antioxidant activity by preventing redox-active transition metals from catalyzing free radical formation. In addition, flavonols also appear to modulate antioxidant enzyme systems.

FIGURE 14 - CATECHIN MOLECULE



The base structure of flavanols consists of two aromatic rings connected with three carbons to form a six-member heterocyclic ring.

FIGURE 15 - FLAVANOLS WITHIN THE FAMILY OF POLYPHENOLS



Monomers: catechin, epicatechin, epigallocatechin galate
Oligomers: procyanidins
Polymers: tannins

Plants that have high flavanol concentrations include cocoa, grapes, and green tea.

Flavanols have been reported to be beneficial in renal disease. Flavanols stimulate the production of nitric oxide which relaxes the vascular system. Daily administration of flavanols to rats was associated with a significant reduction in both systolic and diastolic blood pressure (*Jouad et al, 2001*). Flavanols appear to decrease glomerular capillary pressure in rats with chronic renal failure by:
1) stimulating the production of nitric oxide
2) relaxing the smooth muscle fibers
3) inhibiting angiotensin converting enzyme.

8 - Feeding strategy

Dietary therapy is only effective in ameliorating the clinical signs of uremia if it is administered appropriately. Patients with chronic renal failure often have reduced appetites. In addition, an altered sense of taste and smell has been reported in people. These factors can be aggravated by the handicap of reduced dietary intake due to reduced palatability of the modified protein diets for dogs with chronic renal failure.

However, it is not the palatability of the diets per se, but the effect of uremia on the sense of taste and smell and the development of food aversion that contribute to inappetance. In this regard, it is not advisable to institute dietary changes when patients are hospitalized, as there is a high risk that the patient will develop food aversion. Rather, the renal support diet should be instituted in the home environment when the pet is stable.

Reduced food intake leads to malnutrition and wasting, which contribute to many aspects of uremia including impaired immune function, delayed wound healing, decreased strength and vigor, and increased morbidity and mortality. Indeed, malnutrition has been implicated as a factor influencing outcome in humans with renal failure. Therefore, prevention of malnutrition by ensuring adequate nutrient intake is crucial in the management of renal failure.

Enteral feeding tubes should be instituted for nutritional support upon documentation of a 10-15% loss of BW in conjunction with a declining body condition score and a history of poor dietary intake. Enteral feeding tubes are also advantageous as they circumvent the need for subcutaneous fluid therapy and ease the administration of oral medications.

(For more details concerning enteral tube feeding, **see chapter 14**: critical care nutrition)

► Clinical studies of the influence of the diet on naturally occurring chronic renal failure

The effects of feeding diets with a low phosphorus and moderately restricted protein content have been investigated in dogs with mild to moderate chronic renal failure (*Leibetseder & Neufeld, 1991*). Thirty-two dogs with early chronic renal failure were fed a low phosphorus medium protein commercial diet for 28 weeks, and an additional 28 dogs were fed a home-made diet formulated to mimic the commercial diet. Fourteen dogs were euthanized throughout the course of the study due to progression of renal failure. Within four weeks of feeding either the commercial or the home made diet, the concentrations of blood urea nitrogen and phosphorus had almost normalized. Both diets were found to be palatable, body weights and serum albumin concentrations remained stable, and the physical condition of the dogs was considered improved. The results of this study suggest that dogs with mild to moderate chronic renal failure benefit from early management with a phosphate and protein restricted diet.

The effect of a modified protein, low phosphate diet on the outcome of dogs with stable, naturally occurring CRF has recently been reported (*Jacob et al, 2002*). Dogs with mild to moderate CRF 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 2.5 times longer and had a median survival that was three times longer than dogs with CRF that were fed a maintenance diet. Renal function declined more slowly in the dogs that were fed the renal diet. The primary cause of death in dogs fed the maintenance diet was renal-related.

► Monitoring

Regular monitoring to ensure that dietary and medical management remains optimal for the needs of the patient is crucial for the well being and long term successful treatment of the chronic renal failure patient. Owner compliance may also be improved by frequent patient evaluation. Patients should be reevaluated within 2 weeks of initiating therapy and then 3 to 4 times per year. Recheck examinations should always be made 2 weeks following medication or dietary change. Erythropoietin and antihypertensive therapy will initially require weekly evaluation until the appropriate maintenance dosage is achieved.

A complete history, physical examination, body weight, body condition score and laboratory evaluation including CBC, biochemical panel, urine analysis, urine culture and blood pressure evaluation is indicated. Urine culture should become a routine part of follow up studies as chronic renal failure patients are predisposed to urinary tract infection, which are often clinically "silent".

Practical measures to improve 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.

When oral ulcerations are present, application of local xylocaine gel about 10 minutes before the meal may decrease the pain associated with food intake.

Appetite stimulants such as the benzodiazepam derivatives or serotonin antagonists may be judiciously administered, however, in these cases, more aggressive therapy such as esophagostomy or gastrotomy tube feeding is often more effective *(Elliott et al, 2000)*.

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.

A complete dietary history including the type of diet (dry versus wet), the amount eaten each day (eaten is more important than amount offered), the method of feeding, and all treats, snacks and supplements should also be obtained. This information is invaluable for monitoring the response to dietary therapy.

► Expected outcome and prognosis

CRF is a progressive disease that ultimately results in death. The goal of medical and nutritional management is to ensure the highest quality of life for the patient, for the longest period of time. Success depends on owner acceptance and compliance and a coordinated medical approach.

Despite appropriate tailoring of the therapy to the patient's condition, chronic renal failure is typically dynamic and progressive and eventually leads to end-stage renal failure. The severity of the clinical signs and uremic complications and the probability of improving renal function (by removing pre-renal contributions, controlling infection etc) will aid in determination of the progno-

sis. The severity of the renal function and long term prognosis is best determined by the serum creatinine concentration. Prognosis and outcome will be heavily influenced by the response to conservative medical therapy and the rate of progression of the renal dysfunction.

Dietary and conventional medical therapy generally become poorly accepted or ineffective at stage IV of CRF as defined by IRIS (when plasma creatinine exceeds 5 mg/dL or 400 μmol/L). At this point owners are frustrated with the poor quality of life of their pet and euthanasia is often the ultimate outcome. Renal transplantation or chronic intermittent hemodialysis (two or three times per week) are then the only viable options.

Conclusion

Chronic renal failure is the clinical syndrome resulting from irreversible loss of the metabolic, endocrine and excretory capacities of the kidney. CRF is the third leading cause of death in dogs. Nutrition has been the cornerstone of management for decades. The goals of dietary modification are to meet the patient's nutrient and energy requirements, alleviate clinical signs and consequences of uremia, minimize disturbances in fluid, electrolyte, vitamin, mineral, and acid base balance and to slow progression of renal failure. Regular monitoring to ensure that dietary and medical management remains optimal for the needs of the patient is crucial for the well being and long term successful treatment of the chronic renal failure patient.

Definitions

Azotemia: Increased concentrations of blood urea nitrogen and/or creatinine and other nitrogenous waste products in the blood

Renal Azotemia: Denotes azotemia caused by renal parenchymal lesion

Renal Disease: Implies renal lesions are present, however, does not qualify the etiology, severity or distribution

Renal Failure: State of decreased renal function that allows persistent abnormalities (azotemia, inability to concentrate urine) to exist

Renal Insufficiency: Begins when renal reserve is lost. Animals appear outwardly normal, but have a reduced capacity to compensate for stresses such as infection or dehydration

Renal reserve: The percentage of nephrons not necessary to maintain normal renal function. The renal reserve is generally greater than 50%

Uremic syndrome: Constellation of clinical signs including anemia, gastroenteritis, acidosis which occur at the ultimate stage of renal failure

Frequently asked questions: Chronic Renal Failure

Q	A
Can I add broths and meat juices to the diet to improve palatability?	No, we do not recommend adding any supplements to the diet. Adding supplements to the diet may unbalance the key dietary features that we are trying to control with the diet.
Is dry or canned food better for my pet with renal disease?	For most pets with kidney disease, it will not matter whether they eat canned or dry food, as long as they are both formulated to assist the management of renal disease. For some pets that do not drink adequate amounts of water to maintain hydration, canned food may be beneficial to aid the ingestion of water.
When should you start to feed the renal diet?	Renal diets should be implemented as soon as the diagnosis of kidney disease is made. However, renal diets should not be fed to pets that are sick and hospitalized. Rather they should be implemented in the pets normal home environment. Hospitalization is a very stressful event for pets. Changing the food at that time may foster food aversion.
How often should my pet be rechecked?	The frequency that a pet is rechecked will depend on what concurrent medications that the pet is currently receiving. For pets with early disease, they should be rechecked every 3-4 months. If pets are on hypertensive agents, or erythopoietin therapy, they may need rechecking every two weeks until the ideal dose of the medication is identified to stabilize the pet.
What do I do if the pet is not eating enough food and loosing weight?	If the pet is not eating adequate amounts of food to maintain body weight, then assisted feeding by the placement of esophagostomy or gastrostomy tubes should be considered. Therefore, on the days that the pet will not eat the appropriate amount of food, the food can be blended and administered to the pet.

References

Adams LG - Phosphorus, protein and kidney disease. Proceeding of the Petfood Forum 1995 (13-26).

Bauer JE, Markwell PJ, Rawlings JM et al - Effects of dietary fat and polyunsaturated fatty acids in dogs with naturally developing chronic renal failure. J Am Vet Med Assoc 1999; 215: 1588-1591.

Bauer J, Crocker R, Markwell PJ - Dietary n-6 fatty acid supplementation improves ultrafiltration in spontaneous canine chronic renal disease. J Vet Intern Med 1997; 126: 126.

Bronson RT - Variation in age at death of dogs of different sexes and breeds. Am J Vet Res 1982; 43: 2057-2059.

Brown SA, Finco DR, Crowell WA et al - Single-nephron adaptations to partial renal ablation in the dog. Am J Physiol 1990; 258: F495-503.

Brown SA, Finco DR, Crowell WA et al - Dietary protein intake and the glomerular adaptations to partial nephrectomy in dogs. J Nutr 1991a; 121: S125-127.

Brown SA, Crowell WA, Barsanti JA et al - Beneficial effects of dietary mineral restriction in dogs with marked reduction of functional renal mass. J Am Soc Nephrol 1991b; 1: 1169-1179.

Brown SA, Brown CA, Crowell WA et al - Does modifying dietary lipids influence the progression of renal failure? Vet Clin North Am Small Anim Pract 1996; 26: 1277-1285.

Brown SA, Finco DR, Brown CA - Is there a role for dietary polyunsaturated fatty acid supplementation in canine renal disease? J Nutr 1998a; 128: 2765S-2767S.

Brown SA, Brown CA, Crowell WA et al- Beneficial effects of chronic administration of dietary omega-3 polyunsaturated fatty acids in dogs with renal insufficiency. J Lab Clin Med 1998b; 131: 447-455.

Brown SA, Brown CA, Crowell WA et al - Effects of dietary polyunsaturated fatty acid supplementation in early renal insufficiency in dogs. J Lab Clin Med 2000; 135: 275-286.

Cochrane AL, Ricardo SD - Oxidant stress and regulation of chemokines in the development of renal interstitial fibrosis. Contrib Nephrol 2003; 139: 102-119.

Cowan LA, McLaughlin R, Toll PW et al - Effect of stanozolol on body composition, nitrogen balance, and food consumption in castrated dogs with chronic renal failure. J Am Vet Med Assoc 1997; 211: 719-722.

Cowgill L - Medical management of the anemia of chronic renal failure. In: Osborne C, Finco D, eds. Canine and Feline Nephrology and Urology. Baltimore: Williams & Wilkins; 1995: 539-554.

Cowgill LD, James KM, Levy JK et al - Use of recombinant human erythropoietin for management of anemia in dogs and cats with renal failure. J Am Vet Med Assoc 1998; 212: 521-528.

Elliott DA, Riel DL, Rogers QR - Complications and outcomes associated with use of gastrostomy tubes for nutritional management of dogs with renal failure: 56 cases (1994-1999). J Am Vet Med Assoc 2000; 217: 1337-1342.

Finco DR, Crowell WA, Barsanti JA - Effects of three diets on dogs with induced chronic renal failure. Am J Vet Res 1985; 46: 646-653.

Finco DR, Brown SA, Crowell WA et al - Effects of dietary phosphorus and protein in dogs with chronic renal failure. Am J Vet Res 1992a; 53: 2264-2271.

Finco DR, Brown SA, Crowell WA et al - Effects of phosphorus/calcium-restricted and phosphorus/calcium-replete 32% protein diets in dogs with chronic renal failure. Am J Vet Res 1992b; 53: 157-163.

Finco DR, Brown SA, Crowell WA et al - Effects of aging and dietary protein intake on uninephrectomized geriatric dogs. Am J Vet Res 1994; 55: 1282-1290.

Finco DR, Brown SA, Brown CA et al - Progression of chronic renal disease in the dog. J Vet Intern Med 1999; 13: 516-528.

Gerber B, Hassig M, Reusch CE - Serum concentrations of 1,25-dihydroxycholecalciferol and 25-hydroxycholecalciferol in clinically normal dogs and dogs with acute and chronic renal failure. Am J Vet Res 2003; 64: 1161-6.

Grauer GF, Allen TA - Chronic renal failure in the dog. Compend Contin Educ Pract Vet 1981; 3: 1009-1017.

Grauer GF, Greco DS, Getzy DM et al - Effects of enalapril versus placebo as a treatment for canine idiopathic glomerulonephritis. J Vet Intern Med 2000; 14: 526-533.

Greco DS, Lees GE, Dzendzel GS et al - Effect of dietary sodium intake on glomerular filtration rate in partially nephrectomized dogs. Am J Vet Res 1994a; 55: 152-159.

Greco DS, Lees GE, Dzendzel G et al-Effects of dietary sodium intake on blood pressure measurements in partially nephrectomized dogs. Am J Vet Res 1994b; 55: 160-165.

Hahn S, Kuemmerle NB, Chan W et al - Glomerulosclerosis in the remnant kidney rat is modulated by dietary alpha-tocopherol. J Am Soc Nephrol 1998; 9: 2089-2095.

Hahn S, Krieg RJ Jr, Hisano S et al - Vitamin E suppresses oxidative stress and glomerulosclerosis in rat remnant kidney. Pediatr Nephrol 1999; 13: 195-198.

Hansen B, DiBartola SP, Chew DJ et al - Clinical and metabolic findings in dogs with chronic renal failure fed two diets. Am J Vet Res 1992; 53: 326-334.

Jackson P, Loughrey CM, Lightbody JH et al - Effect of hemodialysis on total antioxidant capacity and serum antioxidants in patients with chronic renal failure. Clin Chem 1995; 41: 1135-1138.

Jacob F, Polzin DJ, Osborne CA et al - Clinical evaluation of dietary modification for treatment of spontaneous chronic renal failure in dogs. J Am Vet Med Assoc 2002; 220: 1163-1170.

Jacob F, Polzin DJ, Osborne CA et al - Association between initial systolic blood pressure and risk of developing a uremic crisis or of dying in dogs with chronic renal failure. J Am Vet Med Assoc 2003; 222: 322-329.

Jouad H, Lacaille-Dubois MA, Lyoussi B et al - Effects of the flavonoids extracted from Spergularia purpurea Pers. on arterial blood pressure and renal function in normal and hypertensive rats. J Ethnopharmacol 2001; 76: 159-163.

Leibetseder JL, Neufeld KW - Effects of medium protein diets in dogs with chronic renal failure. J Nutr 1991; 121: S145-149.

Lefebvre HP, Ferre JP, Watson AD et al - Small bowel motility and colonic transit are altered in dogs with moderate renal failure. Am J Physiol Regul Integr Comp Physiol 2001; 281: R230-238.

Lefebvre HP, Toutain PL - Angiotensin-converting enzyme inhibitors in the therapy of renal diseases. J Vet Pharmacol Ther 2004; 27(5): 265-81.

Locatelli F, Canaud B, Eckardt KU et al - Oxidative stress in end-stage renal disease: an emerging threat to patient outcome. Nephrol Dial Transplant 2003; 18: 1272-1280.

Lund EM, Armstrong PJ, Kirk CA et al - Health status and population characteristics of dogs and cats examined at private veterinary practices in the United States. J Am Vet Med Assoc 1999; 214: 1336-1341.

Nagode LA, Chew DJ, Podell M - Benefits of calcitriol therapy and serum phosphorus control in dogs and cats with chronic renal failure. Both are essential to prevent or suppress toxic hyperparathyroidism. Vet Clin North Am Small Anim Pract 1996; 26: 1293-1330.

Polzin DJ, Osborne CA, Stevens JB et al - Influence of modified protein diets on the nutritional status of dogs with induced chronic renal failure. Am J Vet Res 1983; 44: 1694-1702.

Polzin DJ, Osborne CA - The importance of egg protein in reduced protein diets designed for dogs with renal failure. J Vet Intern Med 1988; 2: 15-21.

Polzin DJ, Leininger JR, Osborne CA et al - Development of renal lesions in dogs after 11/12 reduction of renal mass. Influences of dietary protein intake. Laboratory Investigation 1988; 58: 172-183.

Polzin DJ - Diseases of the kidneys and ureters. In: Ettinger SJ, Feldman EC, eds. Textbook of Veterinary Internal Medicine, 3 ed. Philadelphia: WB Saunders; 1989: 1963-2046.

Polzin DJ, Osborne CA, Jacobs F et al - Chronic Renal Failure. In: Ettinger SJ, Feldman EC, eds. Textbook of Veterinary Internal Medicine Diseases of the Dog and Cat, 5 ed. Philadelphia: WB Saunders; 2000:1634-1661.

Raila J, Forterre S, Kohn B et al - Effects of chronic renal disease on the transport of vitamin A in plasma and urine of dogs. Am J Vet Res 2003; 64:874-879.

Randolph JF, Scarlett J, Stokol T et al - Clinical efficacy and safety of recombinant canine erythropoietin in dogs with anemia of chronic renal failure and dogs with recombinant human erythropoietin-induced red cell aplasia. J Vet Intern Med 2004; 18: 81-91.

Robertson JL, Goldschmidt M, Kronfeld DS et al - Long-term renal responses to high dietary protein in dogs with 75% nephrectomy. Kidney Int 1986; 29: 511-519.

Stepien RL - Diagnosis of canine hypertension. 19th Annual Veterinary Medical Forum, American College of Veterinary Internal Medicine; Denver, 2001: 871.

Tahzib M, Frank R, Gauthier B et al -Vitamin E treatment of focal segmental glomerulosclerosis: results of an open-label study. Pediatr Nephrol 1999; 13: 649-652.

Watson AD, Lefebvre HP, Concordet D et al - Plasma exogenous creatinine clearance test in dogs: comparison with other methods and proposed limited sampling strategy. J Vet Intern Med 2002; 16: 22-33.

EXAMPLES HOME-PREPARED THE DIETETIC TREATMENT OF

Example 1

COMPOSITION
(1000 g diet)

Beef, minced meat, 20% fat . . . . . 250 g
Potato, cooked, with skin . . . . . 700 g
Rapeseed oil . . . . . 50 g

Add a low-phosphorus mineral and vitamin supplement.

ANALYSIS		
The diet prepared in this way contains 30% dry matter and 70% water		
	% dry matter	**g/1000 kcal**
Protein	19	37
Fat	34	66
Available carbohydrate	36	70
Fiber	4	8

INDICATIVE RATIONING			
Energy value (metabolizable energy): 1550 kcal/1000 g of diet prepared 5110 kcal/1000 g DM			
Dog's weight (kg)*	Daily amount (g)**	Dog's weight (kg)*	Daily amount (g)**
2	140	45	1460
4	240	50	1580
6	320	55	1690
10	470	60	1810
15	640	65	1920
20	790	70	2030
25	940	75	2140
30	1080	80	2240
35	1210	85	2350
40	1330	90	2450

Key Points

- **Reducing the phosphorus content** to mitigate the less good phosphorus excretion by the kidney during CRD and prevent the risk of hyperparathyroidism, which aggravates renal failure.
- **Increasing the energy concentration** to help limit the meal volume while covering energy requirements. The goal is to compensate the fall in appetite.
- **Moderating the protein content** to compensate the fall in the glomerular filtration rate

**The rationing is offered in accordance with the dog's healthy weight. In case of obesity, the rationing must be prescribed in accordance with the ideal weight and not the real weight of the dog.*
***The fractioning of the daily amount over two or three meals is recommended to favor good digestion.*

DIETS ADAPTED TO CHRONIC RENAL DISEASE

Example 2

COMPOSITION
(1000 g diet)

Pork, shoulder with skin . . . . . 125 g
Whole egg . . . . . 125 g
Rice, cooked . . . . . 730 g
Rapeseed oil . . . . . 20 g

Add a low-phosphorus mineral and vitamin supplement.

INDICATIVE RATIONING

Energy value (metabolizable energy): 1520 kcal/1000 g of diet prepared 5050 kcal/1000 g DM

Dog's weight (kg)*	Daily amount (g)**	Dog's weight (kg)*	Daily amount (g)**
2	140	45	1490
4	240	50	1610
6	330	55	1730
10	480	60	1840
15	650	65	1960
20	810	70	2070
25	960	75	2180
30	1100	80	2290
35	1230	85	2390
40	1360	90	2500

ANALYSIS

The diet prepared in this way contains 30% dry matter and 70% water

	% dry matter	g/1000 kcal
Protein	18	36
Fat	18	37
Available carbohydrate	62	127
Fiber	1	2

Contra-indications

Gestation
Lactation
Growth

Examples of home-made diets are proposed by Pr Patrick Nguyen
(Nutrition and Endocrinology Unit; Biology and Pathology Department, National veterinary School of Nantes)

© Lanceau

An adapted diet helps triple the median survival time of dogs with chronic renal disease.

Key Points
to remember:

The role of nutrition in the management and prevention of chronic renal disease

Chronic renal disease (CRD) in dogs is often associated with a waxing and waning appetite. Therefore the **palatability of the food** is a key criterion in the management of CRD.

When the kidney loses its functional capacity, phosphorus is no longer adequately excreted and the concentration increases in plasma. Ultimately, hyperphosphatemia causes hyperparathyroidism that aggravates CRD. One of the goals of treatment is to normalize the blood phosphate concentration. It has been clearly shown that the **dietary restriction of phosphorus** slows the progression of renal disease in dogs.

Supplementation with alkalizing agents such as sodium bicarbonate, calcium carbonate or potassium citrate can prove necessary to combat metabolic acidosis.

Contrary to a common misconception, the protein **content of the food** does not have any impact on the progression of renal disease. It is therefore useless to systematically reduce the protein in the diet of an aging dog. Conversely, in dogs with CRD the goal of protein reduction is to reduce the magnitude of uremia. To prevent protein malnutrition, moderate restriction of the order of 35-40 g protein/1000 kcal is preferable. Too severe protein reduction could actually have negative effects, by forcing the dog to catabolize its body proteins to meet its needs.

Energy intake must be sufficient to prevent endogenous protein catabolism that leads to malnutrition and aggravated azotemia.

An **increased intake of omega 3 fatty acids (EPA and DHA)** helps limit the reduction in glomerular filtration rate.

Hypokalemia is commonly observed in dogs with renal disease, except in the terminal stage, when hyperkalemia may be observed. **Reestablishing a normal serum potassium concentration** is essential to the dog's quality of life.

It has long been recommended to reduce the **sodium content** in the diets of patients with CRD. However, recent work (see chapter seven) would appear to show that too low of a sodium content (0.4-0.5 mg/1000 kcal) could have a deleterious effect on renal function. Low sodium intake could contribute to glomerular hypertension by increasing the secretion of aldosterone and activating the renin-angiotensin system. These results are yet to be confirmed but they caution against too severe sodium restriction in the diet of patients with CRD.

Aging dogs generally suffer from renal disease hence it is necessary to **enrich the food with antioxidants** to help combat free radical production.

Focus on:

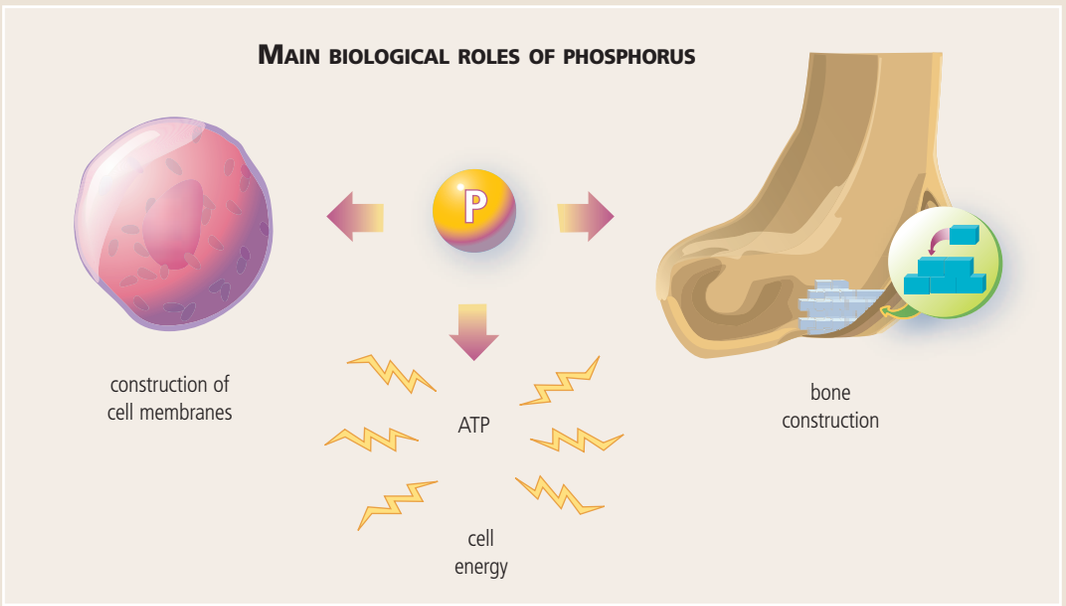
PHOSPHORUS

Etymologically speaking, the word phosphorus means 'light-bringing.' It was discovered in 1669 by a German alchemist, Hennig Brandt. By evaporating urine and calcifying the residue, he obtained phosphorus in gas form that shone in the dark.

In the form of phosphates, phosphorus enters into the composition of bone. Eighty-six percent of the phosphorus in the organism is stored in the structure of the skeleton.

Phosphorus is also incorporated into large molecules such as DNA, RNA and membrane phospholipids. In addition, it is an active constituent of the adenosine triphosphate molecule (ATP), which stores the energy living organisms need to function properly.

The reasons why phosphorus leads to progression of CRD have yet to be determined with certainty. Following the reduction of the renal function, phosphorus accumulates in the blood. The organism responds physiologically by increasing the secretion of parathyroid hormone (PTH). This response initially helps maintain the phosphorus within normal thresholds, but also leads to the release of phosphate and calcium from bone reserves.

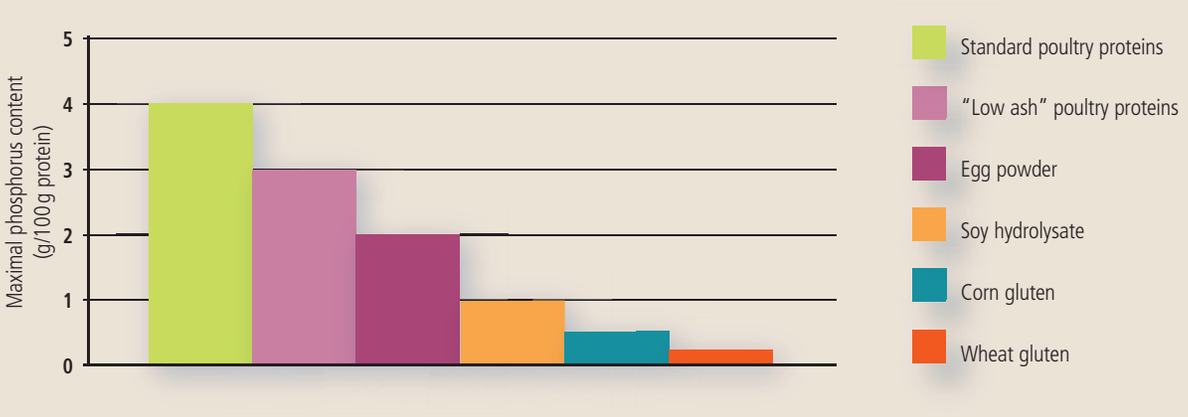


In time, even this compensatory response is not enough to reestablish homeostasis. Phosphorus and calcium accumulate, leading to the mineralization of soft tissue. In the kidney, this phenomenon accelerates the loss of functional nephrons. In addition, PTH may act as an uremic toxin, which also aggravates the clinical symptoms and progression of CRD.

In CRD patients, the goal is therefore to limit the phosphorus content of the food to 0.40-0.80 g/1000 kcal. At the same time, the increase in the calcium content also helps reduce the digestive absorption of phosphorus. If such a level does not help normalize the serum phosphate concentration, the use of phosphate binding agents (aluminum hydroxide, calcium carbonate etc) should be considered.

While it is vital to limit the phosphorus content in the food, the difficulty lies in the necessity of finding raw ingredients that are low in phosphorus. Animal protein sources traditionally used in dog food are fairly high in phosphorus. For example, there is 1.6-2.5% phosphorus on a DMB in dehydrated poultry proteins. This level is dependent on the overall content of remaining mineral matter after sieving. Vegetable protein sources that are lower in phosphate concentration (wheat or corn gluten, soy protein isolate hydrolysate) are an interesting alternative.

PHOSPHORUS CONTENT OF SEVERAL PROTEIN SOURCES USED IN DOG FOOD



Wheat or corn gluten helps supply high quality proteins while simultaneously reducing the ingestion of phosphorus.

Abigail STEVENSON
PhD, BSc, MIBiol, Cbiol

Carolien RUTGERS
DVM, MS, Dipl ACVIM, Dipl ECVIM-CA, DSAM, MRCVS

Nutritional management of canine urolithiasis

1 - Introduction 303
2 - Diagnosis 303
3 - Epidemiology 308
4 - Pathophysiology 311
5 - Nutritional management 313
6 - General management of urolithiasis 314
7 - Specific nutritional management 316

Frequently asked questions: urolithiasis 325
References 326
Examples of home-prepared diets adapted to the dietetic treatment of urolithiasis 328
Royal Canin Nutritional Information 330

Nutritional management of canine urolithiasis

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Abigail graduated from the University of Stirling with a BSc (Hons) in 1992. After working as a research assistant at the University of Anchorage in Alaska for 6 months Abigail was appointed as a research technician at the WALTHAM Centre for Pet Nutrition in 1993 to work on feline metabolism of vitamin A and taurine. In 1995, Abigail was promoted to the position of Research Scientist working in the area of urinary tract health, and obtained her PhD on this subject in 2002. From 2002 to 2005 Abigail was responsible for the bird and fish research programs at WALTHAM. Recently Abigail moved again to take up a position in Scientific Communications at WALTHAM.

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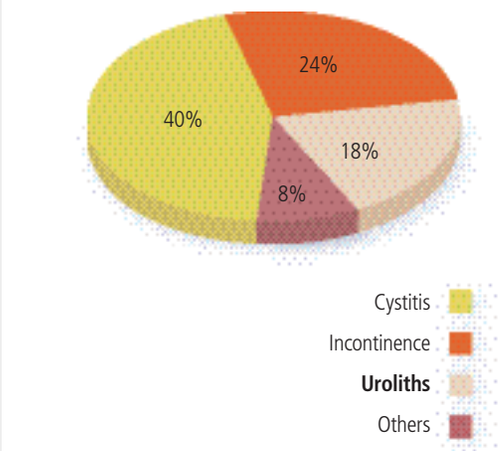
Carolien graduated from Utrecht State University and completed an internship at the University of Pennsylvania and a residency and Masters degree at Ohio State University. In between she worked in referral small animal practice. She joined the University of Liverpool in 1985 as a Lecturer in Small Animal Medicine and moved in 1990 to the Royal Veterinary College, where she later became a Senior Lecturer. She is now an independent consultant.

Carolien has published more than 100 scientific papers and book chapters, and has lectured widely in the UK and abroad. Her major research interests are in gastroenterology and liver disease. She is a Diplomate of the American College of Veterinary Internal Medicine (ACVIM), a Foundation Diplomate of the European College of Veterinary Internal Medicine - Companion Animals (ECVIM-CA), and a RCVS Diplomate in Small Animal Medicine. Carolien has been a foundation Board member of the ECVIM-CA and a member of the RCVS Small Animal Medicine and Surgery Board, and a Diploma examiner for both.

FIGURE 1 - MAIN CONDITIONS RESPONSIBLE FOR THE CLINICAL SIGNS OF LOWER URINARY TRACT DISEASE IN DOGS *(From Lulich et al, 2000)*



Urolithiasis is defined as the formation of sediment, consisting of one or more poorly soluble crystalloids, in the urinary tract. Microscopic sediment is referred to as crystals, and larger macroscopic precipitates are called uroliths.

Urolithiasis is a common problem in dogs. Uroliths can form anywhere in the urinary tract, although in dogs the vast majority occur in the bladder. Urolithiasis is responsible for about 18% of veterinary consultations in dogs with lower urinary tract disorders (Figure 1) *(Lulich et al, 2000)*.

1 - Introduction

The four most common minerals found in canine uroliths are magnesium ammonium phosphate (struvite), calcium oxalate, ammonium urate and cystine *(Osborne et al, 1995; Osborne et al, 1999b; Houston et al, 2004)* **(Figures 2 & 3, Table 1)**. Less common urolith types are calcium phosphate, silicate, drugs and drug metabolites.

Calcium oxalate and struvite are the predominant mineral types in canine nephroliths *(Ross et al, 1999)*. The incidence of urolithiasis and the composition of uroliths may be influenced by a variety of factors including breed, sex, age, diet, anatomic abnormalities, urinary tract infection (UTI), urine pH and medications *(Ling, 1998)*. Identification of these risk factors is essential for effective management and prevention of urolithiasis. Urolithiasis often has a high recurrence rate. This has led to an increasing use of dietary management for both dissolution and prevention of uroliths, although some mineral types are more amenable to dissolution than others.

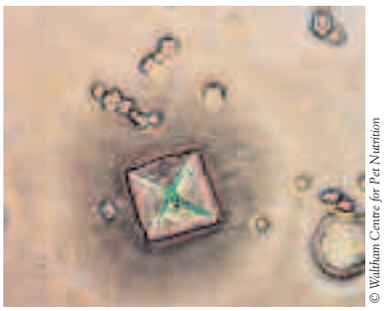


Figure 2: Calcium oxalate crystal

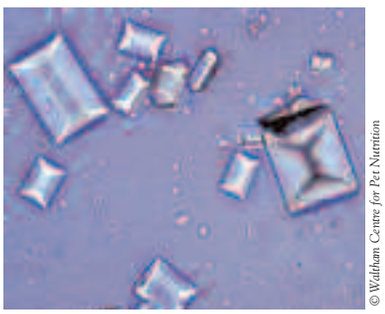


Figure 3: Struvite crystal

TABLE 1 - PREVALENCE OF THE MOST COMMON UROLITHS IN DOGS

Based on 77,000 submissions to the Minnesota Urolith Center from dogs of all ages (Adapted from Osborne et al, 1999c; Houston et al, 2004)

	1981	1982-1986	1981-1997	1997	2003*
Struvite	78%	67%	49%	45%	43.8%
Oxalate	5%	7%	32%	35%	41.5%
Urate		5%	8%	9%	
Cystine		2%	1%	<1%	
Mixed uroliths		12%	9%	8%	

Struvite uroliths used to be the most common type, but during the last twenty years the prevalence of calcium oxalate urolithiasis has been increasing and that of struvite urolithiasis decreasing; although the latter still predominates (Ling et al, 2003).

**data from the Canadian Veterinary Urolith Centre*

2 - Diagnosis

► History and clinical signs

Symptoms of urolithiasis are mainly due to irritation of the mucosa of the lower urinary tract, resulting in signs of cystitis and/or urethritis. The most common signs are hematuria, dysuria and pollakiuria. Occasionally, urolithiasis may lead to urethral obstruction, which is a medical and surgical emergency. Renal calculi may furthermore cause pyelonephritis, outflow obstruction, reduction of renal mass, azotemia and renal failure. Conversely some patients are clinically asymptomatic.

► Differential diagnosis

Other common causes of hematuria, dysuria and frequent urination, with or without urethral obstruction, are UTI, polyps and neoplasia. These can be distinguished by urine culture and imaging studies.

► Laboratory testing and imaging

Urinalysis, quantitative urine culture and imaging (plain and double contrast radiography and/or ultrasonography) are required to confirm urolithiasis and to look for predisposing factors.

Evaluation of serum biochemistries is useful for the recognition of underlying abnormalities and assessment of renal function in dogs with nephrolithiasis. Urine chemistries can furthermore reveal excessive quantities of one or more minerals contained in the urolith.

> Urinalysis

Urinalysis typically shows inflammation: proteinuria, hematuria and pyuria. Urine pH varies, depending upon stone type, presence or absence of infection, and diet. In general, struvite uroliths are associated with alkaline urine, particularly if urease-producing bacteria are present. Urate and cystine formation tends to be associated with acid to neutral pH *(Osborne et al, 1995)*. In contrast urine pH is a less important factor in calcium oxalate formation.

Crystalluria may be present without urolithiasis, and urolithiasis may occur without crystalluria. In addition, crystals are not necessarily representative of the urolith type, since they may be influenced by a urease-producing bacterial infection that could generate struvite crystals. However, ammonium urate crystals **(Figure 4)** may indicate portosystemic shunting, and cystine crystals are pathognomonic of cystinuria **(Figure 5)**. The presence of crystals depends on urine pH, temperature and concentration. Urine samples should be examined within 30 minutes of collection and should not be refrigerated.

> Urine culture

Urine bacterial culture and sensitivity should be performed in all dogs to assess for primary or secondary UTI. Bacterial culture of the inner parts of possible infection-induced stones may also be beneficial, since bacteria in the urine may not be the same as those harbored in the urolith *(Osborne et al, 1995)*. If a cystotomy is performed for stone removal, it is recommended to submit a piece of bladder mucosa for culture and sensitivity as this is more sensitive than culturing the urine *(Hamaide et al, 1998)*.

> Imaging techniques

Radiography and/or ultrasonography are indicated to verify the presence of uroliths, as well as their location, number, size, radiodensity and shape **(Figure 6)**. Uroliths have to be greater than 3 mm to be detected by survey abdominal radiography or ultrasonography. Urate uroliths are the most radiolucent and usually require double contrast cystography for visualization. Retrograde contrast studies are required to assess urethral stones, and excretory urography if renal calculi are suspected.

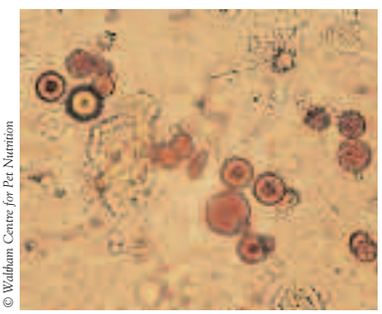


Figure 4: Ammonium urate urinary crystals

Figure 5: Cystine urinary crystals

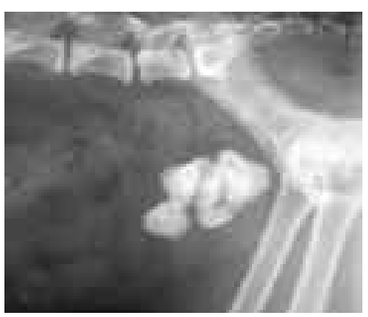


Figure 6: Radiographic appearance of cystic calculi in a dog

Cystoscopy requires specialized equipment and general anesthesia, but it can be very helpful to confirm urolithiasis and to remove small uroliths from the bladder or urethra *(Cannizzo et al, 2001)*.

► Analysis of urolith composition

Uroliths may be collected by spontaneous voiding, voiding urohydropropulsion *(Osborne et al, 1999e)*, aspiration into a urethral catheter, cystoscopy, or surgical removal. Urolith composition should be determined by quantitative physical analyses, which are far more accurate than qualitative chemical techniques. Uroliths can

contain more than one mineral type, and layer-by-layer mineral analysis may be required in compound stones. It is, therefore, important not to crush the uroliths before analysis. The initiating cause of the uroliths can be determined by the mineral composition of the nucleus, which may be different from the surrounding layers *(Osborne et al, 1999c)*.

Determination of the mineral composition of uroliths is vital for specific therapy and to prevent recurrence. Quantitative analysis performed by specialized laboratories is the most reliable method.

► Predicting urolith type

Effective dissolution of uroliths depends on knowledge of their mineral composition. Ideally a urolith should be retrieved and analyzed, and a number of factors can help in predicting urolith composition **(Tables 2, 3).**

TABLE 2 - FACTORS THAT HELP PREDICT UROLITH COMPOSITION IN DOGS
(adapted from Osborne et al, 1995)

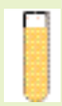
	**Signalment**: breed, age and sex **(see Table 3)**		
	**Radiographic density of uroliths**	- Calcium oxalate, calcium phosphate - Struvite, silica - Cystine - Ammonium urate	++++ ++ to ++++ + to ++ 0 to +
	**Urine pH**	- Struvite - Calcium oxalate - Ammonium urate, silica - Cystine	Usually alkaline No predisposition Acid to neutral Acid
	**Crystalluria**	- Cystine crystals are pathognomonic for cystinuria, which predisposes to cystine urolithiasis	
	**Presence of UTI,** and type of bacteria isolated from the urine	- UTI with urease-producing bacteria (*Staphylococci, Proteus spp*) suggests struvite urolithiasis (primary or secondary)	
	**Disease associations** (serum chemistry evaluation)	- Hypercalcemia may be associated with calcium-containing uroliths - Portosystemic shunts predispose to urate urolithiasis - Hyperchloremia, hypokalemia and acidosis may be associated with distal renal tubular acidosis and calcium phosphate or struvite uroliths	
	**Urine chemistry evaluation**	- Urine relative supersaturation regarding various minerals included in the stone	
Family history of particular uroliths			
Quantitative analysis of uroliths passed during voiding, collected via catheter aspiration or by voiding urohydropropulsion			

TABLE 3 - AGE, BREED AND SEX PREDISPOSITIONS FOR UROLITHIASIS IN DOGS
(adapted from Osborne et al 1999c; Lulich et al, 2000)

Urolith type	Commonly affected ages	Commonly affected breeds		Sex
Struvite	1 - 8 years Mean 6 years	Miniature Schnauzer Bichon frisé Shih Tzu Miniature Poodle Lhasa Apso		Female (>80%)
Calcium oxalate	6 - 12 years Mean 8.5 years	Miniature Schnauzer Lhasa Apso Cairn Terrier Yorkshire Terrier Cocker Spaniel Bichon frisé Shi Tzu Miniature Poodle		Male (>70%)
Calcium phosphate	5 - 13 years	Yorkshire Terrier		Male (>70%)
Urate	Without PSS: mean 3.5 years With PSS: mean <1 year	Dalmatian, English Bulldog, Miniature Schnauzer (PSS), Yorkshire Terrier (PSS)		Male (>85%)
Cystine	2 - 7 years Mean 5 years <1 year in Newfoundland dogs	English Bulldog Dachshund Newfoundland dog		Male (>90%)
Silica	4-9 years	German Shepherd dog Old English Sheepdog		Male (>90%)

PSS = portosystemic shunts

► Specific urolith types

> Struvite

Struvite ($Mg\ NH_4\ PO_4\ 6\ H_2O$) is one of the most common minerals found in canine uroliths **(Figure 7)**. Oversaturation of urine with magnesium ammonium phosphate ions is a requirement, but several other factors – including UTI, alkaline urine, diet and genetic predisposition – may influence formation. In dogs, most struvite uroliths are associated with a bacterial UTI **(Figure 8)** with urease producing bacteria such as Staphylococcus *spp* (often S. *intermedius*) or, less commonly, Proteus spp. Urease is an enzyme that hydrolyzes urea, leading to elevations of ammonium, phosphate and carbonate, resulting in alkaline urine. Many struvite uroliths also contain a small quantity of other minerals, such as calcium phosphate and, less commonly, ammonium urate.

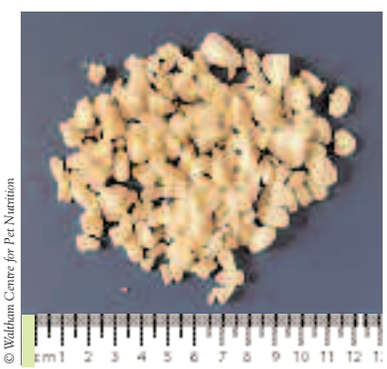


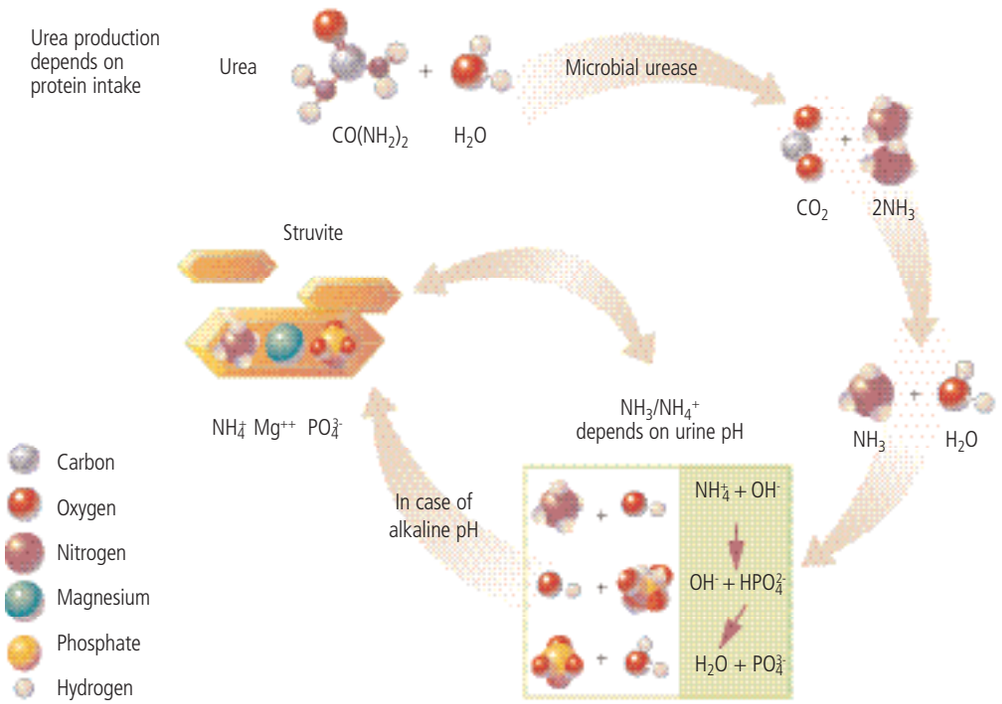
Figure 7: Struvite stones

Sterile struvite uroliths are rare in dogs; their etiopathogenesis may include dietary, metabolic or familial factors, but does not involve bacterial urease *(Osborne et al, 1995)*.

> Calcium oxalate

The main risk factor is supersaturation of urine with calcium and oxalate, with calcium relatively more important *(Stevenson, 2002, Stevenson et al 2003a)*. A major factor is intestinal hyperabsorption of calcium, which is recognized as a cause of calcium oxalate urolithiasis in both humans and dogs susceptible to calcium oxalate urolithiasis *(Lulich et al, 2000; Stevenson, 2002)*. Indirectly, this leads to hyperoxaluria, since it increases the availability of oxalate for absorption. The relationship between intestinal absorption of calcium and oxalic acid is clinically important, since reducing the concentration of calcium increases oxalate absorption, thus maintaining or increasing the risk of stone formation. Diet may have a significant role in the development of these uroliths (see risk factors) *(Lekcharoensuk et al, 2002a; 2002b)*.

FIGURE 8 - THE ROLE OF UTI IN STRUVITE UROLITHIASIS
(From P. Markwell)



Bacterial infection with urease producing organisms results in the cleavage of urea to generate ammonia and carbon dioxide. The carbon dioxide can dissociate with water to alkalinize the urine. The alkaline pH enables phosphate and ammonium ions to bind with magnesium to form a molecule of magnesium ammonium phosphate (struvite).

Diseases that increase urinary excretion of calcium and oxalic acid play a smaller role. Calcium oxalate **(Figure 9)** and phosphate uroliths have been reported in dogs with primary hyperparathyroidism, but not in dogs with paraneoplastic hypercalcemia *(Klausner et al, 1987; Lulich et al, 2000)*.

> Urate

Uric acid is one of several biodegradation products of purine nucleotide metabolism. In non-Dalmatian dogs, almost all urate formed from degradation of purine nucleotides is metabolized by hepatic uricase to allantoin, which is very soluble and excreted by the kidneys. In Dalmatian dogs, only 30-40% of uric acid is converted to allantoin, resulting in increased serum levels and urinary excretion of urate *(Bartges et al, 1999)*. Ensuing uroliths are most commonly composed of ammonium urate **(Figure 10)**. The defective uric acid mechanism in Dalmatian dogs probably involves both alterations in the hepatic and renal pathways, but the exact mechanism is incompletely understood. Reduced urinary excretion of crystallization inhibitors may contribute to stone formation in Dalmatians *(Carvalho et al, 2003)*. Urolithiasis in the Dalmatian is probably autosomal recessive inherited *(Sorenson & Ling, 1993)*, although this does not explain the increased risk of stone formation for male dogs.

Any form of severe hepatic dysfunction may predispose dogs to urate urolithiasis, but there is a specific predisposition in dogs with congenital or acquired portosystemic shunts *(Kruger et al, 1986, Bartges et al, 1999)*. These dogs frequently develop intermittent crystalluria, urate calculi, or both. Hepatic dysfunction in these dogs may be associated with reduced hepatic conversion of uric acid to allantoin and of ammonia to urea, resulting in hyperuricemia and hyperammonemia, but the precise mechanism is uncertain.

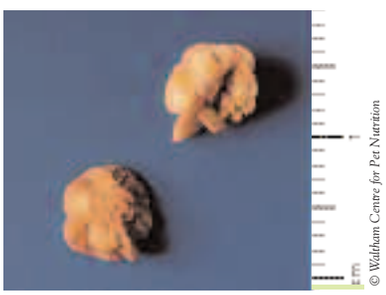


Figure 9: Calcium oxalate stones

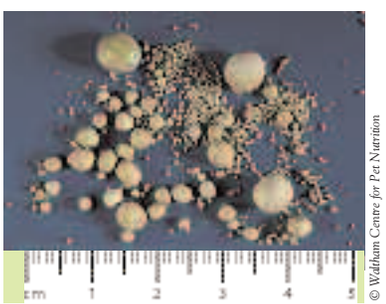


Figure 10: Urate stones

Relatively little is known about urate urolithiasis in non-Dalmatian dogs that do not have portosystemic shunts, although a familial tendency has been suggested for English Bulldogs *(Kruger et al, 1986; Bartges et al, 1994)*. Dietary risk factors for urate urolithiasis include high purine diets (e.g; diets rich in offal) and low water consumption. Urine acidity promotes urate lithogenesis, because purines are less soluble at acid pH. Consumption of diets that promote aciduria such as high protein diets are therefore also a risk factor for predisposed dogs *(Bartges et al, 1999)*.

> Cystine

These uroliths **(Figure 11)** occur in dogs with cystinuria, an inborn error of metabolism characterized by a defective proximal tubular reabsorption of cystine and other amino acids. Cystinuric dogs reabsorb a much smaller proportion of cystine that is filtered by the glomerulus and some may even have net cystine secretion *(Casal et al, 1995)*. Cystinuria is usually the only detectable sign of their amino acid loss unless protein intake is severely restricted. Cystine urolithiasis develops because cystine is only sparingly available at the usual urine pH of 5.5 to 7.0. Not all cystinuric dogs form uroliths, and calculi are often not recognized until maturity. They occur predominantly in male dogs, and other undetermined factors may therefore also play a role in the pathogenesis. Canine cystinuria is genetically heterogeneous and has been recognized in more than 60 breeds of dogs with variable patterns of aminoaciduria *(Case et al, 1992, 1993; Osborne et al, 1999g, Henthorn et al, 2000)*.

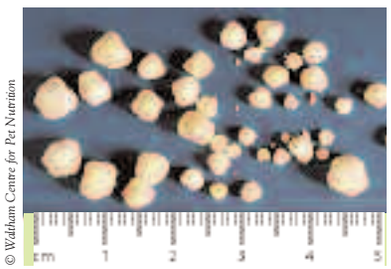


Figure 11: Cystine stones

> Other uroliths

Calcium phosphate uroliths (Figure 12) are commonly called apatite uroliths, with hydroxyapatite and carbonate apatite the most common forms. They occur commonly as a minor component of struvite and calcium oxalate stones. Pure calcium phosphate uroliths are infrequently found, and they are usually associated with metabolic disorders (primary hyperparathyroidism, other hypercalcemic disorders, renal tubular acidosis, idiopathic hypercalciuria) and/or excessive dietary calcium and phosphorus *(Kruger et al, 1999)*. Calcium phosphate crystals can trigger calcium oxalate crystallization by allowing heterogeneous crystallization to occur at a lower urinary supersaturation than homogeneous crystallization. The risks associated with calcium phosphate formation therefore should be taken in account when treating other urolith types.

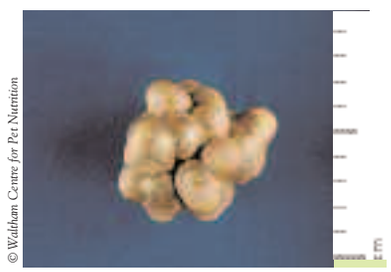


Figure 12: Calcium phosphate stones

Silica urolithiasis is a recently discovered disease *(Aldrich et al, 1997)*. The pathogenesis may involve consumption of an absorbable form of silica in various foods, resulting in urinary silica hyperexcretion. The recent emergence of these uroliths may have some relationship to the increased use of plant-derived ingredients such as fibers and bran in dog foods *(Osborne et al, 1995)*.

Compound uroliths consist of a nucleus of one mineral type and a shell of another mineral type. They form because factors promoting precipitation formation of one type of urolith supersede earlier factors promoting precipitation of another mineral type. Some minerals types may also function as a nidus for deposition of another mineral; for instance, all uroliths predispose to UTI, which may result in secondary struvite precipitation.

3 - Epidemiology

► Causes

Urolithiasis is the result of underlying inherited, congenital or acquired disorders, resulting in increased urinary excretion of certain minerals and/or predisposition to urolith formation *(Osborne et al, 1995)*. Urine composition may be altered by metabolic abnormalities. An inherited mechanism has been proven in Dalmatians (urate) and Newfoundland dogs (cystine) *(Sorenson & Ling, 1993; Henthorn et al, 2000)*, and the predilection in several other breeds suggests a possible genetic basis. Congenital causes can directly (e.g. congenital cystinuria) or indirectly (e.g. urogenital malformations) predispose an individual to form uroliths. Acquired disorders include

UTI with urease forming bacteria as well as metabolic disorders that result in an increased mineral excretion (e.g. hypercalcemia). Administration of drugs may be an aggravating cause in some cases *(Osborne et al, 1999f)*.

The incidence and mineral composition of uroliths may be influenced by a complex interaction of multiple factors, including age, sex, genetic predisposition and breed, diet, water consumption, lifestyle and the presence of UTI.

► Predisposition and risk factors

> Breed, sex, age

Urolithiasis tends to affect smaller dog breeds more often than larger breeds *(Lulich et al, 2000)*. The predisposition for smaller breeds may be related to their lower urine volume, fewer numbers of micturitions, and therefore increased mineral concentrations *(Ling, 1998; Stevenson & Markwell, 2001)* **(Table 4)**.

Breed predisposition for specific mineral types may suggest a genetic basis, and is often significantly correlated with the sex **(Table 3)** *(Stevenson, 2002)*. The genetic mode of inheritance has been determined for cystinuria in Newfoundland dogs, where it has been shown that the disease is transmitted in a simple autosomal recessive pattern *(Casal et al, 1995; Henthorn et al, 2000)*.

Most forms of urolithiasis are more common in male dogs, whereas struvite urolithiasis has a high incidence in female dogs, probably related to their greater susceptibility to develop bacterial UTIs **(Table 5).**

Urolithiasis usually occurs in mature dogs, although the age range is wide. Calcium containing stones (phosphate and oxalate) tend to be found in older dogs.

> Diet and water consumption

Diet can influence urine composition and dietary factors therefore play a significant role in increasing the risk of urolithiasis, although this may differ for certain mineral types **(Table 6)**.

TABLE 4 - RISK FACTORS FOR UROLITHS IN SMALL DOGS
(Adapted from Stevenson et al, 2001)

Small breeds are more commonly affected: Bichon frisé, Dachshund, Lhasa Apso, Miniature Poodle, Miniature Schnauzer, Shih Tzu, Yorkshire Terrier

Urinary differences observed in 8 Miniature Schnauzers and 8 Labrador Retrievers.

Urinary volume * (mL/kg $BW^{0.75}$)	Miniature Schnauzer (12 ± 3) < Labrador (22 ± 15)
Number of micturitions /day	Miniature Schnauzer (1.5 ± 0.5) < Labrador (2.9 ± 1.1)
Urinary pH	Miniature Schnauzer (6.52 ± 0.18) > Labrador (6.14 ± 0.34)

** Reduced urinary volume also observed in the Cairn Terrier (< Labrador)*

Several dietary factors have been suggested to play a role in the development of calcium oxalate urolithiasis, including low dietary moisture and sodium, and high protein content. A greater risk is associated with dry formulations *(Ling et al 1998; Lekcharoensuk et al, 2002a, 2002b)*. High moisture diets and a moderate increase in dietary sodium have been shown to reduce the risk of calcium oxalate formation in susceptible breeds of dog *(Stevenson et al, 2003b; 2003c)*. Severe purine restriction has been found to reduce urinary urate excretion in both healthy dogs and Dalmatians. There is also a strong link between silica urolithiasis and the feeding of diets high in plant ingredients such as bran or soybean hulls *(Lulich et al, 2001)*.

TABLE 5 - FACTORS THAT HELP TO PREDICT THE COMPOSITION OF CANINE UROLITHS
(Ling, 1998 ; Lulich, 2000)

	Urate	Cystine	Struvite	Oxalate
Sex	**Males: 85% of cases**	**Males: 90% of cases**	**Females: 80% of cases**	**Males: 70% of cases**
Breed predispositions	**Dalmatian** English Bulldog Miniature Schnauzer Yorkshire Terrier	**English Bulldog** Dachshund Basset Hound Yorkshire Terrier	Shi Tzu Miniature Schnauzer Miniature Poodle Bichon frisé Lhasa Apso English Cocker Spaniel	Shi Tzu Miniature Schnauzer Miniature Poodle Bichon frisé Lhasa Apso Yorkshire Terrier
Mean age	**1 - 4 years**	**1 - 8 years**	**2 - 8 years**	**5 - 12 years**
Urinary pH	**acid or neutral**	**acid or neutral**	**alkaline or neutral**	**–**
Urine infection	**–**	**–**	**2/3 cases**	**–**

> Urinary tract infections (UTIs)

UTIs predispose an individual to struvite urolithiasis, especially when associated with urease-forming bacteria. As urinary infections are more frequent in females than in males, this helps to explain why struvite uroliths occur more frequently in females and in particular spayed females.

> Environment

Differences in the pattern of urolith formation are observed between countries. Factors that predispose an individual to dehydration (e.g. hot climate, limited access to fresh water), or urinary retention in the bladder (indoor lifestyle) can increase the likelihood of urolith formation *(Franti et al, 1999)*.

> Drug administration

Diagnostic and therapeutic drugs may enhance urolithiasis by altering urine pH, tubular reab-

TABLE 6 - RISK FACTORS FOR UROLITH FORMATION LINKED TO DIET, URINE COMPOSITION AND METABOLISM IN DOGS
(adapted from Osborne et al 1999c ; Lulich et al, 2000)

Urolith type	Diet	Urine	Metabolic/other
Struvite	High magnesium* High phosphorus* Low water consumption	Alkaline pH UTI with urease-producing bacteria Low urine volume	-
Calcium oxalate	High calcium* High oxalate* (esp. when dietary calcium is low) Excess vitamin C*	Low urine volume Hypercalciuria Hyperoxaluria	Hypercalcemia Hyperadrenocorticism Chronic metabolic acidosis
Calcium phosphate	Excess dietary calcium and phosphorus*	-	Hypercalcemia (primary hyperparathyroidism) Renal tubular acidosis
Urate	High purine diets (e.g; diets rich in offal)	-	Genetically inherited defect in uric acid metabolism Hepatic dysfunction
Cystine	-	Cystinuria	Defective proximal tubular reabsorption of cystine and other basic amino acids
Silica	High dietary silica*	-	

**The level from which this dietary factor becomes important depends on the urinary environment (urinary pH, presence of inhibitors, urinary infection etc)*

sorption or secretion, and precipitation of drugs and their metabolites *(Osborne et al, 1999b,1999f)*. The prevalence of drug-induced urolithiasis is unknown, although drugs and their metabolites are more likely to precipitate in urine if uroliths are already present. The older generation sulfonamides have been most frequently implicated, although precipitation and urolithiasis may also occur with the newer generations drugs when given for prolonged times at high concentrations.

> Metabolic influences

Prolonged hypercalcemia and subsequent calciuria may increase the risk of calcium containing stones. Hyperadrenocorticism has been associated with calcium oxalate stones, since glucocorticosteroids increase mobilization of calcium from bone and reduce tubular resorption, resulting in calciuria *(Hess et al, 1998; Lulich et al, 1999)*.

Chronic metabolic acidosis may also contribute to calcium oxalate urolithiasis, which is attributed to buffering of excess hydrogen ions by bone phosphorus and carbonates, with concurrent release of calcium *(Lulich et al, 1999)* **(Figure 13)**.

Cystinuria is an inherited inborn error of metabolism that predisposes to cystine urolith formation, although not all dogs with cystinuria or cystine crystalluria form uroliths.

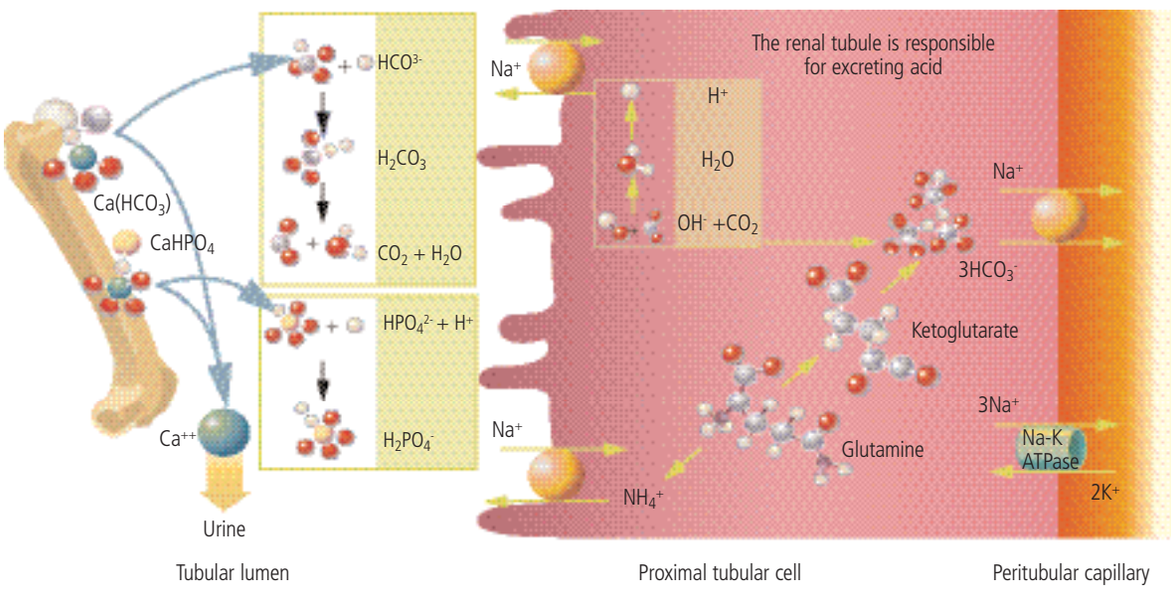
4 - Pathophysiology

► Urolith formation

> Relative supersaturation (Figure 14)

Urine supersaturation is the driving force for the formation of crystals within the urinary tract. Determination of the relative supersaturation (RSS) of urine with specific minerals has been used to identify dogs at risk for urolith formation. RSS is considered a more accurate predictor of urine crystallization potential than the formerly used activity product ratio (APR). The main limitation of the APR technique is the assumption that a steady state with respect to the solid phase will be reached by the end of the 48-hour incubation period, whereas it may take urine up to nine

FIGURE 13 - THE EFFECT OF METABOLIC ACIDOSIS ON URINARY CALCIUM EXCRETION



In the presence of metabolic acidosis the bone is stimulated to release calcium phosphates and carbonate buffers into the blood stream. The excess calcium is excreted into the urine, which increases the risk of calcium oxalate formation.

days to reach the equilibrium, particularly when coming from oversaturation *(Robertson et al, 2002; Stevenson et al, 2003c)*. In a simple solution, an RSS less than one corresponds to the undersaturated zone, and an RSS greater than one indicates the supersaturated zone. However, as urine is a complex solution, even if the urine is supersaturated, significant urine flow, inhibitors of crystallization or aggregation, and ionic forces can prevent stone formation. This is the metastable zone **(Figure 14)**. If the urine becomes even more concentrated, crystals will form spontaneously, which is called supersaturation. The RSS at which the urine will become supersatured depends upon the mineral(s) involved; it is around 2.5 for struvite and 10 to 14 for calcium oxalate in human urine *(Robertson, personal communication)*.

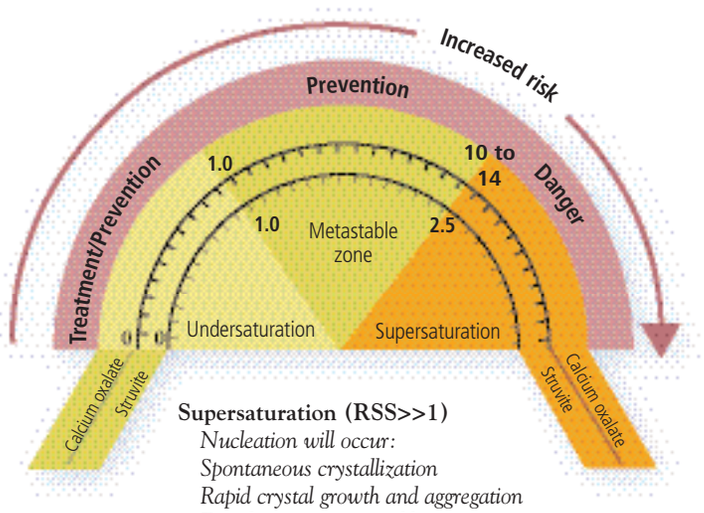
> Nucleation

The first step in the urolith development process is the formation of a crystal nidus (embryo). This phase, called nucleation, is dependent on supersaturation of urine with calculogenic substances, so that precipitation of salts and crystallization can occur *(Robertson, 1993)*. The degree of urine supersaturation may be influenced by factors such as the magnitude of renal excretion of crystalloids, favorable urine pH for crystallization **(Figure 15)**, urinary retention, and a decreased concentration of crystallization inhibitors in the urine *(Robertson et al, 2002)*.

There are many documented urinary inhibitors of calcium oxalate formation including magnesium, citrate, and macromolecular inhibitors such as nephrocalcin and glycosaminoglycans *(Robertson et al, 2002)*. The role of inhibitors within canine calcium oxalate formation has yet to be fully explored.

Urinary ion composition can affect nucleation and precipitation when there is interaction between elements in the urine. For example, magnesium binds to oxalate and citrate can bind to calcium; magnesium and citrate are therefore considered inhibitors of calcium oxalate urolithiasis.

FIGURE 14 - URINE RELATIVE SUPER SATURATION

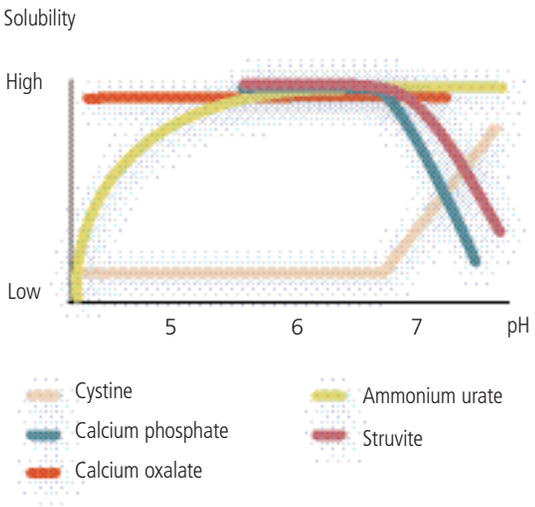


Supersaturation (RSS>>1)
Nucleation will occur:
Spontaneous crystallization
Rapid crystal growth and aggregation
Dissolution is not possible

Metastable zone (RSS>1)
Possible growth of preformed crystals
Heterogeneous nucleation may occur
Dissolution is not possible

Undersaturation (stable) (RSS<1)
No crystallization
Existing uroliths/crystals may dissolve

FIGURE 15 - SOLUBILITY AND PH
(personal communication with Dr WG Robertson)



Urinary pH can have a marked influence on the solubility of certain crystals and calculi. Struvite crystals are the most sensitive to changes in urine pH. Acidification of urine increases the solubility of struvite crystals, reducing the risk of struvite urolithiasis. Other crystals, particularly calcium oxalate, are less sensitive to urine pH.

> Growth of crystals

Once nucleation has occurred, crystal growth may occur at lesser degrees of supersaturation. Further growth of the crystal nidus then depends on the duration of its passage through the urinary tract, degree and duration of urine supersaturation for similar or other crystalloids, and crystal properties. The mechanisms leading to crystal growth are still uncertain and may include growth around a nidus or a matrix lattice, which might be facilitated by a lack of crystal aggregation inhibitors *(Osborne et al, 1995)*.

► Fate of uroliths

Uroliths may pass through various parts of the urinary tract and/or be voided, undergo spontaneous dissolution, become inactive or continue to grow. Not all persistent uroliths result in clinical signs.

5 - Nutritional management

► Stimulating diuresis

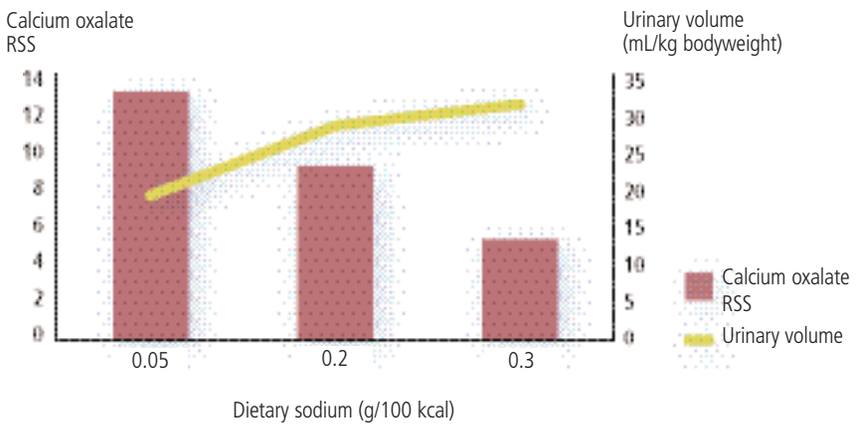
The easiest way to produce undersaturated urine is to promote diuresis. Increasing urinary flow reduces the concentration of lithogenic substances, which outweighs the disadvantage of diluting crystallization inhibitors. High urine volumes also increase the frequency of urination, which helps remove any free crystals that form in the urinary tract *(Borghi et al, 1999)*. To stimulate diuresis, drinking must be encouraged. This can be done either by feeding canned diets that contain 70 to 80% water, by adding water to the diet or by slightly increasing the sodium chloride content of dry diets. Increased dietary sodium chloride has been shown to increase water intake as well as urine production, and to decrease urine supersaturation in dogs and cats *(Stevenson et al, 2003b, Lulich et al, 2005)* **(Figure 16)**.

There has nonetheless been some controversy about the use of sodium chloride to stimulate thirst and diuresis, because it could potentially affect urinary calcium excretion and blood pressure *(Lulich et al, 1999; Osborne et al, 2000)*.

In humans, high salt intake has been associated with increased urinary calcium excretion, and similar observations were initially made in dogs *(Lulich et al, 1999; Devois et al, 2000; Biourge et al, 2001)*. This led to the assumption that salt-enriched diets could promote calcium oxalate urolithiasis and that diets for management of LUTD should thus be salt-restricted *(Osborne et al, 2000; Allen et al, 2000)*.

However, later studies failed to observe an effect of dietary salt on urinary calcium excretion in dogs *(Stevenson et al, 2003b)*. Epidemiological studies in dogs furthermore showed that increasing dietary sodium actually reduced the risk of calcium oxalate urolithiasis, because the dilutional effect of higher dietary sodium offsets the tendency towards hypercalciuria *(Lekcharoensuk et al, 2001; 2002)*.

FIGURE 16 - THE EFFECT OF DIETARY SODIUM CONTENT ON CALCIUM OXALATE RELATIVE SUPERSATURATION AND URINE VOLUME IN MINIATURE SCHNAUZERS
(Stevenson et al, 2003b)



Moderate levels of dietary sodium, which will promote diuresis, will not affect blood pressure in healthy dogs and those with moderate renal disease.

Several studies have shown that moderately increased dietary salt intakes (up to 3.2 g Na/1000 Kcal ME) do not alter blood pressure in healthy dogs, and dogs with induced renal disease *(Greco et al, 1994; Biourge et al, 2002; Kirk, 2002; Burankarl et al, 2003; Luckschander et al, 2004)*.

► Changing urine pH

Changing urine pH, via dietary manipulation or medical means, can be very effective in the management of some but not all uroliths. Urine acidification markedly increases struvite solubility and is essential in the medical dissolution of these uroliths. In contrast, urine alkalinization is important in increasing the solubility of urate and cystine uroliths **(Figure 15)**. Diet efficacy is generally increased if it also reduces urinary excretion of the crystalloids that participate in urolith formation *(Lulich et al, 2000)*.

Most other urolith types are less amenable to dissolution based upon pH changes. It is furthermore advisable to aim for a urine pH that prevents further precipitation and potentiates excretion of other minerals that may co-precipitate or act as inhibitors.

6 - General management of urolithiasis

Dissolution protocols are aimed at dissolving the urolith or arresting further growth by reducing the supersaturation of urine with calculogenic substances.

► Relief of urinary tract obstruction if necessary

This will generally require surgical removal once the patient has been stabilized. Urethral calculi in male dogs may be flushed retrograde into the bladder prior to surgery or medical dissolution.

► Elimination of existing uroliths

> Medical dissolution

Dietary modification may reduce intestinal absorption and urinary excretion of crystalloids and can also modulate urine pH. The balance between different nutrients (including calcium, phosphorus, sodium, acidifiers, dietary fiber and oxalate) depends on the formulation of the diet. This allows manufacturers to formulate diets that can change the urinary pH, stimulate diuresis, and reduce urinary mineral excretions, thereby assisting in the management of urinary stone diseases. Strategies vary according to stone type (see nutritional management). Calcium oxalate, calcium phosphate and silica uroliths cannot be dissolved medically at a physiologically useful rate and therefore need to be surgically removed before appropriate protocols to prevent recurrence are implemented *(Osborne et al, 1995)*.

GENERAL TREATMENT CONSIDERATIONS

- Cystouroliths may be managed by medical dissolution, voiding urohydropropulsion, or cystotomy
- Ureteral and urethral stones are less amenable to medical dissolution because they are not consistently in contact with undersaturated urine. Ureteroliths, when associated with complete ureteral obstruction and hydronephrosis mandate surgical removal. Ureteroliths that are associated with partial ureteral obstruction can be managed conservatively as they may move into the bladder. With respect to urethroliths it is often possible to flush them retrograde into the bladder where they can be managed with medical dissolution
- Nephroliths maybe treated by surgical removal, although medical dissolution for struvite uroliths is a consideration. Benign neglect is possible in uninfected and non-obstructing nephroliths

Adjunctive medical management is indicated when UTI is present, the urolith type is poorly amenable to dietary changes, or when there is further urolith growth. Certain drugs act specifically by interrupting metabolic pathways of crystalloid excretion, for example allopurinol in purine urolithiasis of Dalmatian dogs. Acidifying or alkalizing drugs can help alter urine pH.

During dissolution, uroliths become smaller and may pass into the urethra (in the male dog) or ureters, causing urinary obstruction and/or hydronephrosis. Owners should be warned about this possibility, and regular radiographic re-evaluation is required during

medical dissolution of nephroliths to detect ureteral calculi before they cause hydronephrosis *(Osborne et al, 1999d, Lulich et al, 2000)*. The dissolution process can last from 1 to 6 months.

> Mechanical removal

Surgery is indicated for stone types that are not or poorly amenable to medical dissolution and too large to be voided through the urethra, or when they are causing urinary obstruction. It is also required in dogs with anatomic defects of the urinary tract (e.g. bladder diverticulum) that predispose to UTI; in these cases stone removal can be combined with correction of the defect. Surgery alone is associated with a high rate of recurrence, since it does not correct the underlying factors causing urolithiasis and because it may be difficult to remove very small stones or fragments, which can later function as a nidus for further stone formation *(Lulich et al, 2000)*. Post-operative imaging is necessary to ensure that all calculi have been removed.

THE GENERAL AIM OF DIETARY MANAGEMENT OF UROLITHIASIS IS TO REDUCE SUPERSATURATION OF URINE WITH CALCULOGENIC SUBSTANCES BY:

- increasing water intake and thus urine volume to decrease urine crystalloid concentration
- altering the urine pH to increase the solubility of crystalloids in the urine
- changing the diet to decrease the quantity of crystalloids excreted in the urine

Small uroliths in the bladder and/or urethra can sometimes be removed during voiding urohydropropulsion or cystoscopy *(Osborne et al, 1999e)*.

Lithotripsy has recently been described as a means of fragmenting uroliths. Fragmentation of renal and ureteral uroliths using electrohydraulic or extracorporeal shock-wave lithotripsy has been documented in a small number of dogs *(Block et al, 1996; Adams et al, 1999)*. Laser lithotripsy has been reported effective in fragmenting bladder uroliths *(Davidson et al, 2004)*. However, all these techniques have limited availability.

► Eliminate miscellaneous risk factors

Acidifying diets are useful in preventing struvite urolithiasis but should be avoided in dogs with urate urolithiasis.

Treatment of UTI is mandatory to reduce the risk of struvite urolith formation.

Treat underlying diseases that may potentiate urolithiasis (e.g. hyperparathyroidism, hyperadrenocorticism).

► Prevention of recurrence

Correct underlying causes.

Minimize risk factors (dietary adaptation).

Increase diuresis and reduce urinary supersaturation

Struvite uroliths are generally sensitive to medical dissolution using a calculolytic diet in association with antibiotic therapy.

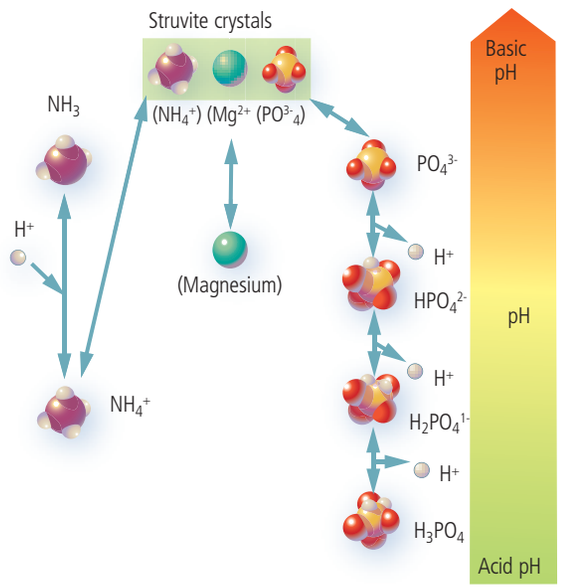
7 - Specific nutritional management

► Struvite urolithiasis

> Medical dissolution

Infection-induced struvite uroliths require a combination of appropriate antimicrobial and calculolytic dietary therapy. Sterile struvite uroliths do not need antibiotics, and can be dissolved using calculolytic dietary therapy alone or by using urinary acidifiers *(Osborne et al, 1999d; Rinkardt & Houston, 2004)* **(Figure 17)**.

FIGURE 17 - FORMATION OF STRUVITE CRYSTALS IN URINE

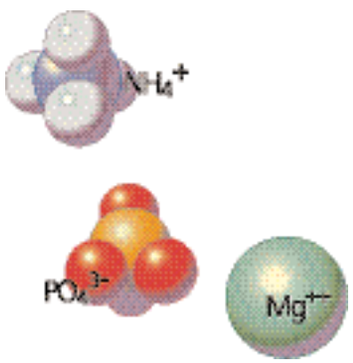


When the urine pH falls by one unit the ion balance is changed:

- *The PO_4^{3-} phosphate ions evolve towards the H_3PO_4 form and become unavailable for struvite formation (the PO_4^{3-} ion concentration is divided by 170)*
- *Ammonia (NH_3) on the other hand evolves towards the ammonium (NH_4^+) (concentration multiplied by 10)*

The final balance is that the crystal concentration of struvite is divided by 17.

STRUVITE MOLECULE



Three molecules are needed to form one struvite molecule. This reaction is reversible in an acid environment.

> Eliminate UTI

Antibiotic treatment should be based upon culture and sensitivity determination of urine obtained by cystocentesis. It should be continued until uroliths can no longer be detected radiographically, since viable bacteria may remain inside the urolith *(Seaman & Bartges, 2001)*. Urine should be sterile on repeated cultures, and antibiotics should be changed (according to sensitivity results) if UTI persists.

> Calculolytic diet to dissolve uroliths

These diets are aimed to reduce urine concentrations of urea, phosphorus and magnesium *(Lulich et al, 2000)*. Commercial calculolytic diets contain moderate amounts of protein (15-20% in a 4000 kcal/kg diet), are highly digestible, low in fiber (to reduce fecal water loss), and contain increased levels of NaCl. Dietary protein restriction reduces the amount of substrate (urea) available in urine for urease-producing bacteria. Dietary efficacy has been shown in clinical studies *(Osborne et al, 1999d; Rinkardt & Houston, 2004)*. Calculolytic diets should be given for at least one month after removal or dissolution of struvite uroliths, because uroliths too small for radiographic detection may still be present. Dogs can then be changed to a normal diet.

Dissolution therapy should be monitored with monthly abdominal radiographs or ultrasound examination and regular urinalyses (pH of morning urine should be 6.5, with no evidence of UTI). The average time for dissolution of infection-induced struvite uroliths is approximately 3 months, although clinical signs usually resolve in the first 2 weeks, probably due to control of the UTI. Sterile struvite stones tend to dissolve more rapidly, typically taking 5-6 weeks *(Osborne et al, 1999d)*.

> Drug therapy

Urinary acidifying agents such as ammonium chloride are not necessary provided a calculolytic diet and antimicrobials are given. Persistent alkaline urine pH indicates continued UTI, and pH will not go down until this is controlled *(Lulich et al, 2000)*.

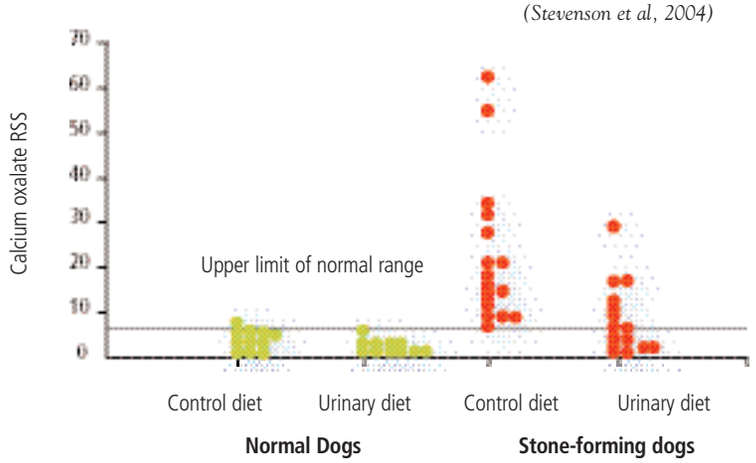
Acetohydroxamic acid (AHA) is a microbial urease inhibitor that blocks the hydrolysis of urea to ammonia, consequently lowering urine pH and ammonium concentration. It may therefore inhibit struvite growth and promote dissolution. AHA (12.5 mg/kg orally every 12 h) may be helpful in dogs with infection-induced struvite urolithiasis that is refractory to antibiotic therapy and dietary dissolution (Krawiec et al, 1984). However, this drug has many side effects, including hemolytic anemia, anorexia and vomiting. It should not be given to dogs with renal failure, since it is excreted via the kidneys, or to pregnant animals, since it is teratogenic *(Baillie et al, 1986; Osborne et al, 1995)*.

Amino acid preparations have been reported effective in the dissolution of sterile struvite nephroliths, although this concerned only 2 dogs; their efficacy is probably due to urine acidification *(Mishina et al, 2000)*. There are no reports of its use in dogs with infection-induced struvite stones.

The most important factor in preventing infection-induced struvite urolithiasis is resolution of the underlying UTI and prevention of recurrence. Preventative dietary therapy is particularly important for the rare dogs with sterile struvite calculi without concomitant infection. Only those diets specifically designed for long term feeding should be fed for prolonged periods.

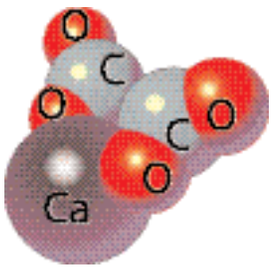
FIGURE 18 - COMPARISON OF CALCIUM OXALATE RSS IN HEALTHY DOGS AND DOGS PREDISPOSED TO CALCIUM OXALATE STONES BASED ON DIET

(Stevenson et al, 2004)



These results illustrate the influence of diet on the urinary oxalate supersaturation (RSS) in healthy dogs and dogs predisposed to calcium oxalate stones receiving either a standard food (control diet) or an acidifying food to dilute the urine (Royal Canin Veterinary Diet Canine Urinary SO canned).

CALCIUM OXALATE MOLECULE



One molecule of oxalate will associate with one molecule of calcium to form a very stable molecule of calcium oxalate.

► Calcium oxalate urolithiasis

Calcium oxalate uroliths do not respond to medical dissolution. Symptomatic calculi require mechanical removal, after which preventative medical protocols should be implemented to prevent recurrence. Dogs predisposed to calcium oxalate urolithiasis may also benefit from a preventative diet (Figure 18).

> Prevention of recurrence

These uroliths have a high recurrence rate, up to 50% by 2 years after initial removal *(Lulich et al, 1995; 1998)*. Medical protocols are therefore essential to reduce urolith recurrence following removal and dietary modification can greatly reduce the risk of recurrence in affected individuals *(Stevenson et al, 2004)*.

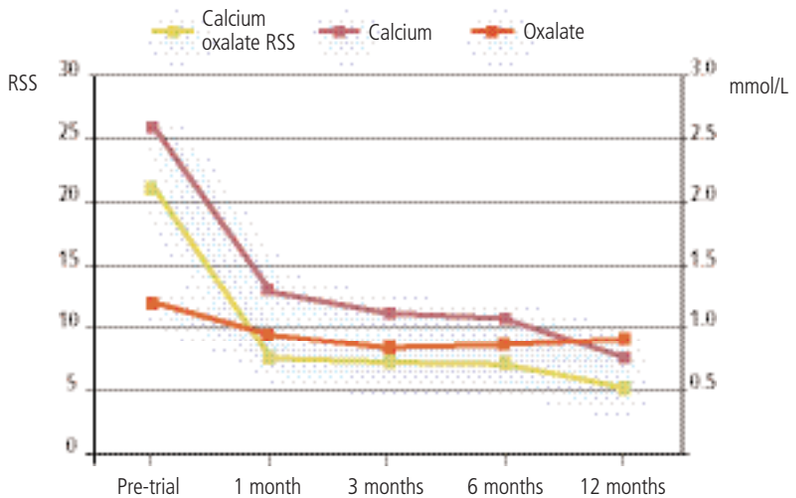
> Eliminate risk factors

If the dog is hypercalcemic or has other diseases (e.g. hyperadrenocorticism), the underlying cause should be corrected. Usually no further preventative measures will be required *(Lulich et al, 1998)*.

If the dog is normocalcemic, risk factors for urolithiasis should be identified and controlled. Dry acidifying diets that have not been formulated to increase diuresis and drugs that promote excessive urinary calcium excretion (urinary acidifiers, furosemide, glucocorticosteroids) should be avoided.

FIGURE 19 - EFFECT OF A DIET SPECIFICALLY DESIGNED TO LOWER THE URINARY CALCIUM OXALATE RSS IN DOGS WITH NATURALLY OCCURING CALCIUM OXALATE UROLITHIASIS

(Stevenson et al, 2004)



No treats or dietary supplements containing calcium, vitamin D or excessive amounts of vitamin C should be given, since these can promote increased excretion of calcium and/or oxalate *(Lulich and Osborne, 1995)*.

Calcium oxalate preventative diets should stimulate water consumption, and should not be restricted in protein, calcium or phosphorus. A recent clinical study has proven that dietary modification can reduce the risk factors associated with calcium oxalate formation thereby reducing the risk of recurrence in susceptible individuals **(Figure 19)** *(Stevenson et al, 2004)*.

> Dietary modification

• *Diuresis*

Augmenting water intake, either by feeding a canned diet or by adding water and/or sodium chloride to the food, remains the major factor in managing and preventing calcium oxalate urolithiasis *(Lulich et al, 1998; Lekcharoensuk et al, 2002b; Stevenson et al, 2003a, 2003b, Lulich et al, 2005)*.

• *Sodium*

Dry diets have been associated with a greater risk of stone formation *(Lekcharoensuk et al, 2002a)*, particularly if the diet is low in sodium chloride. This may be due to the fact that these diets do not stimulate adequate diuresis, particularly in small-breed dogs that have been shown to eliminate smaller quantities of urine less frequently than large-breed dogs *(Stevenson et al, 2001)*.

Research has shown that urinary calcium oxalate RSS, and therefore the risk of calcium oxalate formation, can be significantly decreased by increasing the dietary sodium content from 0.06 g/100 kcal to 0.30 g/100 kcal *(Stevenson et al, 2003a)*.

• *Calcium and phosphorus*

Recommendations for dietary calcium and phosphorus levels in calcium oxalate preventative diets are changing. Previously it was advised to restrict dietary calcium and phosphorus, but recent studies suggest that this may actually promote calcium oxalate stone formation *(Curhan et al, 1993; Lekcharoensuk et al, 2002a, 2002b)*. Restriction of dietary calcium without concomitant reduction in oxalate results in augmented intestinal absorption and urinary excretion of oxalate, which increases the risk of urolithiasis *(Lulich et al, 2000; Stevenson et al, 2003a)*. Dietary phosphorus restriction also increases calcium absorption *(Lulich & Osborne, 1995)*. Consequently, calcium oxalate preventative diets should not be calcium or phosphorus restricted *(Curhan et al, 1993, 1997)*.

• *Protein*

Dietary protein content is controversial. Previously it was recommended to lower protein content, since protein could increase calcium excretion and reduce excretion of citrate (citrate chelates calcium to form a soluble salt) *(Lulich et al, 1995, 2000)*. However, studies indicate that higher levels of dietary protein reduced the risk of urolithiasis *(Lekcharoensuk et al, 2002a; 2002b)*. The mechanism is unknown but may well be due to other factors, since high protein diets stimulate diuresis and also contain more phosphorus and potassium.

• *Urinary pH*

Calcium oxalate crystals are generally not sensitive to urine pH, although pH affects the minerals that co-precipitate with calcium oxalate *(Robertson, 1993)*. Marked acidification that induces metabolic acidosis can increase urinary calcium concentration to such extent that it promotes calcium oxalate stone formation *(Lekcharoensuk et al, 2002a; 2002b)*. Marked alkalinization should also be avoided since it promotes calcium phosphate urolithiasis. Diets resulting in mild acidification (pH 5.5-6.5) and increased diuresis may reduce the risk of both calcium oxalate and struvite crystal formation, useful in breeds predisposed to both stone types *(Stevenson et al, 2002)*.

> Drug therapy

Adjunct medical therapy is used if there is persistence of calcium oxalate crystalluria or recurrence of urolithiasis.

Potassium citrate has been useful in humans to prevent recurrent calcium oxalate urolithiasis, via its alkalinizing properties and by forming soluble salts with calcium.

Oral potassium citrate increases urine pH, which causes decreased tubular resorption of citrate, thus increasing urinary citrate excretion. However, oral administration of up to 150 mg/kg/day did not cause a consistent increase in urine citrate concentrations in healthy dogs, although it main-

tained a higher urine pH later in the day *(Stevenson et al, 2000)*. There was no difference between wax matrix and powder supplements.

Hydrochlorothiazide (2-4 mg/kg orally BID) reduces urine calcium excretion, possibly by promoting mild volume contraction resulting in increased proximal tubular reabsorption of several solutes, including calcium and sodium *(Lulich et al, 2000)*. Its hypocalciuric effects may be helpful in minimizing recurrence of calcium oxalate urolith formation, especially when combined with a urolith prevention diet *(Lulich et al, 2001)*. However, long-term clinical studies are needed to confirm safety and effectiveness of prolonged administration; it has the potential to cause hypokalemia, hypercalcemia and dehydration.

> Monitoring

Efficacy of therapy should initially be monitored with urinalysis (pH, specific gravity) every 2 to 4 weeks. With hydrochlorothiazide treatment serum electrolytes should also be checked. Imaging every 6 to 12 months may help to detect any new uroliths when they are small enough to be removed non-invasively (e.g. voiding urohydropropulsion) *(Lulich et al, 2000)*.

► Urate urolithiasis

> Medical dissolution in dogs without portosystemic shunts

The chief goal in dietary dissolution of urate uroliths in Dalmatian dogs is to raise urine pH and to lower urine concentrations of uric acid, ammonium and/or hydrogen ions.

> Calculolytic diet

The dietary strategy aims at decreasing the purine content of the diet. This goal is achieved through general protein restriction (18 to 10%). However, it is possible to design a low purine diet without imposing a severe protein restriction if appropriate ingredients are selected. Fish or glandular organs, which are high in purine, should be avoided. Alternative protein sources that are relatively low in purine precursors include: vegetable proteins, eggs and dairy products *(Ling & Sorenson, 1995)*. No other food supplements should be given. Low protein anti-uric acid diets may contain insufficient protein to sustain growth and lactation. Experimental diets have been designed that could meet both requirements *(Bijster et al, 2001)*. As with all urolith types, feeding a canned diet, adding supplemental water to the food, or increasing the sodium content can help to increase urinary volume. In addition, low-protein diets impair urinary concentrating capacity by decreasing the medullary concentration gradient, due to the lower urea concentration in the renal medulla.

THE MEDICAL DISSOLUTION OF URATE CALCULI INCLUDES A COMBINATION OF:

- feeding a low purine diet that has been designed to dissolve urate calculi
- alkalinization of the urine
- increasing urine volume
- controlling urinary tract infections
- administering xanthine oxidase inhibitors (allopurinol)

> Alkalinization of urine

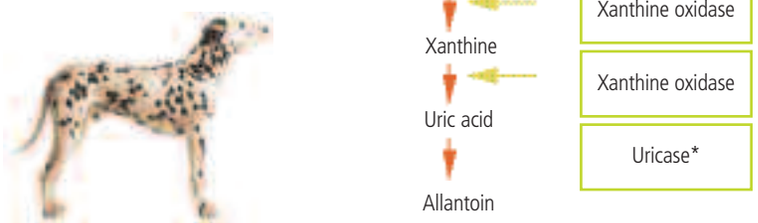
Alkaline urine contains low concentrations of ammonia and ammonium ions, and thus decreases the risk of ammonium urate urolithiasis. Low-protein diets have an alkalinizing effect, but it may be necessary to administer additional urine alkalinizing agents *(Lulich et al, 2000)*. Sodium bicarbonate (25-50 mg/kg every 12 hours) and potassium citrate (50-150 mg/kg every 12 hours) are used most commonly. The dose should be individualized to maintain a urine pH of approximately 7.0. Urine pH >7.5 should be avoided since this promotes formation of secondary calcium phosphate deposits, which will hamper stone dissolution *(Bartges et al, 1999)*.

> Xanthine oxidase inhibitors

Urinary urate excretion is lowered most effectively by using allopurinol, which is an inhibitor of xanthine oxidase, the enzyme responsible for catalyzing the conversion of xanthine and hypoxanthine to uric acid **(Figure 20)**. As a result of allopurinol therapy, xanthine and hypoxanthine concentrations in the urine increase, but urate decreases.

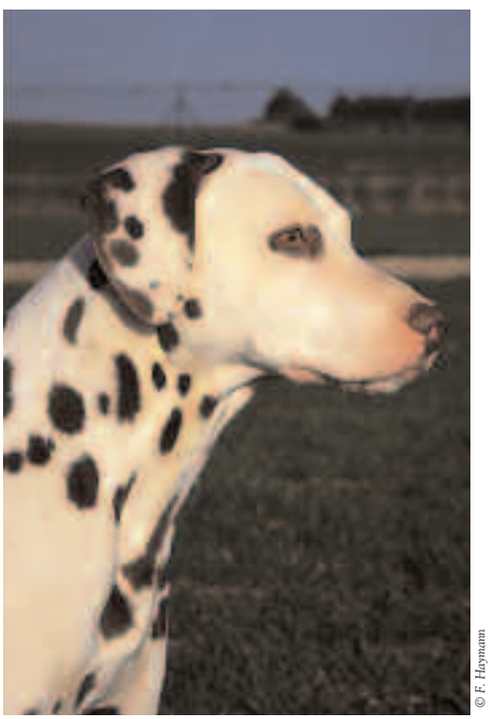
Allopurinol should be given in conjunction with a low-purine diet, in order to minimize the risk of xanthine stone formation *(Ling et al, 1991; Bartges et al, 1999)*. The recommended dose for dissolution of urate uroliths is 15 mg/kg every 12 hours *(Lulich et al, 2000)*. The dose must be reduced in patients with renal dysfunction, since allopurinol is excreted by the kidneys. A variety of adverse effects, including skin rashes, GI upsets and hemolytic anemia, have been described in

FIGURE 20 - NORMAL CANINE PURINE DEGRADATION



* *reduced activity in Dalmatian dogs.*

humans, but these are rare in the dog. The most common adverse effect of allopurinol therapy in dogs is development of xanthine uroliths, either in pure form or as an outer shell around pre-existing urate stones. Discontinuing allopurinol and instituting a low-purine diet can sometimes dissolve xanthine uroliths *(Ling et al, 1991)*.



In Dalmatian dogs, 82% of stones are urate stones (Bartges et al, 1994).

> Monitoring

During dissolution the size of the urolith(s) must be periodically monitored by survey and/or double contrast radiography, or ultrasonography. Excretory urography or ultrasonography are used to monitor dissolution of renal urate stones *(Bartges et al, 1999)*. Time required for dissolution is highly variable and can take between 4 and 40 weeks although average length of time in one study was 14 weeks *(Bartges et al 1999)*. Following removal or dissolution, urinalysis and ultrasonographic examination (or double contrast cystography) should be performed every 1 to 2 months for 6 months.

Even if uroliths do not reoccur the purine-restricted alkalinizing diet should be continued. Follow-up examinations can then be extended to every 2 to 4 months, and the intervals between examinations can be gradually increased.

> Medical dissolution in dogs with portosystemic shunts

Little is known about the biologic behavior of urate calculi following surgical correction of portosystemic shunts. When the urolith cannot be removed at the time of shunt ligation, postsurgical medical dissolution should be considered. However, more studies are needed to compare the relative value of calculolytic diet, alkalinization and/or allopurinol in dissolving ammonium urate uroliths in dogs with portosystemic shunts.

> Prevention

- *Dalmatian dogs*

Preventative treatment following removal or dissolution is important in Dalmatian dogs because of their high risk for urate urolith recurrence. As a first choice, low-purine diets that promote the formation of dilute alkaline urine should be fed. If urine pH is not consistently alkaline and/or crystalluria persists, alkalinizing agents may be added. Preventative treatment with allopurinol is not recommended routinely due to the risk of xanthine urolith formation, but it may be added to the protocol if difficulties persist. Long-term allopurinol therapy is not recommended.

It is not necessary to feed purine-restricted diets to Dalmatian dogs that have not had urate urolithiasis. Acidifying high-protein diets that enhance excretion of ammonium ions should however be avoided as ammonium ions are likely to get linked to urate ions to from ammonium urate crystals.

- *Non-Dalmatian dogs*

Recurrence of urate urolithiasis has been described in English bulldogs, and preventative measures as discussed for Dalmatian dogs should be implemented *(Bartges et al, 1999)*. Dogs fed protein-restricted diets (10 %) long-term may develop taurine deficiency, which might lead to dilated cardiomyopathy. Commercial protein-restricted diets are therefore now supplemented with taurine *(Sanderson et al, 2001a)*.

► Cystine uroliths

> Medical dissolution

The aim of therapy is to reduce the concentration of cystine in the urine and to increase cystine solubility. This usually requires dietary modification in combination with a thiol-containing drug.

> Calculolytic diet

Reduction of dietary protein can reduce cystine excretion, presumably because these diets contain fewer cystine precursors *(Osborne et al, 1999g)*. However, the optimal degree of protein restriction is controversial, since cystinuric dogs also excrete carnitine and therefore have the potential to develop carnitine deficiency and dilated cardiomyopathy when fed low-protein diets. It is therefore recommended to supplement cystinuric dogs eating a protein-restricted diet with carnitine as well as taurine *(Sanderson et al, 2001b)*.

> Alkalinization of urine

CYSTINE UROLITHS CAN BE DISSOLVED MEDICALLY, USING A COMBINATION OF:

- protein-restricted alkalinizing diet
- increasing urine volume
- alkalinization of urine (pH around 7.5)
- administration of thiol-containing drugs

The solubility of cystine is pH dependent. It is markedly more soluble at urine pH of 7.5-7.8. Urine alkalinization may be achieved using a commercial moderate to low-protein alkalinizing diet. If urine pH does not become sufficiently alkaline on dietary therapy alone, additional potassium citrate may be given to sustain a urine pH of approximately 7.5 (*Osborne et al, 1999g*). This has to done cautiously, since alkalinization can be a risk factor for calcium phosphate urolithiasis.

- *Thiol-containing drugs*

These drugs react with cystine by a thiol disulfide exchange reaction, resulting in the formation of a complex that is more soluble in urine than cystine. N-(2-mercaptopropionl)-glycine (2-MPG) is most commonly used, at a dose of 20 mg/kg twice daily orally. It has proven effec tive in dissolving cystine uroliths, especially when used in conjunction with a calculolytic diet (*Lulich et al, 2000*).

Time for dissolution ranges from 1 to 3 months. Side-effects are relatively uncommon; aggression, myopathy, anemia and/or thrombocytopenia have been reported, but signs resolved when the treatment was stopped *(Osborne et al, 1999g; Hoppe & Denneberg, 2001)*. D-penicillamine is an older thiol-containing drug that has been used with some efficacy in the past, but it is no longer used due to an unacceptable number of adverse effects, including frequent hypersensitivity reactions.

> Monitoring

Urolith dissolution should be monitored at 30-day intervals by urinalysis (pH, specific gravity, sediment) and serial radiography to evaluate stone location, number, size, density and shape. Contrast radiography may be used for radiolucent stones. The calculolytic diet, 2-MPG and alkalinizing therapy should be continued for at least one month following radiographic disappearance of uroliths.

> Prevention

Preventative therapy is important, because cystinuria is an inherited metabolic defect and because cystine uroliths recur in most stone-forming dogs within 12 months following surgical removal. Recurrence is more likely to occur if the dog excretes large amounts of cystine. A moderate to low-protein diet that promotes formation of alkaline urine can be effective in preventing cystine urolith recurrence in dogs with low to moderate cystinuria. If necessary, dietary therapy may be combined with alkalinzation therapy to increase urinary pH and prevent cystine urolithiasis *(Hoppe et al, 1993; Hoppe & Denneberg, 2001)*.

Treatment should be titrated to maintain a negative urine cyanide-nitroprusside test. The severity of cystinuria may decline with advancing age in some dogs; consequently, the dose of 2-MPG may be decreased or even stopped *(Hoppe & Denneberg, 2001)*.

► Calcium phosphate urolithiasis

> Medical dissolution

- ***Underlying metabolic disease***

Calcium phosphate uroliths may rarely dissolve spontaneously following parathyroidectomy for treatment of primary hyperparathyroidism. If stones are clinically silent, one might wait for this to occur before contemplating surgical or non-surgical removal. Medical dissolution is not effective in distal renal tubular acidosis.

- ***Idiopathic uroliths***

If a specific underlying disorder is not diagnosed, calcium phosphate uroliths are removed surgically and then managed as for calcium oxalate urolithiasis *(Lulich et al, 2000)*.

Calcium phosphate uroliths cannot be medically dissolved, and surgical removal is usually necessary. Correction of underlying metabolic abnormalities may minimize recurrence. If no underlying cause is found, management is similar to that of calcium oxalate urolithiasis.

> Prevention

Recognition and management of underlying contributing conditions is the first and most important step in the prevention of calcium phosphate urolithiasis. The patient should be assessed for evidence of primary hyperparathyroidism, hypercalcemia, excessive urine concentrations of calcium and/or phosphate, and inappropriately alkaline urine pH. There may also be a previous history of dietary therapy and administration of alkalinizing agents to prevent another urolith type.

If a specific underlying disorder is not diagnosed, calcium phosphate uroliths are generally managed similar to strategies used for calcium oxalate urolithiasis *(Lulich et al, 2000)*. One should however be careful to avoid excessive urine alkalinization, which may occur with some diets used for prevention of calcium oxalate uroliths.

► Silica urolithiasis

> Prevention

Because the initiating and precipitating causes of silica urolithiasis are not well known, only nonspecific recommendations are available.

Silica uroliths may occur in dogs with pica (i.e. eating soil) or in dogs eating diets high in cereal grains containing silicates. Empiric recommendations are to change the diet to one with high quality protein and if possible reduced quantities of non nutritive plant ingredients *(Osborne et al, 1999a)*.
As with all uroliths, increased water intake should be promoted to decrease the resulting concentration of calculogenic material in urine.

► Compound uroliths

Dissolution of compound uroliths should theoretically be aimed at implementing subsequent protocols for dissolving the various layers of the urolith, starting with the outer layer. In practice, most compound uroliths are removed surgically or by other non-surgical means. The post-removal strategy is generally aimed at preventing the reformation of the mineral that composed the core of the removed urolith, since the outer layer(s) were probably deposited secondarily due to heterogeneous nucleation *(Osborne et al, 1999c)*.

Conclusion

Following removal of compound (mixed) uroliths, medical dissolution strategies are usually based on preventing the reformation of the mineral that composed the core of the compound urolith.

Dietary modification is an important part of the management regimen for struvite urolithiasis. Diet influences the saturation of urine with struvite as it impacts urine pH, volume and solute concentration. Urine pH is the most important factor controlling struvite saturation. Reduction of urine pH through dietary manipulation is thus likely to be the most reliable means of achieving urine which is undersaturated with struvite. Restriction of dietary crystalloid intake may also be beneficial, although changes in urinary magnesium or phosphate concentration individually, have much less impact on struvite saturation than changing urine pH.

The goal of dietary management for calcium oxalate urolithiasis is to create urine that has a low saturation with calcium oxalate. Ideally, urine should be undersaturated as new crystal formation cannot occur under these circumstances; however, this may be difficult to achieve in some patients. Homogeneous crystal formation will not occur, and heterogeneous crystal formation is unlikely to occur, in the lower part of the metastable zone of supersaturation. Therefore this represents a reasonable target that should reduce the risk of recurrence in patients.

Enhancing urine volume for a given solute load will also reduce saturation, as it will decrease the concentrations of crystalloids. In addition, increasing urine volume may influence crystal transit time through the urinary tract, thus reducing the potential for crystal growth.

Frequently asked questions: urolithiasis

Q	A
A dog with signs of cystitis has cystic calculi on abdominal radiography. What is the next approach?	(1) Culture the urine to look for UTI. Primary UTI may predispose to struvite urolithiasis, and other stones may result in a secondary UTI resulting in a struvite shell around the primary stone. Treatment of the UTI will be helpful in both situations. (2) Assessment of the type of crystals in the urine may help to suspect which stones are present. (3) Spontaneous voiding, aspiration through a urethral catheter, voiding urohydropropulsion or surgical removal will identify the stone type, enabling specific therapy. Note: urate and cystine stones are usually radiolucent, and require positive contrast studies or ultrasound for demonstration. They are therefore less likely when stones are radiographically visible.
How do I treat renal calculi?	Nephroliths are generally treated by surgical removal, although medical dissolution may be possible for struvite uroliths. Lithotripsy may be available in some cases. Benign neglect is possible in uninfected and non-obstructing nephroliths.
What is the best way to manage a dog with both renal and cystic calculi?	First, find out what the composition of the stones is. Calcium oxalate, calcium phosphate and silica uroliths cannot be dissolved medically and need to be surgically removed before protocols to prevent recurrence are implemented. Adjunctive medical management is indicated when UTI is present, the urolith type is poorly amenable to dietary changes, or when there is further urolith growth.
How do I handle a dog with struvite calculi?	Struvite uroliths are generally sensitive to medical dissolution using a calculolytic diet in association with antibiotic therapy. Commercial calculolytic diets are aimed to acidify and to reduce urine concentrations of urea, phosphorus and magnesium. They should be given for at least one month after removal or dissolution of struvite uroliths, because uroliths too small for radiographic detection may still be present. Dogs can then be changed to a normal diet. Urinary acidifying agents such as ammonium chloride are not necessary provided a calculolytic diet and antimicrobials are given.
What diet should I feed to a dog after surgery for calcium oxalate uroliths?	Calcium uroliths have a high incidence of recurrence, so preventative therapy is important. First, identify and treat any underlying causes that may have contributed to calcium urolithiasis, such as hyperparathyroidism and hyperadrenocorticism. Subsequently risk factors should be minimized by dietary adaptation. It will help to feed wet diets or special sodium-enriched dry diets that promote diuresis, and to avoid drugs that promote calciuresis, e.g. furosemide and urinary acidifiers. The diet should contain normal levels of protein, calcium and phosphorus.
How to manage a Dalmatian dog with suspected ammonium urate urolithiasis?	Since this is a Dalmatian, the most likely diagnosis is ammonium urate stones. A presumptive diagnosis can be achieved by looking for urate crystals in the urine. As a first choice, low-purine diets (e.g. vegetables, eggs and dairy products) that promote the formation of dilute alkaline urine should be fed. As with all urolith types, feeding a canned diet or adding supplemental water to the food helps to increase urinary volume. Allopurinol therapy will help to further reduce urinary urate excretion.

References

Allen TA, Kruger JM. Feline lower urinary tract disease - In: Hand MS, Thatcher CD, Remillard RL (eds). Small animal clinical nutrition. Walsworth, Missouri, 2000: 689-723.

Adams LG, Senior DF -Electrohydraulic and extracorporeal shock-wave lithotripsy. Vet Clin North Am Small Anim Pract 1999; 29: 293-302.

Aldrich J, Ling GV, Ruby AL et al - Silica-containing urinary calculi in dogs (1981-1993). J Vet Intern Med. 1997; 11: 288-295.

Baillie NC, Osborne CA, Leininger JR - Teratogenic effects of acetohydroxamic acid in clinically normal beagles. Am J Vet Res 1986; 47:2604-2611.

Bartges JW, Osborne CA, Felice LJ et al - Prevalence of cystine and urate uroliths in English bulldogs and urate uroliths in Dalmatian dogs. J Am Vet Med Assoc 1994; 204: 1914-1918.

Bartges JW, Osborne CA, Lulich JP et al - Canine urate urolithiasis. Vet Clin North Am 1999; 29: 161-191.

Biourge V, Devois C, Morice G et al - Increased dietary NaCl significantly increases urine volume but does not increase urinary calcium oxalate supersaturation in healthy cats. Proceedings of the 19th American Congress of Veterinary Internal Medicine, Denver, Colorado, 2001: 866.

Biourge V, Iben C, Wagner E et al - Does increasing dietary NaCl affect blood pressure in adult healthy dogs. Proceedings of the 12th Congress of the European College of Veterinary Internal Medicine, Munich, 2002: 153.

Borghi L, Meschi T, Amato F et al - Urine volume: stone risk factor and preventive measure. Nephron 1999; 81(suppl): 31-37.

Block G, Adams LG, Widmer WR et al - Use of extracorporeal shock wave lithotripsy for treatment of nephrolithiasis and ureterolithiasis in five dogs. J Am Vet Med Assoc 1996; 208: 531-536.

Bijster S, Nickel RF, Beynen AC - Comparison of the efficacy of two anti-uric acid diets in Dalmatian dogs. Acta Vet Hung 2001; 49: 295-300.

Burankarl C, Mathur SS, Cartier LI et al - Effects of dietary sodium chloride (NaCl) supplementation on renal function and blood pressure (BP) in normal cats and in cats with induced renal insufficiency. Proceeding of the WSAVA congress, Bangkok, Thailand. 2003:749.

Cannizzo KL, McLoughlin MA, Chew DJ et al - Uroendoscopy. Evaluation of the lower urinary tract. Vet Clin North Am Small Anim Pract 2001; 31: 789-807.

Carvalho M, Lulich JP, Osborne CA et al - Role of urinary inhibitors of crystallization in uric acid nephrolithiasis: Dalmatian dog model. Urology 2003; 62: 566-570.

Casal ML, Giger U, Bovee KC et al - Inheritance of cystinuria and renal defect in New foundlands. J Am Vet Med Assoc 1995; 207: 1585-1589.

Case LC, Ling GV, Franti CE et al - Cystine-containing urinary calculi in dogs: 102 cases (1981-1989). J Am Vet Med Assoc. 1992; 201: 129-133.

Case LC, Ling GV, Ruby AL et al - Urolithiasis in Dalmatians: 275 cases. J Am Vet Med Assoc 1993; 203: 96-100.

Curhan GC, Willett WC, Rimm EB et al - A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. N Engl J Med 1993; 328: 833-838.

Curhan GC, Willett WC, Speizer FE et al - Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. Ann Intern Med 1997; 126:497-504.

Davidson EB, Ritchey JW, Higbee R et al - Laser lithotripsy for treatment of canine uroliths. Vet Surg. 2004; 33: 56-61.

Devois C, Biourge V, Morice G et al - Influence of various amounts of dietary NaCl on urinary Na, Ca, and oxalate concentrations and excretions in adult cats. Proceed 10th Congress Eur Soc Vet Int Med, Neuchâtel, Switzerlands 2000: 85.

Franti CE, Ling GV, Ruby AL et al - Urolithiasis in dogs. V: regional comparisons of breed, age, sex, anatomic location, and mineral type of calculus. Am J Vet Res 1999; 60: 29-42.

Greco DS, Lees GE, Dzendzel G et al - Effects of dietary sodium intake on blood pressure measurements in partially nephrectomized dogs. Am J Vet Res 1994; 55: 160-165.

Hamaide AJ, Martinez SA, Hauptman J et al - Prospective comparison of four sampling methods (cystocentesis, bladder mucosal swab, bladder mucosal biopsy, and urolith culture) to identify urinary tract infection in dogs with urolithiasis. J Am Anim Hosp Assoc 1998; 34: 423-430.

Henthorn PS, Liu J, Gidalevich T et al - Canine cystinuria: polymorphism in the canine SLC3A1 gene and identification of a nonsense mutation in cystinuric Newfoundland dogs. Hum Genet 2000; 107: 295-303.

Hess RS, Kass PH, Ward CR - Association between hyperadrenocorticism and development of calcium-containing uroliths in dogs with urolithiasis. J Am Vet Med Assoc 1998; 212: 1889-1891.

Hoppe A, Denneberg T, Jeppsson JO, et al - Canine cystinuria: an extended study on the effects of 2-mercaptopropionylglycine on cystine urolithiasis and urinary cystine excretion. Br Vet J. 1993;149(3):235-51

Hoppe A, Denneberg T - Cystinuria in the dog: clinical studies during 14 years of medical treatment. J Vet Intern Med 2001;15(4):361-7.

Houston DM, Moore AEP, Favrin et al - Canine urolithiasis : a look at over 16000 urolith submissions to the Canadian Veterinary Urolith Centre from February 1998 to April 2003. Can Vet J 2004; 45: 225-230.

Kirk CA - Dietary Salt and FLUTD: Risk or Benefit? Proceedings of the 20th American College of Veterianary Internal Medicine Forum. Dallas, Texas, 2002: 553-555.

Klausner JS, O'Leary TP, Osborne CA - Calcium urolithiasis in two dogs with parathyroid adenomas. J Am Vet Med Assoc 1987; 191: 1423-1426.

Krawiec DR, Osborne CA, Leininger JR - Effect of acetohydroxamic acid on the dissolution of canine uroliths. Am J Vet Res 1984; 45: 1276-1284.

Kruger JM, Osborne CA - Etiopathogenesis of uric acid and ammonium urate uroliths in non-Dalmatian dogs. Vet Clin North Am 1986: 16: 87-126.

Kruger JM, Osborne CA, Lulich JP - Calcium phosphate urolithiasis: etiopathogenesis, diagnosis and management. Vet Clin N Am 1999; 29: 141-159.

Lekcharoensuk C, Osborne CA, Lulich JP et al - Associations between dry dietary factors and canine calcium oxalate uroliths. Am J Vet Res 2002a; 63: 330–337.

Lekcharoensuk C, Osborne CA, Lulich JP et al - Associations between dietary factors in canned food and formation of calcium oxalate uroliths in dogs. Am J Vet Res 2002b; 63: 163-169.

Ling GV - Urolithiasis in dogs. II: breed prevalence and interrelations of breed, sex, age and mineral composition. Am J Vet Res 1998; 59: 630-642.

Ling GV, Ruby AL, Harrold DR et al - Xanthine-containing urinary calculi in dogs given allopurinol. J Am Vet Med Assoc 1991; 198: 1935-1940.

Ling GV, Sorenson JL - CVT Update: Management and prevention of urate urolithiasis. In: Kirk's Current Veterinary Therapy XII, Bonagura JW (ed). Philadelphia: WB Saunders Co, 1995: 985-989.

Ling GV, Thurmond MC, Choi YK et al - Changes in proportion of canine urinary calculi composed of calcium oxalate or struvite in specimens analysed from 1981 to 2001. J Vet Int Med 2003; 17: 817-823.

Luckschander N, Iben C, Hosgood G et al - Dietary NaCl does not affect blood pressure in healthy cats. J Vet Intern Med 2004; 18(4): 463-7.

Lulich JP, Osborne CA - Canine calcium oxalate uroliths. In: Kirk's Current Veterinary Therapy XII, Bonagura JW (ed). Philadelphia: WB Saunders Co, 1995: 992-996.

Lulich JP, Osborne CA, Bartges JW et al - Canine lower urinary tract disorders. In Ettinger SJ, Feldman EC, (eds). Textbook of Veterinary Internal Medicine Diseases of the Dog and Cat. 5th edition. Philadelphia: WB Saunders Co, 2000: 1747-1781.

Lulich JP, Osborne CA, Thumchai R et al - Management of canine calcium oxalate urolith recurrence. Comp Cont Educ Pract Vet 1998; 20: 178-189.

Lulich JP, Osborne CA, Thumchai R et al - Epidemiology of calcium oxalate urolithiasis - identifying risk factors. Vet Clin North Am 1999; 29: 113-122.

Lulich JP, Osborne CA, Lekcharoensuk C et al - Effects of hydrochlorothiazide and diet in dogs with calcium oxalate urolithiasis. J Am Vet Med Assoc 2001; 218: 1583-1586.

Lulich JP, Osborne CA, Sanderson SL - Effects of dietary supplementation with sodium chloride on urinary relative supersaturation with calcium oxalate in healthy dogs. Am J Vet Res 2005; 66: 319-324.

Mishina M, Watanabe T, Fujii K et al - Medical dissolution of struvite nephrolithiasis using amino acid preparation in dogs. J Vet Med Sci 2000; 62: 889-892.

Osborne, CA, Bartges JW, Lulich JP et al - Canine urolithiasis. In Hand MS, Thatcher CD, Remillard RL (eds). Small animal clinical nutrition. Missouri: Walsworth Publishing, 2000: 605-688.

Osborne CA, Jacob F, Lulich JP et al - Canine silica urolithiasis. Vet Clin North Am 1999a; 29: 213-229.

Osborne CA, Lulich JP, Bartges JW et al - Canine and feline urolithiasis: Relationship of etiopathogenesis to treatment and prevention. In Osborne CA, Finco DR (eds). Canine and feline nephrology and urology. Philadelphia: Lea & Febiger, 1995: 798-888.

Osborne CA, Lulich JP, Bartges JW et al - Drug-induced urolithiasis. Vet Clin North Am 1999b; 29: 251-266.

Osborne CA, Lulich JP, Polzin DJ et al - Analysis of 77,000 canine uroliths. Vet Clin North Am 1999c; 29: 17-38.

Osborne CA, Lulich JP, Polzin DJ et al - Medical dissolution and prevention of canine struvite urolithiasis. Vet Clin North Am Small Anim Pract 1999d; 29: 17-38.

Osborne CA, Lulich JP, Polzin DJ - Canine retrograde urohydropropulsion. Lessons from 25 years of experience. Vet Clin North Am Small Anim Pract 1999e; 29: 267-281.

Osborne CA, Lulich JP, Ulrich LK et al - Adverse effects of drugs on formation of canine and feline crystalluria and uroliths. In: Kirk's Current Veterinary Therapy XIII, Bonagura JW (ed). Philadelphia: WB Saunders Co, 1999f: 846-848.

Osborne CA, Sanderson SL, Lulich JP et al - Canine cystine urolithiasis. Vet Clin North Am Small Anim Pract 1999g; 29: 193-211.

Rinkardt NE, Houston DM - Dissolution of infection-induced struvite bladder stones using a non-calculolytic diet and antibiotic therapy. Can Vet J 2004; 45: 838-840.

Robertson WG, Jones JS, Heaton MA et al - Predicting the crystallisation potential of urine from cats and dogs with respect to calcium oxalate and magnesium ammonium phosphate (struvite). J Nutr 2002; 132: 1637S-1641S.

Robertson WG - Urinary tract calculi. In: Nordin BEC, Need AG, Morris HA (eds). Metabolic bone and stone disease. New York: Churchill Livingstone, 1993: 249-311.

Ross SJ, Osborne CA, Lulich JP et al - Canine and feline nephrolithiasis. Epidemiology, detection, and management. Vet Clin North Am Small Anim Pract 1999; 29: 231-250.

Sanderson SL, Gross KL, Ogburn PN et al - Effects of dietary fat and L-carnitine on plasma and whole blood taurine concentrations and cardiac function in healthy dogs fed protein-restricted diets. Am J Vet Res 2001a; 62: 1616-1623.

Sanderson SL, Osborne CA, Lulich JP et al - Evaluation of urinary carnitine and taurine excretion in 5 cystinuric dogs with carnitine and taurine deficiency. J Vet Intern Med 2001b; 15: 94-100.

Seaman R, Bartges JW - Struvite urolithiasis. Comp Cont Edu 2001; 23: 407-426.

Sorenson JL, Ling GV - Metabolic and genetic aspects of urate urolithiasis in Dalmatians. J Am Vet Med Assoc. 1993; 203(6): 856-62.

Stevenson AE - The incidence of urolithiasis in cats and dogs and the influence of diet in formation and prevention of recurrence. Thesis, Institute of Urology and Nephrology, University College London, 2002.

Stevenson AE, Markwell PJ - Comparison of urine composition of healthy Labrador Retrievers and Miniature Schnauzers. Am J Vet Res 2001; 62: 1782-1786.

Stevenson AE, Hynds WK, Markwell PJ - The relative effects of supplemental dietary calcium and oxalate on urine composition and calcium oxalate relative supersaturation in healthy adult dogs. Res Vet Sci 2003a; 75: 33-41.

Stevenson AE, Hynds WK, Markwell PJ - Effect of dietary moisture and sodium content on urine composition and calcium oxalate relative supersaturation in healthy miniature Schnauzers and Labrador retrievers. Res Vet Sci 2003b; 74: 145-151.

Stevenson AE, Robertson WG, Markwell P - Risk factor analysis and relative supersaturation as tools for identifying calcium oxalate stone-forming dogs. J Sm Anim Pract 2003c; 44: 491-496.

Stevenson AE, Wrigglesworth DJ, Smith BH et al - Effects of dietary potassium citrate supplementation on urine pH and urinary relative supersaturation of calcium oxalate and struvite in dogs. Am J Vet Res 2000; 61: 430-435.

Stevenson AE, Blackburn JM, Markwell PJ et al - Nutrient intake and urine composition in calcium oxalate stone- forming dogs: comparison with healthy dogs and impact of dietary modification. Vet Ther 2004; 5 (3): 218-231.

EXAMPLES OF HOME-PREPARED TO THE DIETETIC TREATMENT

Example 1

COMPOSITION
(1000 g diet)

Chicken, boiled . . . . . 300 g
Hard-boiled egg . . . . . 50 g
Rice, cooked . . . . . 560 g
Wheat bran . . . . . 30 g
Brewer's yeast . . . . . 10 g
Rapeseed oil . . . . . 50 g

Add a low-magnesium mineral and vitamin supplement.

ANALYSIS		
The diet prepared in this way contains 38% dry matter and 62% water		
	% dry matter	**g/1000 kcal**
Protein	22	41
Fat	31	59
Available carbohydrate	40	75
Fiber	4	8

INDICATIVE RATIONING			
Energy value (metabolizable energy) 2040 kcal/1000 g diet prepared (5310 kcal/1000 g dry matter)			
Dog's weight (kg)*	Daily amount (g)**	Dog's weight (kg)*	Daily amount (g)**
2	110	45	1110
4	180	50	1200
6	240	55	1290
10	360	60	1370
15	490	65	1460
20	600	70	1540
25	710	75	1620
30	820	80	1700
35	920	85	1780
40	1010	90	1860

Key Points

- **Acid urinary pH** to effectively combat struvite stones by limiting the availability of phosphate ions. An acid pH is also unfavorable to bacterial growth
- **Low magnesium content** to limit the presence of struvite stone precursors (or magnesium ammonium phosphate)
- **High water content**: a moist food is a natural urine diluter

**The rationing is offered in accordance with the dog's healthy weight. For obesity, the diet must be prescribed in accordance with the ideal weight and not the real weight of the dog.*
***Dividing the daily amount over two or three meals is recommended to limit the postprandial alkaline tide.*

DIETS ADAPTED OF UROLITHIASISA

Example 2

COMPOSITION
(1000 g diet)

Veal, shoulder . . . . . 400 g
Beef, minced meat 5% fat . . . . . .100 g
Rice, cooked . . . . . 400 g
Wheat bran . . . . . 50 g
Tomato . . . . . 25 g
Rapeseed oil . . . . . 25 g

Add a low-magnesium mineral and vitamin supplement.

INDICATIVE RATIONING			
Energy value (metabolizable energy) 1335 kcal/1000 g diet prepared (4230 kcal/1000 g dry matter)			
Dog's weight (kg) *	Daily amount (g)**	Dog's weight (kg) *	Daily amount (g) **
2	110	45	1110
4	180	50	1200
6	240	55	1290
10	360	60	1370
15	490	65	1460
20	600	70	1540
25	710	75	1620
30	820	80	1700
35	920	85	1780
40	1010	90	1860

ANALYSIS		
The diet prepared in this way contains 32% dry matter and 68% water		
	% dry matter	**g/1000 kcal**
Protein	39	92
Fat	13	31
Available carbohydrate	36	86
Fiber	8	19

Contra-indications

Gestation
Lactation
Growth
Chronic renal disease
Metabolic acidosis

Examples of home-made diets are proposed by Pr Patrick Nguyen
(Nutrition and Endocrinology Unit; Biology and Pathology Department, National veterinary School of Nantes)

© PaulaLanceau

The small breeds (Shih Tzu, Yorkshire Terrier, Miniature Schnauzer, Pekingese) are among the breeds of dog at most risk of urolithiasis.

Key Points
to remember:

The role of nutrition in the treatment and prevention of canine urolithiasis

Stimulation of water intake and diuresis

For all stone types, encouraging the dog to drink to promote the production of dilute urine is an essential part of preventing stone formation. Diluting the urine limits the concentration of the crystal precursors in the urine. There are three simple ways to encourage water intake: selecting a wet food, hydrating dry food before serving, and slightly increasing the food's sodium content. A dietary sodium content of 3.2 g /1000 kcal does not have any effect on blood pressure in a healthy dog or a dog with moderate renal pathology.

Urinary pH

Acidifying the urine is the best method to lower urinary **struvite** saturation and therefore to prevent this type of urinary stone. Struvite stones are highly soluble in acid pH, so acidification will even help to dissolve the stones.

Calcium oxalate stones are not sensitive to urinary pH. Urinary alkalinization indirectly limits the presence of precursors in the urine (by limiting the calciuria and promoting the excretion of citrate, which forms a soluble salt with calcium), but at the same time it increases the risk of struvite formation. It is preferable to combine increased diuresis with a moderate pH (6-6.5) to simultaneously prevent the appearance of both oxalate and struvite stones.

Conversely, for both **cystine and urate urolithiasis** it is necessary to achieve a more alkaline pH (around 7) to increase the solubility of these stones. However, alkalinizing the urine further increases the risk of secondary calcium phosphate urolithiasis.

Proteins

Protein restriction has been recommended to help manage both urate and cystine urolithiasis. In particular, dogs predisposed to **urate stones** (Dalmatians, English Bulldogs) need a diet that is low in purines, without necessarily reducing the overall protein ingested. These two goals are compatible when a protein source that is low in purine content is selected.

If protein restriction is implemented to assist the management of cystine stones, the diet should be supplemented with taurine and L-carnitine to help prevent the risk of dilated cardiomyopathy.

Focus on:

SODIUM

After calcium and potassium, sodium is the most abundant ion in the organism. It represents around 0.13% of the body weight of a mammal. Extracellular sodium is found in the skeleton (43% of total sodium), the interstitial fluid (29%) and the plasma (12%). The remaining body sodium is located intracellularly.

Sodium plays several essential roles in the function of the cell:

- It maintains the balance in osmotic pressure between the intra- and extra-cellular environments thus regulating the volume of extra-cellular fluids. This function of water balance regulation gives sodium an important role in the sense of hunger and micturition.

- It is involved in acid base balance

- It participates in nerve transmission

The digestive absorption of sodium is very important. The maintenance of a constant sodium level in the organism is based on regulation of both renal and intestinal excretion. Dogs do not sweat, hence they are not at risk of excessive sodium loss.

What is the sodium content in the various sodium salts?

- Sodium chloride (NaCl) contains 39% sodium.
1% sodium in a food therefore corresponds to approximately:
1 / 0.39 = 2.5% NaCl.

- Sodium carbonate contains 37% sodium.

- Sodium bicarbonate contains 27% sodium.

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1 • Is blood pressure affected by high dietary salt content?

In dogs, increasing the sodium content in the food has a clear role in stimulating diuresis and lowering the urinary calcium oxalate saturation. The relationship between the salt content in human food and hypertension is a subject of intense debate, hence the question of the influence of salt (NaCl) on canine blood pressure is a logical one to ask.

Vienna University in association with Royal Canin studied the development of blood pressure based on the dietary NaCl content *(Biourge et al, 2002)*.

Eight healthy female Beagles age 2 to 4 years were divided into two groups and fed for two weeks with the same dry (acidified) food. The only difference between the two diets was the NaCl content:

- the control diet contained:

0.38% Na and 1.40% Cl

- the NaCl-enriched diet contained:

0.96% Na and 2.40% Cl (DMB).

The two groups consumed the two formulations in turn, with a one-week transition period during which they were fed a standard maintenance food.

	Results	
	Control diet (0.38% Na; 1.40% Cl)	NaCl enriched diet (0.96% Na; 2.40% Cl)
Body weight	Food consumption was limited to 256 ± 31 g/day and the dogs body weight remained stable during the whole study (11.4 + 0.9 kg).	
Urinary volume (mL/kg weight/day)	22,8 ± 3,4	37 ± 3,1
Mean blood pressure (mm Hg)	152 ± 9 mm Hg	158 ± 10 mm Hg

The results of this study clearly demonstrated that moderate enrichment of NaCl in the diet increased urine volume (p<0.001) but did not alter blood pressure of healthy dogs when compared with a standard food. The blood pressure values observed are within the normal reference range (<160 mm Hg).

Four other studies have also failed to provide any evidence that moderate increases in dietary sodium (up to 3.2 g Na/1000 kcal) influences the blood pressure of dogs and cats, be they healthy or moderate renal disease patients *(Burankarl et al, 2003; Greco et al, 1994; Kirk 2002; Luckschander et al, 2002)*.

The National Research Council Committee on Animal Nutrition (NRC) has been tasked with establishing nutritional requirements for the dog and cat by the U.S. Academy of Sciences. Their latest recommendations indicate that there is no adverse health risk for the dog when the sodium content of the diet contains 3.75 g /1000 kcal in a dry food providing 4000 kcal/kg. This is equivalent to a sodium content of 1.5%.

References

Biourge V, Iben C, Wagner E et al - Does increasing dietary NaCl affect blood pressure in adult healthy dogs. Proceedings of the 12th Congress of the European College of Veterinary Internal Medicine, Munich, 2002; 153.

Burankarl C, Mathur SS, Cartier LI et al - Effects of dietary sodium chloride (NaCl) supplementation on renal function and blood pressure (BP) in normal cats and in cats with induced renal insufficiency. Proceeding of the WSAVA congress, Bangkok. 2003: 749.

Greco DS, Lees GE, Dzendel G et al - Effects of dietary sodium intake on blood pressure measurements in partially nephrectomized dogs. Am J Vet Res 1994; 55:160-165.

Kirk CA - Dietary Salt and Flutd Risk or Benefit? Proceedings of the 20th American College of Veterinary Internal Medicine Forum. Dallas, Texas, 2002; 553-555.

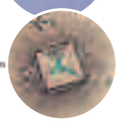
Luckschander N, Iben C, Desprez G et al - Does increasing dietary NaCl affect blood pressure in adult healthy cats. Proceedings of the 20th American College of Veterinary Internal Medicine Forum, Dallas, Texas, 2002: 788.

National Research Council of the National Academies - Nutrient requirements of dogs and cats. The National academies Press, Washington DC; 2006 in press.

2 • Determination of the relative supersaturation of canine urine

Goals: to predict the formation of urinary crystals dependent on the urinary pH and composition induced by the consumption of a specific diet. The ultimate goal is the prevention of urinary stones in dogs.

Struvite (magnesium ammonium phosphate)



Calcium oxalate

pH analysis and acidification of urine for optimal storage

Urinalysis

- Urate, Creatinine : High Performance Liquid Chromatography (HPLC)
- Calcium, Magnesium
- Sodium, Potassium
- Ammonium, Sulfate
- Citrate, Oxalate, Phosphate

} Ionic chromatography

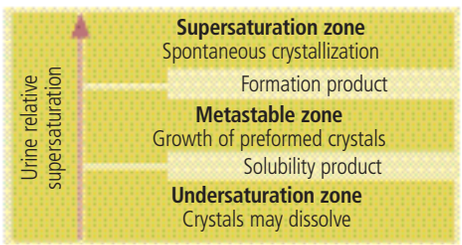
High Performance Liquid Chromatography (HPLC)

Ionic chromatography

Calculation of the urinary saturation values, using Supersat® program

1. Calculation of activity coefficients for monovalent, divalent, trivalent and quadrivalent ions
2. Evaluation of the concentration of different soluble complexes formed with these ions
3. Calculation of the concentrations of free ions (Ox^{2-}, Ca^{2+}, PO_4^{3-}, NH_4^{+}, Mg^{2+}…)
4. Calculation of the activity product for different salts involved in uroliths formation
5. Comparison with the solubility and the formation products of the considered salts ⇨ RSS estimation

Evaluation of the probability of forming of calcium oxalate and struvite uroliths in a dog fed with a specific diet



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Cardiovascular diseases: nutritional modulation

1 - Epidemiology 337
2 - Diagnosis of canine cardiac disease 337
3 - Treatment of cardiac disease 340
4 - Pathophysiology and specific issues of nutritional management 341
5 - General issues in feeding dogs with cardiac disease 357

References 359
Examples of home-prepared diets adapted
to the treatment of cardiac complaints 362
Royal Canin Nutritional Information 364

Cardiovascular diseases: nutritional modulation

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Many scientific advances have improved our knowledge of cardiac disease and congestive heart failure (CHF) in dogs. In addition to new cardiac medications, recent advances have improved our understanding of nutritional interventions and nutritional pharmacology. Cardiovascular disease is still one of the most common life-threatening disorders in dogs. Most canine cardiac diseases cannot be cured and the disease process is typically progressive, leading to advanced CHF or lethal cardiac arrhythmias. Nutritional interventions for cardiac disease remain one of the mainstays of therapy and one of the more exciting avenues for further scientific investigation.

1 - Epidemiology

Many risk factors and clinical associations have been identified for cardiovascular disorders in dogs. Breed predispositions are recognized for most of the common cardiovascular diseases **(Table 1)**. Many small to medium sized dog breeds are predisposed to acquired chronic valvular disease (CVD; endocardiosis), while dilated cardiomyopathy (DCM) and pericardial disease are the most common causes of congestive heart failure (CHF) in large breed dogs.

Certain cardiovascular disorders are recognized to have a sex predisposition; for example, female dogs are predisposed to patent ductus arteriosus and male dogs are predisposed to CVD, idiopathic pericardial disease, and bacterial endocarditis.

Dogs with renal or adrenal disease can develop systemic hypertension and this can predispose or contribute to existing cardiac disease.

2 - Diagnosis of canine cardiac disease

Congenital and acquired cardiac diseases often lead to similar compensatory responses and neuroendocrine activation. Due to the similarities in response of the heart, systemic and pulmonary vasculature and the neuroendocrine systems, several common historical findings and clinical signs result from most of the canine cardiovascular diseases.

► Clinical signs

Common historical complaints include cough, shortness of breath, and syncope **(Table 2)**. Cardiac disease can be quite advanced when the owner is first able to detect clinical abnormality, however many cardiac diseases can be detected by the attending veterinarian well in advance of the development of clinical signs.

Most congenital cardiac diseases are accompanied by a loud cardiac murmur. The most common form of cardiovascular disease in the dog, CVD, typically has a cardiac murmur that can be readily identified well before outward clinical signs of cardiovascular disease are evident. The abnormalities that are most commonly identified on physical examination from dogs with cardiovascular disease are listed in **Table 3**.

TABLE 1 - COMMON HISTORICAL FINDINGS IN DOGS WITH CARDIOVASCULAR DISEASE

- Coughing
- Gagging
- Shortness of breath or difficulty breathing
- Inability to sleep comfortably through the night
- Fainting or "seizure" (syncope)
- Weight loss
- Abdominal distension
- Weakness
- Exercise intolerance
- Poor growth (congenital heart disease)

TABLE 2 - COMMON PHYSICAL EXAMINATION FINDINGS FROM DOGS WITH CARDIOVASCULAR DISEASE

Cardiac murmur	Dyspnea
Cardiac gallop	Pulmonary crackles
Cardiac arrhythmia	Ascites
Tachycardia	Abdominal organomegaly
Bradycardia	Cyanosis
Weak arterial pulses	Mucous membrane pallor
Pulsus paradoxus	Delayed capillary refill time (> 2 seconds)
Jugular vein distension	

TABLE 1 - BREED PREDISPOSITIONS FOR VARIOUS CARDIOVASCULAR DISEASES
(Compiled from Buchanan, 1992; Kittleson, 1998; Sisson, 2000b; and the computer database at Cummings School of Veterinary Medicine at Tufts University)

Breed	Cardiovascular disease predisposition	Breed	Cardiovascular disease predisposition
Airedale Terrier	PS	Keeshond	PDA, Tetralogy of Fallot, MVD
Akita	Pericardial disease	Kerry Blue Terrier	PDA
Basset Hound	PS	Labrador Retriever	TVD, PS, PDA, DCM, supraventricular tachycardia, pericardial disease
Beagle	PS, CVD	Maltese	PDA, CVD
Bichon Frisé	PDA, CVD	Mastiff	PS, MVD
Boston Terrier	CVD, HBT	Miniature Pinscher	CVD
Boxer	SAS, PS, ASD, Boxer cardiomyopathy, HBT, BE, vasovagal syncope	Miniature Schnauzer	PS, CVD, sick sinus syndrome
Boykin Spaniel	PS	Newfoundland	SAS, PS, DCM
Bull Terrier	MVD, acquired mitral and aortic fibrosis	Old English Sheepdog	DCM, atrial standstill
Cavalier King Charles Spaniel	CVD	Papillon	CVD
Chihuahua	PS, PDA, CVD	Pomeranian	PDA, sick sinus syndrome, CVD
Chow Chow	PS, CTD, VSD	Poodle (miniature and toy)	PDA, CVD
Cocker Spaniel	PDA, PS, CVD, DCM, sick sinus syndrome	Portuguese Water Dog	Juvenile DCM
Collie	PDA	Rottweiler	SAS, DCM, BE
Dalmatian	DCM	Saint Bernard	DCM
Dachshund	CVD	Samoyed	PS, ASD, SAS, VSD
Doberman Pinscher	ASD, DCM	Scottish Deerhound	DCM
English Bulldog	PS, SAS, VSD, MVD, Tetralogy of Fallot	Scottish Terrier	PS
English Springer Spaniel	VSD, PDA, atrial standstill	Shetland Sheepdog	PDA
Fox Terrier	PS, CVD	Terrier breeds	PS, CVD
German Shepherd	PDA, SAS, TVD, MVD, PRAA, juvenile ventricular arrhythmia, pericardial disease, DCM, BE	Weimaraner	TVD, peritoneopericardial diaphragmatic hernia
German Short-Haired Pointer	SAS, HCM, pericardial disease, BE	Welsh Corgi	PDA
Golden Retriever	SAS, MVD, TVD, DCM, pericardial disease, BE	West Highland White Terrier	PS, VSD, sick sinus syndrome, CVD
Great Dane	MVD, TVD, SAS, PRAA, DCM	Whippet	CVD
Irish Setter	PRAA, PDA	Yorkshire Terrier	PDA, CVD
Irish Wolfhound	DCM, atrial fibrillation		

Key: ASD = Atrial septal defect, BE = Bacterial endocarditis, CTD = Cor triatriatum dexter, CVD = Chronic valvular disease, DCM = Dilated cardiomyopathy, HBT = Heart base tumor, HCM = Hypertrophic cardiomyopathy, MVD = Mitral valve dysplasia PDA = Patent ductus arteriosus, PRAA = Persistent right aortic arch, PS = Pulmonic stenosis, SAS = Subaortic stenosis, TVD = tricuspid valve dysplasia, VSD = ventricular septal defect.

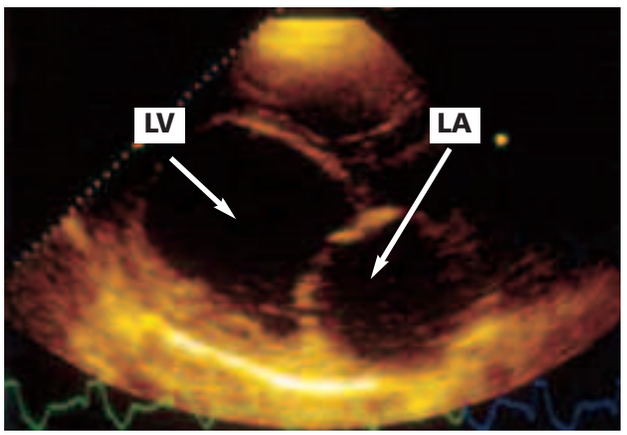
► Diagnostic tests

Once cardiovascular disease is established as a differential diagnosis, a battery of routine tests are often performed to confirm cardiovascular disease, establish the severity of disease, and permit an informed decision to be made regarding treatment.

An electrocardiogram should be performed in all dogs with evidence of cardiac arrhythmia, including those with arrhythmia noted on cardiac auscultation and those with femoral arterial pulse deficits, bradycardia, tachycardia, or a history of syncope, seizure, or collapse.

Thoracic radiographs are indicated to establish whether CHF is present and to help determine the degree of cardiac enlargement, the size of the pulmonary vessels, and the size of the caudal vena cava. Thoracic radiographs are the best diagnostic test to exclude respiratory diseases as either the cause or a contributor to the animal's clinical signs. For many cardiovascular diseases, echocardiography is the key diagnostic test to establish the exact cause of the disease. Echocardiography also facilitates the evaluation of cardiac chamber enlargement and permits quantitative evaluation of cardiac chamber size, wall thickness, and myocardial and valve function **(Figure 1)**.

FIGURE 1 - ECHOCARDIOGRAPHY INDICATING DILATED CARDIOMYOPATHY IN A BOXER



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Right parasternal long axis view showing the dilatation of the left atrium (LA) and left ventricule (LV).

In dogs with congenital disease, echocardiography is used to confirm the type of defect, establish the severity of the defect, and is an invaluable aid in offering therapeutic and prognostic advice. Echocardiography is a key tool for the diagnosis and management of cardiac disease and should be offered in all cases where serious cardiovascular disease is a differential diagnosis.

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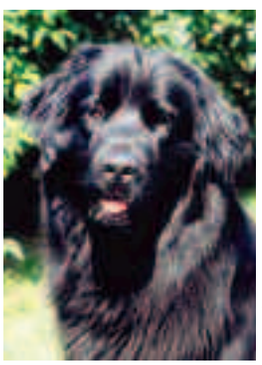
Dilated cardiomyopathy may be associated with taurine deficiency in certain breeds, such as the Golden Retriever, the Newfoundland and the Cocker Spaniel.



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Many additional tests are useful in the diagnosis and management of dogs with cardiac disease.

- Heartworm (*Dirofilaria immitis*) antigen testing should be carried out in dogs from endemic areas.
- A complete blood count and biochemistry profile should be carried out to search for concurrent diseases and establish baseline values prior to therapy. Alterations in blood urea nitrogen, creatinine, and the serum electrolytes sodium, potassium, chloride and magnesium can develop following the initiation of various cardiac medications, and knowledge of these alterations is useful in selecting or altering the diet.
- Plasma and whole blood taurine levels may be indicated in dogs with evidence of reduced systolic function on echocardiography, especially in certain breeds of dogs (e.g. Cocker Spaniel, Golden Retriever, Newfoundland) and in dogs consuming certain diets (see below).
- Measurement of systemic blood pressure is useful to exclude systemic hypertension as a contributing factor to the cardiovascular disease. In addition, when hypotension develops following initiation of pharmacologic therapy, a baseline blood pressure measurement can be used for comparison.
- A variety of additional specialized cardiovascular tests, such as Holter monitor recorders, event monitor recorders, computed tomography, phonocardiography, and cardiac catheterization are available for specific clinical settings.

3 - Treatment of cardiac disease

It is beyond the scope of this chapter to mention the appropriate treatment for each cardiovascular disease recognized in dogs and the reader is referred to the many excellent textbooks on specific pharmacologic or surgical treatments *(Kittleson & Kienle, 1998; Fox et al, 1999; Kittleson, 2000; Sisson et al, 2000a; Ware & Keene, 2000)*. Common cardiovascular medications include furosemide, angiotensin converting enzyme (ACE) inhibitors, digoxin, positive inotropes, beta-blockers, antiarrhythmic drugs, and additional diuretics such as thiazide diuretics and aldosterone receptor blockers (eg, spironolactone). Medications used in an individual patient can impact appropriate diet selection (see below).

In general, dietary management of dogs with cardiac disease depends upon the clinical signs and stage of heart failure, rather than the underlying disorder. Therefore, the dietary management of a dog with CHF secondary to ventricular septal defect or bacterial endocarditis would be similar to that of a dog with CVD and CHF. When selecting a diet for a dog with cardiac disease, clinicians should take into consideration a number of factors including clinical signs and laboratory parameters. Another important issue to consider is the dog's stage of disease. In the face of acute CHF, the initial goal should be to titrate medication doses and to get the dog stabilized. In a dog with pulmonary edema or pleural effusion, the only diet change routinely advised during the initial period or even when first discharging the dog is to limit intake of very high sodium diets or high sodium treats. Once the dog is home and stabilized on medications, a gradual change to a new diet can be made - usually at the time of the first recheck 7-10 days after discharge. Forced dietary changes when the animal is sick or starting new medications may induce food aversions.

Failure to respond to pharmacologic and nutritional therapies can be the result of advanced or progressive disease, drug side effects, or incorrect diagnosis. Common pitfalls in the treatment of dogs with cardiac disease are shown in **Table 4**.

TABLE 4 - COMMON PITFALLS IN THE TREATMENT OF DOGS WITH CARDIAC DISEASE

Older small breed dogs with a cardiac murmur often have concurrent respiratory disease and it can be difficult to determine whether the clinical signs result from respiratory or cardiac disease Thoracic radiographs should always be obtained prior to initiation of diuretics and other cardiac medications.	**Large breed dogs with acquired cardiac disease often have either dilated cardiomyopathy or pericardial disease** Since both of these diseases can occur without significant abnormalities on cardiac auscultation, there may be a delay in accurate diagnosis unless one maintains a high degree of suspicion for these diseases.	**Failure to accept a new diet** Causes can include abrupt change, particularly if the diet is introduced at the same time that drug interventions are being introduced or adjusted.	**Anorexia** Both congestive heart failure and drug side effects can lead to anorexia. Failure to eat a cardiac diet is too often attributed to lack of palatability for the diet rather than consideration of the many other factors that might impact appetite.

4 - Pathophysiology and specific issues of nutritional management

In addition to medications, optimal treatment of dogs with cardiac disease also includes careful attention to the diet. Although sodium restriction is the nutritional modification most often thought of for dogs with cardiac disease (and sometimes is the only nutrient modification thought of), adjustment of a variety of nutrients may be beneficial for these animals. Research is now beginning to show that dietary factors may be able to modulate canine cardiac disease, either by slowing the progression, minimizing the number of medications required, improving quality of life, or in rare cases, actually curing the disease.

In the past, the goal of nutritional management for animals with cardiac disease was purely symptomatic. This was primarily due to the limited number of medications available for treatment, and in that situation, severe sodium restriction was beneficial for reducing fluid accumulation in animals with CHF. Now, with more effective medications available for use in dogs, severe sodium restriction is not critical in most dogs. The emphasis in the nutritional management of dogs with CHF is on providing the optimal number of calories for the individual patient, avoiding nutritional deficiencies and excesses, and gaining potential beneficial effects from pharmacologic doses of certain nutrients.

► Optimal weight maintenance

Both weight loss and obesity can be problems in animals with cardiac disease, and can adversely affect the dog's health.

> Cardiac cachexia

Dogs with CHF commonly demonstrate weight loss, termed cardiac cachexia **(Figure 2)**. This weight loss in animals with CHF is unlike that seen in a healthy dog that loses weight. In a healthy animal that is receiving insufficient calories to meet requirements (eg, a starving dog, a dog on a weight reduction diet), fat serves as the primary energy source and this helps to preserve lean body mass. In a dog with injury or illness, including CHF, amino acids from muscle are the primary source of energy, resulting in loss of lean body mass.

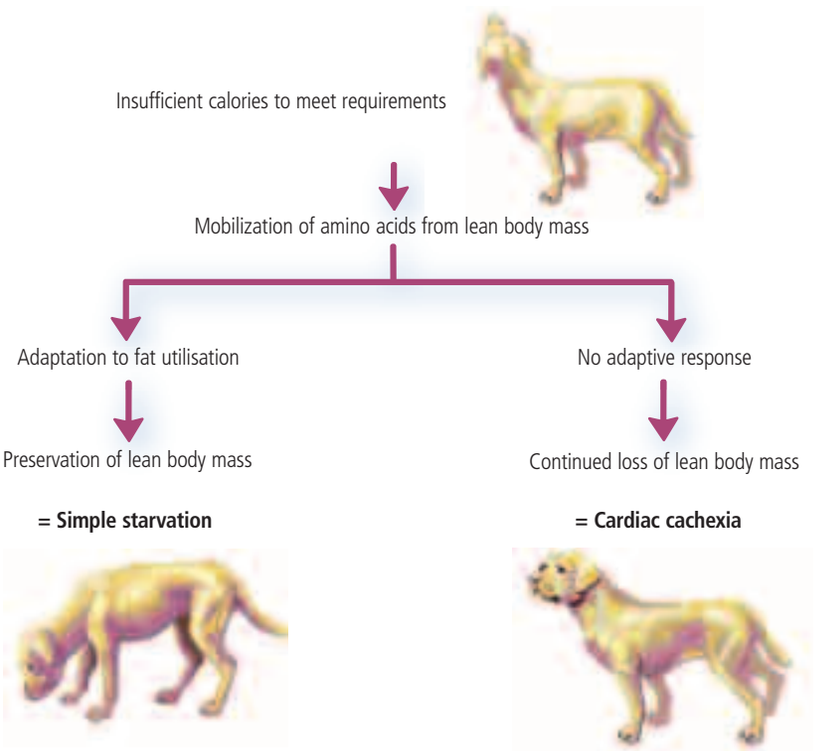
FIGURE 2 - CARDIAC CACHEXIA IN DOGS WITH CHF

a: Cardiac cachexia is often viewed as an end-stage situation like the dog shown here with severe dilated cardiomyopathy and congestive heart failure.

b: Cardiac cachexia is actually a process during which lean body mass is gradually lost. Cachexia can be very subtle initially and may be manifested only by mild muscle loss over the epaxial and gluteal muscles.

Therefore, a loss of lean body mass is the hallmark of cachexia. There is a spectrum of severity of cachexia and the term does not necessarily equate with an emaciated, end-stage patient **(Figures 3 & 4)**. In the early stages, it can be very subtle and may even occur in obese dogs (i.e. a dog 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. Cardiac cachexia typically does not occur until CHF has developed.

FIGURE 3 - EFFECTS OF STARVATION: DIFFERENCES BETWEEN A HEALTHY DOG AND A DOG WITH CARDIAC DISEASE



There is a dramatic difference between simple starvation, which occurs in a healthy animal and cachexia, the weight loss seen in animals with cardiac disease. A healthy animal will primarily lose fat tissue, whereas cachexia is distinguished by a loss of lean body mass.

Cardiac cachexia can occur with any underlying cause of CHF (eg, DCM, CVD, congenital heart diseases) but most commonly occurs in dogs with DCM, particularly those with right-sided CHF. In one study of dogs with DCM, over 50% of patients had some degree of cachexia *(Freeman et al, 1998)*. Loss of lean body mass has deleterious effects on strength, immune function, and survival, so it is important to recognize cachexia at an early stage to explore opportunities to manage it effectively *(Freeman & Roubenoff, 1994)*.

The loss of lean body mass in cardiac cachexia is a multifactorial process caused by anorexia, increased energy requirements, and metabolic alterations *(Freeman & Roubenoff, 1994)*. The anorexia may be secondary to the fatigue or dyspnea or may be due to medication toxicity or feeding an unpalatable diet. Anorexia is present in 34-75% of dogs with cardiac disease *(Mallery et al, 1999; Freeman et al, 2003b)*. Although not yet measured in dogs with CHF, energy requirements up to 30% above normal have been documented in people with CHF *(Poehlman et al, 1994)*.

FIGURE 4 - DIFFERENT STAGES OF CACHEXIA

(a) Despite being trim, this dog has good muscle tone with no evidence of muscle wasting (Cachexia score = 0).

(b) Early, mild muscle wasting is present in this dog, especially in the hindquarters and lumbar region (Cachexia score = 1).

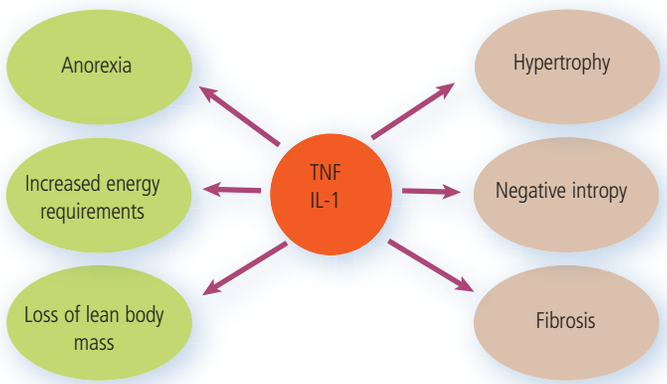
(c) Moderate muscle wasting, apparent in all muscle groups, is present. Note especially the atrophy of the temporal muscles and muscles over the shoulder (Cachexia score = 2).

(d) Marked muscle wasting is present in this dog, as evidenced by the atrophy of all muscle groups (Cachexia score = 3).

(e) Severe muscle wasting can readily be seen in this dog (Cachexia score= 4).

While these factors play a role in the loss of lean body mass, a major factor in this syndrome is an increased production of inflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin-1 (IL-1) *(Freeman et al, 1998; Meurs et al, 2002)*. These inflammatory cytokines are known to directly cause anorexia, to increase energy requirements, and to increase the catabolism of lean body mass. Of particular pertinence to cardiac disease, TNF and IL-1 also cause cardiac myocyte hypertrophy and fibrosis and have negative inotropic effects (Figure 5).

FIGURE 5 - CARDIOVASCULAR AND NUTRITIONAL EFFECTS OF THE INFLAMMATORY CYTOKINES, TUMOR NECROSIS FACTOR (TNF) AND INTERLEUKIN-1 (IL-1)

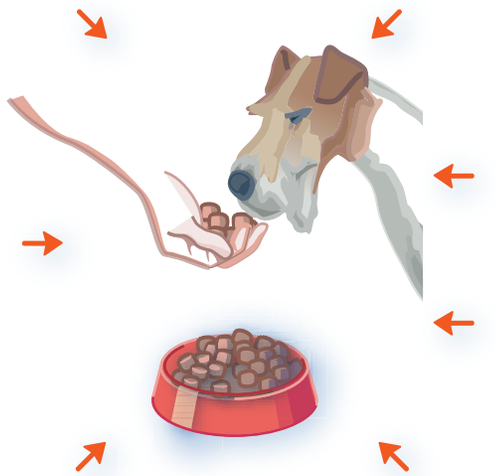


Nutritional management of dogs with cardiac cachexia consists primarily of providing adequate calories and protein and modulating cytokine production.

Anorexia can be detrimental to the dog with CHF in more than one way. Anorexia can be deleterious because it contributes to the syndrome of cardiac cachexia but, in addition, anorexia is one of the most common factors that contribute to a dog owner's decision of euthanasia. In one study of owners of dogs euthanized for CHF, anorexia was one of the most common contributing factors to the euthanasia decision *(Mallery et al, 1999)*. Anorexia is more common in dogs with CHF compared to asymptomatic dogs, and it also is more common in dogs with DCM compared to dogs with CVD *(Freeman et al, 2003b)*.

One of the most important issues for managing anorexia is to maintain optimal medical control of CHF. An early sign of worsening CHF is a reduction in food intake in a dog that has previously been eating well. Another possible cause of decreased appetite is the side effects of medications. Digoxin toxicity or azotemia secondary to ACE inhibitors or overzealous diuretic use can both cause anorexia. Ensuring a diet that is palatable to the dog while maintaining other nutritional goals is key to minimizing the

Figure 6 - Keys to nutritional management of anorexia in patients with cardiac disease



effects of cachexia in dogs with CHF. Tips that may assist in food intake include feeding small, more frequent meals or warming the food to body temperature (or for some dogs, feeding refrigerated food increases appetite). Gradual introduction of a more palatable diet may be beneficial for some dogs (e.g., switching from a dry food to a canned food, changing to a different brand, or having a veterinary nutritionist formulate a balanced homemade diet). It also may be useful to use flavor enhancers to increase food intake (e.g., yogurt, maple syrup, or honey) **(Figure 6)**.

Modulation of cytokine production can also be beneficial for managing cardiac cachexia. Although specific anti-TNF agents have not proven to be beneficial for people with CHF, dietary supplementation may be a safer method of reducing inflammatory cytokines. One method of decreasing the production and effects of cytokines is with n-3 polyunsaturated fatty acid supplementation (see discussion of n-3 fatty acids below). Supplementation of fish oil, which is high in n-3 fatty acids, can decrease cytokine production in dogs with CHF and improve cachexia *(Freeman et al, 1998)*. A reduction of IL-1 has been correlated with survival in dogs with CHF *(Freeman et al, 1998)*.

Optimal medical and nutritional therapy can help to reverse cachexia and improve nutritional status. Nutritional status is difficult to measure objectively in the ill patients but one parameter that can be evaluated is insulin-like growth factor-1 (IGF-1). In people and in dogs, IGF-1 concentrations have been used as an indicator of nutritional status *(Clark et al, 1996; Maxwell et al, 1998)*. Mean IGF-1 concentrations have been shown to be positively correlated with survival, suggesting that maintaining good nutritional status may be able to improve survival *(Freeman et al, 1998)*. In people with CHF, the presence of cachexia has proven to be a poor prognostic indicator *(Anker et al, 2003; Davos et al, 2003)*.

> Obesity

Although many dogs, particularly those with more advanced cardiac disease, have weight and muscle loss, some dogs with cardiac disease are overweight or obese **(Figure 7)**. Although cardiac implications of obesity have not been well-studied in dogs and coronary artery disease is not a

major concern in dogs, obesity is thought to be deleterious in dogs with cardiac disease because of its documented adverse effects on cardiac output, pulmonary function, neurohumoral activation, blood pressure, and heart rate in people and in experimental animal models *(Alexander, 1986)*. In any obese dog, underlying endocrine diseases such as hypothyroidism and Cushing's disease should be ruled out, but most obese animals simply suffer from excess consumption of calories.

Figure 7 - A dog with chronic valvular disease complicated by severe obesity. *Obesity may exacerbate the disease. Owners of obese dogs with cardiac disease often report that, when the dog loses weight, it acts less dyspneic and more active.*

Weight reduction programs are a difficult and often frustrating endeavor. For information on obesity and weight reduction programs, **see Chapter 1**. However, one advantage when a dog has cardiac disease is that there is automatically an increased incentive for the owner to commit to a weight reduction plan. Although this may not ensure success, it aids in the first step of successful weight loss.

As with any weight reduction program, it is critical to perform a careful dietary history to determine and control all sources of caloric intake. This diet history is also beneficial in finding other food sources for the dog that may be contributing both calories and sodium. Typically, the pet food is only one source of calories for the pet and as many, or more, calories may be consumed from treats and table food. In one study of dogs with cardiac disease, calorie intake from treats and table food ranged from 0-100%, with a median calorie intake from treats of 19% *(Freeman et al, 2003b)*. Therefore, it is important to recommend specific treats that are reduced in both calories and sodium. Fresh non-starchy vegetables (or frozen/canned forms that are labeled as, "no salt added") are excellent low calorie treats for dogs that are obese and have cardiac disease.

If possible, an exercise program will help with the weight reduction program but, for dogs with CHF in which exercise restriction is recommended, this is not possible. For these dogs, the weight reduction program must rely on control of calorie intake.

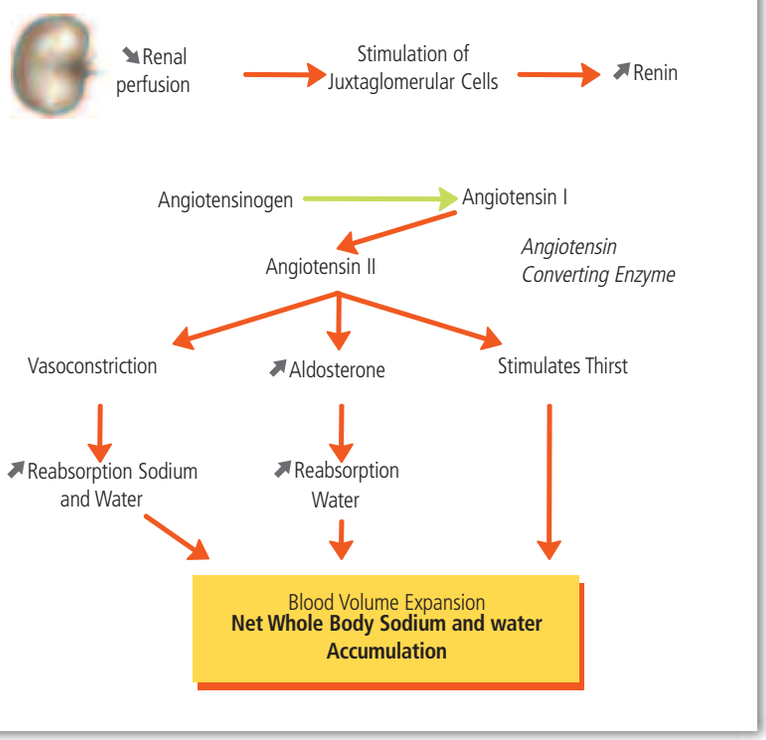
► Preventing nutrient excesses

Veterinarians have extrapolated from the human literature since the 1960's in applying nutritional recommendations to dogs with cardiac disease.

> Sodium and chloride

A prime example is sodium restriction. Healthy dogs can easily excrete excess dietary sodium in the urine but, even before clinical signs become apparent in dogs with cardiac disease, there is activation of the renin-angiotensin-aldosterone (RAA) system and abnormal excretion of sodium **(Figure 8)** *(Barger et al, 1955)*. Based on this pathophysiologic change, sodium restriction has been a mainstay of therapy for dogs with cardiac disease for nearly 50 years. However, very few studies have been conducted on dietary sodium in dogs with cardiac disease. Many questions remain on the specific intake of sodium recommended for dogs with different stages of disease, at what stage sodium restriction should be instituted, and if there are any detrimental effects of sodium restriction.

FIGURE 8 - PATHOGENESIS OF SODIUM RETENTION IN HEART DISEASE



- ***Normal dogs***

Healthy dogs are relatively tolerant toward the sodium content of their diet.
An early study in 1964 showed no significant changes in extracellular water, sodium, or chloride in normal dogs fed a low sodium diet (*Pensinger, 1964)*. This study also showed that healthy dogs were able to maintain sodium and potassium balance on both low and high sodium diets.

Two other studies found that normal dogs fed a low sodium diet had no changes in plasma sodium, chloride, or extracellular fluid volume compared to those fed a high sodium diet *(Hamlin et al, 1964; Morris et al, 1976)*. In 1994, a study examined the effects of a low sodium diet and furosemide in healthy dogs with or without captopril *(Roudebush et al, 1994)*. Although there were no within-group changes in electrolytes in this study, 3 of 6 dogs became hyperkalemic while receiving a low sodium diet plus furosemide and 2 of 6 became hyperkalemic while receiving a low sodium diet plus furosemide and captopril *(Roudebush et al, 1994)*. The effects of the low sodium diet alone were not reported.

In normal dogs, low sodium diets caused an increase in plasma renin activity (PRA) and plasma aldosterone concentration compared to a high sodium diet, although plasma concentrations of ACE, atrial natriuretic peptide (ANP), arginine vasopressin (AVP), and endothelin-1 (ET-1) remained unchanged *(Pedersen et al, 1994a, Pedersen et al, 1994b)*. Normal dogs receiving enalapril while eating a low-sodium diet, however, had an exaggerated increase in PRA and a larger decrease in ACE and ANP compared to a dogs eating a high sodium diet *(Koch et al, 1994)*. These investigators also found an inverse correlation between PRA and sodium content of the diet *(Koch et al, 1994)*.

- ***Dogs with CHF***

Dogs with CHF respond differently to dietary sodium restriction. Sodium restriction is one method, along with the use of diuretics and venous vasodilators, to treat excessive increases in preload in patients with CHF. In the 1960's, when few medications were available for treating dogs with CHF, dietary sodium restriction was one of the few methods of reducing fluid accumulation. In this situation, severe sodium restriction clearly was beneficial in reducing signs of congestion.

In one study, dogs with CHF retained sodium on the high sodium diet but did not retain sodium on the low sodium diet *(Pensinger, 1964)*. Untreated dogs with mild, asymptomatic mitral valve insufficiency had a larger increase in PRA and PAC and a lower ACE activity when changed from a high sodium diet to a low sodium diet *(Pedersen, 1996)*. Sodium intake had no effect on endothelin-1, ANP, and AVP *(Pedersen, 1996)*.

A randomized double-blind, placebo-controlled clinical trial of low sodium diets in dogs with CHF secondary to either CVD or DCM demonstrated no significant changes in neurohormones between a low sodium and moderate sodium diet *(Rush et al, 2000)*. Serum sodium and chloride concentrations decreased significantly while dogs were eating the low sodium diet *(Rush et al, 2000)*. Measures of cardiac size decreased significantly on the low sodium diet compared to the moderate sodium diet, especially in dogs with endocardiosis *(Rush et al, 2000)*. The effects of a low sodium diet on survival were not tested.

The biggest gap in the issue of sodium restriction is for dogs with early cardiac disease [Stage I or II: **Table 5]** (International Small Animal Cardiac Health Council *(ISACHC), 2001)*. Based on the pathogenesis of sodium retention, authors in the 1960's recommended institution of low-sodium diets for dogs when a heart murmur was first detected, even before clinical signs were present *(Morris, 1976)*. Only recently have the benefits and potential problems been questioned. One of the earliest and major compensatory responses in cardiac disease is activation of the renin-angiotensin-aldosterone (RAA) system. Sodium restriction can further activate the RAA system *(Pedersen et al, 1994a-1994b; Koch et al, 1994)*.

Table 5 - Dietary sodium recommendations for dogs based on stage of disease

International Small Animal Cardiac Health Council Classification*	Description	Dietary sodium recommendations
1 Asymptomatic Heart disease is detectable but patient is not overtly affected and does not demonstrate clinical signs of heart failure. Diagnostic findings could include a cardiac murmur, arrhythmia, or cardiac chamber enlargement that is detectable by radiography or echocardiography.	**1a** Signs of heart disease are present but no signs of compensation, such as volume or pressure overload or ventricular hypertrophy, are evident.	Severe sodium restriction is not required. Counsel the owner to avoid diets high in sodium (>100 mg/100 kcal) and to avoid treats and table foods that are high in sodium.
	1b Signs of heart disease are present in conjunction with radiographic or echocardiographic evidence of compensation, such as volume or pressure overload ventricular hypertrophy.	Sodium content of 50-80 mg/100 kcal in the main diet. Also counsel the owner to avoid treats and table foods that are high in sodium.
2 Mild to Moderate Heart Failure Clinical signs of heart failure are evident at rest or with mild exercise and adversely affect quality of life. Typical signs of heart failure include exercise intolerance, cough, tachypnea, mild respiratory distress (dyspnea), and mild to moderate ascites. Hypoperfusion at rest is generally not present.		Sodium content of 50-80 mg/100 kcal in the main diet. Greater sodium restriction (<50 mg/100 kcal) is recommended if large diuretic doses are necessary to control clinical signs. Limiting sodium intake from treats and table foods becomes more important. Counsel owner on appropriate methods for medication administration.
3 Advanced Heart Failure Clinical signs of advanced congestive heart failure are immediately obvious. These clinical signs include respiratory distress (dyspnea), marked ascites, profound exercise intolerance, or hypoperfusion at rest. In the most severe cases, the patient is moribund and suffers from cardiogenic shock. Death or severe debilitation is likely without therapy.	**3a** Home care is possible.	Sodium content <50 mg/100 kcal in the main diet. Limiting sodium intake from treats and table foods is very important. Counsel owner on appropriate methods for medication administration.
	3b Hospitalization is mandatory because cardiogenic shock, life-threatening pulmonary edema, refractory ascites, or a large pleural effusion is present.	Stabilization of acute CHF should be the goal. Diet changes should be avoided until the dog is home and stabilized on medications; a gradual change to a new diet can be instituted at that time.
	Note that these recommendations assume that the dog is not eating high sodium treats, table foods, or foods used for medication administration in addition to the main diet. If dogs are eating high sodium foods in addition to the main diet, the owner should be counselled regarding these foods or a diet lower in sodium should be selected. **From: International Small Animal Cardiac Health Council.*	

Thus, severe sodium restriction in dogs with early cardiac disease could theoretically be detrimental by early and excessive activation of the RAA system. Studies by Pensinger showed that dogs with cardiac disease but without CHF were able to maintain sodium and potassium balance on both low and high sodium diets, similar to normal dogs *(Pensinger, 1964)* but neurohormone changes were not measured. While any potential detrimental effects of early institution of severe dietary sodium restriction have not been shown, it is clear that all drug therapies shown to improve survival in CHF act by blunting neurohumoral activation. Therefore, severe sodium restriction (i.e., near the AAFCO minimum of 20 mg/100 kcal) is not currently recommended for dogs with ISACHC Stage 1 or 2 cardiac disease. Conversely, high dietary sodium intake in early disease is likely detrimental. **Table 5** summarizes the authors' current recommendations, based on available literature and clinical experience.

Most owners are unaware of the sodium content of pet foods and human foods and need very specific instructions regarding appropriate dog foods, acceptable low salt treats, and methods for administering medications **(Table 6)**. Owners also should be counselled on specific foods to avoid such as baby food, pickled foods, bread, pizza, condiments (e.g., ketchup, soy sauce), lunch meats and cold cuts (e.g., ham, corned beef, salami, sausages, bacon, hot dogs), most cheeses, processed foods (e.g., potato mixes, rice mixes, macaroni and cheese), canned vegetables (unless "no salt added"), and snack foods (e.g., potato chips, packaged popcorn, crackers).

Mildly reduced dietary sodium can be achieved with a therapeutic diet designed for animals with early cardiac disease or with certain diets designed for use in older dogs. If using a diet designed for senior dogs, be sure to look at the characteristics of the individual product. There is no legal definition for a senior diet so the levels of calories, protein, sodium, and other nutrients can vary dramatically between different companies' products. Diets designed for animals with renal disease are not recommended for most cardiac patients because of the protein restriction (unless severe renal dysfunction is present).

TABLE 6 - LOW SODIUM METHODS FOR ADMINISTERING MEDICATIONS

- Switch from pills to a compounded, flavored liquid medication. Be cautious in this approach because the pharmacokinetics of certain drugs may be altered when compounded
- Teach the owner to pill the animal without using foods. This may be done without any devices or by using devices designed for this purpose
- Use low sodium foods to insert the pills before administration
  - Fresh fruit (e.g., banana, orange, melon)
  - Low sodium canned pet food
  - Peanut butter (labeled as "no salt added")
  - Home-cooked meat (without salt) - not lunch meats

As CHF becomes more severe, more sodium restriction may allow lower dosages of diuretics to be used to control clinical signs. To achieve severe sodium restriction, it is usually necessary to feed a commercial therapeutic diet designed for cardiac patients. Typically, these diets are severely restricted in both sodium and chloride; levels of other nutrients vary with the individual product.

Dietary chloride levels are often ignored but research suggests that chloride may be important in the optimal management of CHF. Research in people has shown that sodium and chloride administration are necessary for the full expression of hypertension in people *(Boegehold & Kotchen, 1989)*. Chloride administration also appears to decrease plasma renin activity in salt depleted rats *(Kotchen et al, 1980; Muller, 1986)*.

The patient with heart failure has chronic activation of the RAA system, which could be significantly influenced by dietary chloride. In addition, furosemide is known to block chloride transport in the ascending loop of Henle, and hypochloremia (and hyponatremia) can develop in advanced CHF. Therefore, chloride is likely to play an important role in the CHF patient. Unfortunately, little is known about optimal dietary intake for CHF patients and additional research will be required to make specific recommendations.

> Potassium

In the past, when digoxin and diuretics were the mainstays of therapy for people and dogs with CHF, hypokalemic was a major consideration. Now, ACE inhibitor therapy has gained widespread

use in the management of dogs with CHF and this medication results in renal potassium sparing. Therefore, ACE inhibitors are known to cause increased serum potassium, with some animals developing hyperkalemia *(Roudebush et al, 1994; COVE Study Group, 1995; Rush et al, 1998)*. This can especially be a problem in animals eating commercial cardiac diets since some commercial cardiac diets contain increased potassium concentrations to counteract the theoretical loss due to diuretics.

In addition to the importance of the diets' compatibility with current ACE inhibitor use, other newer cardiac medications may also be used more commonly. Spironolactone, an aldosterone antagonist and a potassium-sparing diuretic is being used with greater frequency in veterinary patient after reports of improved survival in human CHF patients *(Pitt et al, 1999)*. This medication is even more likely than other diuretics to cause hyperkalemia. Finally, many people know about the association between diuretics and hypokalemia either from their own medical condition or that of a friend or relative, and some mistakenly give their dogs with CHF bananas or potassium supplements in an effort to prevent this problem. Routine monitoring of serum potassium is recommended for all patients with CHF, particularly those receiving an ACE inhibitor or spironolactone. If hyperkalemia is present, a diet with a lower potassium content should be selected.

► Preventing nutritional deficiencies versus nutritional pharmacology

Historically, a variety of nutritional deficiencies have been known to cause cardiac disease in various species. These include thiamine, magnesium, vitamin E, selenium, and taurine. Although nutritional deficiencies are generally uncommon (except in owners feeding unbalanced homemade diets), they may still play a role in some cardiac diseases of dogs. Nutritional deficiencies may also develop secondary to the disease or its treatment. There is also blurring of the lines between the benefits of correcting a nutritional deficiency (e.g. as in a cat with taurine deficiency-induced dilated cardiomyopathy) and the pharmacological effects of a nutrient (e.g. the positive inotropic effects of taurine). In addition, new information is coming out on species and even breed differences in nutrient requirements. Thus, there appears to be much more to providing optimal levels of nutrients than just preventing a deficiency.

> Protein and amino acids

- ***Protein***

In addition to sodium restriction, the dietary recommendations in the 1960's for dogs with CHF were to restrict protein intake to "reduce the metabolic load on congested, aging, and diseased kidneys and liver" *(Pensinger, 1964)*. Restricting protein can actually be detrimental in terms of lean body mass loss and malnutrition. Dogs with CHF should not be protein restricted, unless they have concurrent advanced renal disease. Some of the diets designed for dogs with cardiac disease are low in protein (3.6-4.2 gm/100 kcal). In addition, some veterinarians recommend protein-restricted renal diets for dogs with cardiac disease because these diets often (but not always) are also moderately sodium restricted.

Unless severe renal dysfunction is present (i.e., serum creatinine>3.0 mg/dL), high-quality protein should be fed to meet canine AAFCO minimums for adult maintenance requirements (5.1 gm/100 kcal; *Association of American Feed Control Officials (AAFCO), 2005*). In one study, daily protein intake of dogs with cardiac disease ranged from 2.3-18.8 g/100 kcal so some dogs with cardiac disease are clearly not eating sufficient dietary protein *(Freeman et al, 2003b)*.

Another misconception that impacts cardiac disease is the still widespread belief that dietary protein should be restricted in early renal disease **(see chapter 8)**. Although the majority of dogs treated with ACE inhibitors do not develop azotemia, some dogs receiving ACE inhibitors can develop azotemia *(COVE Study Group, 1995)*. Azotemia occurs more frequently when ACE inhibi-

tors are used in conjunction with diuretics although, in a small number of dogs, azotemia can develop from ACE inhibitors alone. When concurrent ACE inhibitor and diuretic use causes azotemia, reduction of the furosemide dose is indicated to reduce azotemia. A protein-restricted diet is not necessary in this situation unless medication changes do not correct the problem and the renal disease progresses.

- ***Taurine***

The association between taurine and feline DCM described in the late 1980's prompted investigators to examine the role of taurine in canine DCM *(Pion et al, 1987)*. Unlike cats, dogs are thought to be able to synthesize adequate amounts of taurine endogenously and taurine is not considered to be required in canine diets. Although initial studies showed that most dogs with DCM did not have low plasma taurine concentrations, certain breeds of dogs with DCM (eg, Cocker Spaniels and Golden Retrievers) did have low taurine concentrations *(Kramer et al, 1995)*. The association between dogs with DCM and low taurine concentrations has been best established in the American Cocker Spaniel *(Kramer et al, 1995; Kittleson et al, 1997)*.

In a study by Backus *et al*, 12 of 19 Newfoundlands tested had taurine concentrations consistent with taurine deficiency. However, none of these dogs had DCM *(Backus et al, 2003)*. Other commonly reported breeds of dogs with DCM and taurine deficiency include Golden Retriever, Labrador Retriever, Saint Bernard, English Setter *(Freeman et al, 2001; Fascetti et al, 2003)*.

When concurrent ACE inhibitor and diuretic use causes azotemia, reduction of the diuretic dose is indicated to reduce azotemia. A protein restricted diet is not necessary in this situation unless medication changes do not correct the problem and the renal disease progresses.

The first question about the relationship between canine DCM and taurine deficiency is whether DCM is caused by dietary deficiency.

In one retrospective study, 20 of 37 dogs with DCM tested for plasma and whole blood taurine concentrations were considered to be taurine-deficient **(***Freeman et al, 2001)*. There was no significant difference in mean dietary taurine content (based on manufacturers' information) between taurine deficient and non taurine deficient dogs, nor was there a correlation between dietary content and circulating taurine concentrations *(Freeman et al, 2001)*. Of the taurine deficient dogs, 7 were eating a lamb and rice based diet and seven were eating an increased fiber diet.

Twelve dogs with DCM and taurine deficiency were reported to be eating dry diets containing lamb meal, rice, or both as primary ingredients *(Fascetti et al, 2003)*.

In another study, 131 normal dogs were tested for plasma and whole blood taurine concentrations. In this study, dogs consuming diets containing rice bran or whole grain rice had lower taurine concentrations *(Delaney et al, 2003)*. Thus, it may be the rice bran component of diets that affects taurine concentrations although lamb meal also is known to have decreased amino acid digestibility *(Johnson et al, 1998)*.

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In a retrospective study, of the taurine deficient dogs, 7 were eating a lamb and rice based diet and 7 were eating an increased fiber diet.

Alternatively, dietary protein quality and quantity may also play a role in taurine deficiency. In one study, a group of Beagles fed a low taurine, very low protein diet for 48 months had a decrease in whole blood taurine concentrations and 1 of the 16 dogs developed DCM *(Sanderson, 2001)*.

Finally, some dog breeds may be predisposed to taurine deficiency when fed certain types of diets because of higher requirements or breed-specific metabolic abnormalities.

A second question that still remains is whether taurine supplementation reverses DCM in dogs with concurrent taurine deficiency.

In one small study, 11 Cocker Spaniels supplemented with taurine and carnitine showed improvement in clinical parameters and echocardiographic measurements *(Kittleson et al, 1997)*. Whether the response would be similar with taurine alone remains to be seen. In one small retrospec-

tive study that compared dogs with DCM that were taurine deficient and were treated with taurine (plus medical therapy) to dogs that were not taurine deficient, there was no difference in the number that were able to discontinue medications, in the furosemide dosage, in echocardiographic measurements, or survival *(Freeman et al, 2001)*. Another retrospective study of 12 dogs with DCM and taurine deficiency showed a within-group improvement in E-point to septal separation and fractional shortening after taurine supplementation but there was no comparison group *(Fascetti et al, 2003)*.

Minimum taurine requirements for dogs have not been established by AAFCO, but the minimum taurine requirement for adult cats is 25 mg/100 kcal for dry food and 50 mg/100 kcal for canned foods *(AAFCO, 2005)*. A diet with a taurine content of 50 mg/100 kcal would provide approximately 1000 mg/day of taurine to a 40 kg dog.

Response to therapy may be breed dependent. In a study of a litter of Portugese Water Dogs with DCM, taurine was below the reference range in eight of eight puppies tested, and DCM was diagnosed in eight of the nine puppies *(Alroy, 2000)*. Taurine supplementation was instituted in 6 of the puppies, which significantly increased plasma and whole blood taurine concentrations as well as cardiac function *(Alroy, 2000)*. In a study of Beagles fed a low taurine, very low protein diet for 48 months, the one dog that developed DCM had improvement in fractional shortening after three months of taurine supplementation *(Sanderson et al, 2001)*. Some of the potential benefits of taurine in dogs with DCM may be due to its positive inotropic effects or role in calcium regulation in the myocardium. Beneficial effects of taurine have been shown in animal models with experimentally-induced heart failure and in unblinded human clinical trials *(Elizarova et al, 1993, Azuma, 1994)*.


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In Cocker Spaniels with DCM, measuring plasma and whole blood taurine concentrations is recommended.

While it is unlikely that the breeds at high risk for DCM such as the Doberman Pinscher or the Boxer have taurine deficiency, certain breeds (eg, Cocker Spaniel, Newfoundlands, Golden Retrievers) and atypical breeds (eg, Scottish Terrier, Border Collie) may have concurrent taurine deficiency. Therefore, in these latter breeds, measuring plasma and whole blood taurine concentrations is recommended. In addition, taurine concentrations should be measured in dogs with DCM that are eating lamb meal and rice, very low protein, or increased fiber diets. Although the extent of the benefit of supplementation is not yet clear, taurine supplementation is recommended until plasma and whole blood taurine concentrations from the patient are available. Even in dogs with taurine deficiency that do respond to taurine supplementation, the response is generally not as dramatic as in taurine deficient cats with DCM. The optimal dose of taurine for correcting a deficiency has not been determined but the currently recommended dose is 500-1000 mg q 8-12 hours. Taurine can be provided as a supplement although certain diets may contain enough taurine to raise plasma taurine concentrations.

- ***Arginine***

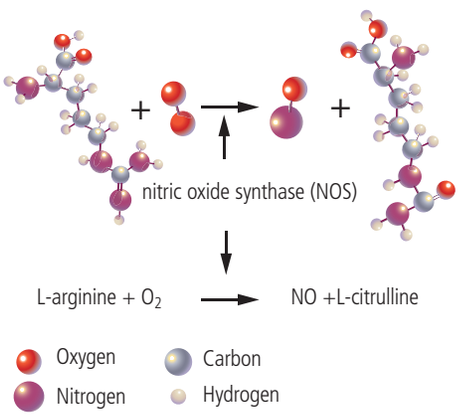
Nitric oxide is an endogenous vascular smooth muscle relaxant. It is synthesized from L-arginine and molecular oxygen **(Figure 9)**.

Circulating nitric oxide is elevated in people with CHF, regardless of the underlying cause and in two studies of dogs and cats with heart disease *(De Belder et al, 1993; Comini et al, 1999; De Laforcade et al, 2000; Freeman et al, 2003a)*. However, one study of dogs showed lower nitric oxide concentrations in dogs with untreated CVD *(Pedersen et al, 2003)*. High circulating nitric oxide levels may have an initial beneficial compensatory effect but can be detrimental when this response is prolonged. High levels of nitric oxide can have a negative inotropic effect and can decrease the responsiveness to beta-adrenergic stimulation *(Gulick et al, 1989; Yamamoto et al, 1997)*. There appear to be competing responses occurring in CHF. While iNOS is upregulated in patients with CHF producing high circulating levels of nitric oxide, eNOS is actually downregulated and reduces endothelium-dependent vasodilation *(Agnoletti et al, 1999, Katz et al, 2000)*.

The reduction in eNOS and resulting loss of normal vasodilation have adverse effects in the patient with CHF *(Feng et al, 1998)*. People with CHF have a reduction of peripheral blood flow both at rest and during exercise *(Maguire et al, 1998)*. This abnormality may contribute to exercise intolerance in these patients. Endothelial dysfunction has also been demonstrated in dogs with experimentally-induced CHF and is associated with decreased gene expression of eNOS *(Wang et al, 1997)*.

Based on the findings of endothelial dysfunction in patients with CHF, investigators have begun to study the effects of arginine supplementation in this group. In normal patients, L-arginine supplementation is unlikely to have an effect on nitric oxide production because L-arginine is found in concentrations much higher than the Km values for NOS *(Tsikas et al, 2000)*. But the situation in patients with CHF may be very different and, in fact, L-arginine supplementation has been shown to improve endothelial dysfunction *(Kubota et al a, 1997; Feng et al, 1999; Kanaya et al, 1999; Hambrecht et al, 2000)*. L-arginine supplementation has been tested in people with CHF in a number of studies *(Kubota et al, 1997; Kanaya et al, 1999; Banning & Prendergast, 1999; Bocchi et al, 2000; Hambrecht et al, 2000)*. These studies have shown increased circulating concentrations of nitric oxide but improved endothelium-dependent vasodilation and cardiac output. These studies also have shown reduced heart rate and systemic vascular resistance, with no negative effects on cardiac contractility or other echocardiographic variables *(Kubota et al, 1997; Hambrecht et al, 2000; Bocchi et al, 2000)*. Although one study of arginine supplementation found no effect on exercise tolerance, another study showed that L-arginine reduced dyspnea in response to increasing CO_2 production during exercise in people with severe chronic heart failure *(Kanaya et al, 1999; Banning & Prendergast, 1999)*. Thus, while much research is needed in this area, arginine supplementation may provide beneficial effects in patients with CHF.

FIGURE 9 - ORIGIN OF NITRIC OXIDE



The reaction is catalyzed by the enzyme, nitric oxide synthase (NOS). There are three forms of NOS:

- ***endothelial NOS (eNOS):*** *eNOS is required for maintenance of normal vascular tone and as a physiologic messenger*
- ***neuronal NOS (nNOS):*** *eNOS and nNOS are constitutive forms and are always produced in low levels*
- ***inducible NOS (iNOS):*** *iNOS is inducible by a variety of inflammatory mediators including the cytokines, tumor necrosis factor (TNF), and interleukin-1 (IL-1), and free radicals.*

> Fat

Fat is a source of calories and essential fatty acids and increases the palatability of the diet. However, depending upon the type of fat, it can have significant effects on immune function, the production of inflammatory mediators and even hemodynamics.

• *n-3 fatty acids*

Most human and canine diets contain primarily n-6 fatty acids. In n-6 fatty acids (eg linoleic acid, γ-linolenic acid, and arachidonic acid), the first double-bond is at the position of the 6th carbon from the methyl end. However, n-3 fatty acids [α-linolenic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)] have the first double-bond at the 3rd carbon from the methyl end. Although this seems like a minor change, it confers very different structure and characteristics to the fatty acid. Plasma membranes normally contain very low concentrations of n-3 fatty acids, but levels can be increased by a food or supplement enriched in n-3 fatty acids.

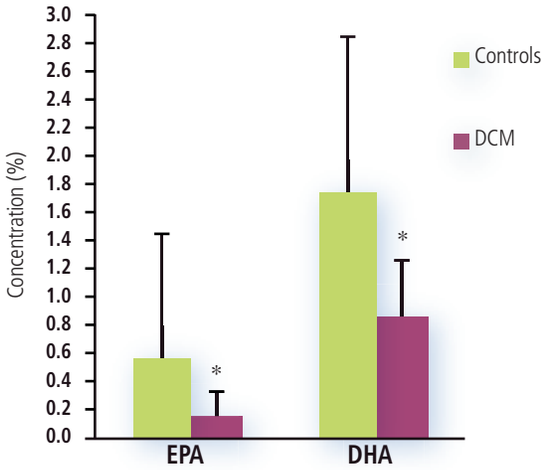
Dogs with heart failure have lower plasma concentrations of eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-6), regardless of the underlying disease **(Figure 10)** *(Freeman et al, 1998; Rush et al, 2000)*. This alteration in plasma fatty acids has also been found in people with various diseases as well, suggesting that metabolic changes may occur in certain diseases that increase the use of n-3 fatty acids. Therefore, supplementation may improve an absolute or relative n-3 fatty acid "deficiency".

n-3 fatty acid supplementation also reduces the more inflammatory eicosanoids. n-3 fatty acids are known to reduce the production of the more inflammatory 2- and 4-series eicosanoids (eg, there is a shift from production of prostaglandin E2 to prostaglandin E3). In a study of dogs with DCM, dogs supplemented with fish oil had a greater reduction in prostaglandin E2 production compared to dogs receiving the placebo *(Freeman et al, 1998)*. This may have benefits in terms of reduced inflammation. n-3 fatty acids also are known to decrease the production of the inflammatory cytokines, TNF and IL-1, which are elevated in CHF *(Endres et al, 1989; Meydani et al, 1991; Freeman et al, 1998)*.

Fish oil supplementation reduced cachexia and, in some, but not all dogs with CHF-induced anorexia, improved food intake *(Freeman et al, 1998)*. Finally, n-3 fatty acids have been shown in a number of rodent, primate, and canine models to reduce arrhythmogenesis *(Charnock, 1994; Kang & Leaf, 1996; Billman et al, 1999)*. Many dogs with CVD and most dogs with DCM have arrhythmias. In some dogs with cardiac disease, sudden death due to arrhythmias is the first manifestation of the disease in otherwise asymptomatic dogs. Therefore, n-3 fatty acid supplementation may be beneficial even before CHF develops.

FIGURE 10 - PLASMA FATTY ACID CONCENTRATIONS IN DOGS WITH DILATED CARDIOMYOPATHY (DCM) AND HEART FAILURE (N=28) COMPARED TO HEALTHY CONTROL DOGS (N=5)

(From Freeman et al, 1998)



Dogs with DCM and heart failure had significantly lower plasma eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) concentrations compared to healthy control dogs.
**P<0.05.*
(mean +/- standard deviation)

- ***n-3 fatty acid supplementation***

There is controversy as to whether dose of n-3 fatty acids or the ratio of n-6: n-3 fatty acids is more important for the beneficial effects of n-3 fatty acids. Some evidence points to the primary importance of the total n-3 dose but it may also be important to avoid a high n-6:n-3 ratio as well. Although an optimal dose has not been determined, the authors currently recommend a dosage of 40 mg/kg EPA and 25 mg/kg DHA for dogs with anorexia or cachexia. Unless the diet is one of a few specially designed therapeutic diets, supplementation will be necessary since other commercial diets will not achieve this n-3 fatty acid dose.

Although an optimal dose has not been determined, the authors currently recommend a dosage of 40 mg/kg EPA and 25 mg/kg DHA for dogs with anorexia or cachexia. Unless the diet is one of a few specially designed therapeutic diets, supplementation will be necessary since other commercial diets will not achieve this n-3 fatty acid dose.

The exact content of EPA and DHA in individual fish oil supplements varies widely. The most common formulation of fish oil, however, is one gram capsules that contain 180 mg EPA and 120 mg DHA. At this concentration, fish oil can be administered at a dose of 1 capsule per 10 pounds of body weight to achieve the authors' recommended EPA and DHA dose. Fish oil with higher concentrations of EPA and DHA can be obtained from medical supply catalogs and may be more feasible for large dogs.

Fish oil supplements should always contain vitamin E as an antioxidant, but other nutrients should not be included to avoid toxicities. Similarly, cod liver oil should not be used because of the possibility for vitamins A and D toxicity. Finally, although flax seed oil contains high levels of α-linolenic acid, this fatty acid must be converted to EPA and DHA for its beneficial effects. Species vary in the ability to make this conversion: dogs have the enzymes to convert it but with limited efficiency. **Therefore, flax seed oil is not recommended as an n-3 fatty acid supplement.**

> Minerals and vitamins

• *Potassium*

Potassium is an important electrolyte in cardiac patients for a number of reasons. Hypokalemia potentiates arrhythmias, causes muscle weakness, and predisposes patients to digitalis toxicity. In addition, Class I antiarrhythmic drugs, such as procainamide and quinidine, are relatively ineffective in the face of hypokalemia. Hypokalemia was considered to be a common problem in the past when diuretics were the mainstays of therapy. Many of the medications used in dogs with CHF can predispose a patient to hypokalemia, including loop diuretics (eg, furosemide) and thiazide diuretics (eg, hydrochlorothiazide). However, with the increased use of ACE inhibitors, hypokalemia is no longer very common in dogs with CHF.

In addition to medication effects, inadequate dietary intake could predispose a dog to hypokalemia. In one study, 49% of dogs with cardiac disease ate less potassium than the AAFCO minimum value (170 mg/100 kcal). Intakes ranged from 37-443 mg/100 kcal *(Freeman et al, 2003b)*. This suggests that, based on dietary intake alone, some dogs may be predisposed to hypokalemia (in addition to the risk for hyperkalemia previously discussed) and underscores the importance of monitoring serum potassium in dogs with CHF.

• *Magnesium*

Magnesium is an essential prosthetic group in hundreds of enzymatic reactions involving carbohydrate and fatty acid metabolism, protein and nucleic acid synthesis, the adenylate cyclase system, and cardiac and smooth muscle contractility. Thus, magnesium plays an important role in normal cardiovascular function. It is also clear that alterations in magnesium homeostasis in people and dogs are common, and can have deleterious effects in a variety of cardiovascular conditions including hypertension, coronary artery disease, congestive heart failure, and cardiac arrhythmias *(Resnick, 1984; Rayssiguer, 1984; Gottleib et al, 1990; Iseri, 1986; Cobb & Michell, 1992)*. In addition, numerous drugs used to treat cardiac conditions, including digoxin and loop diuretics are associated with magnesium depletion *(Quamme & Dirks, 1994)*. Therefore, dogs with heart failure receiving these medications have the potential to develop hypomagnesemia. Hypomagnesemia can increase the risk of arrhythmias, decrease cardiac contractility, and can potentiate the adverse effects of cardiac medications.

There have been conflicting reports on the prevalence of hypomagnesemia in dogs with cardiac disease. Reports range from "uncommon" *(O'Keefe et al, 1993)* to 2/84 *(Edwards et al, 1991)*; fifty percent *(Rush, 2000)* to two-thirds of Lasix-treated dogs *(Cobb & Michell, 1992)*.

Hypokalemia was considered to be a common problem in the past when diuretics were the mainstays of therapy. Many of the medications used in dogs with CHF can predispose a patient to hypokalemia, including loop diuretics (eg, furosemide) and thiazide diuretics (eg, hydrochlorothiazide). However, with the increased use of ACE inhibitors, hypokalemia is no longer very common in dogs with CHF.

One of the difficulties in diagnosing magnesium deficiency is that only one percent of the total body magnesium is in the extracellular space. Therefore, normal serum magnesium does not necessarily mean there are adequate total body stores. Serial measurements of serum magnesium are currently recommended, especially in dogs with arrhythmias or those receiving large doses of diuretics. If low serum magnesium concentrations do arise and the dog is eating a diet that is low in magnesium, a diet higher in magnesium may be beneficial. Magnesium concentrations vary widely in commercial pet foods. Commercial reduced sodium diets for dogs can contain between 9-40 mg magnesium/100 kcal (compared to an AAFCO minimum of 10 mg/100 kcal). If the dog remains hypomagnesemic, oral magnesium supplementation will be required (e.g. magnesium oxide).

• *B vitamins*

(Table 7)

Little research has been conducted on the prevalence of B vitamin deficiencies in dogs with cardiac disease. However, there have long been concerns over the risk of B vitamin deficiencies in CHF due to anorexia and urinary loss of water soluble vitamins secondary to diuretic use. This

may be less of a problem now that there are more effective medications for treatment of CHF but even in one study from 1991, 91% of people with CHF had low thiamine concentrations *(Seligmann et al, 1991)*. In this study, patients were being treated with furosemide, ACE inhibitors, nitrates, and digoxin (where appropriate).

Low doses of furosemide were shown to cause increased urinary loss of thiamine in healthy people and in rats *(Rieck et al, 1999; Lubetsky et al, 1999)*. Although B vitamin status has not been reported for dogs with CHF, they may have higher dietary B vitamin requirements. Most commercial cardiac diets contain increased levels of water soluble vitamins to offset urinary losses so supplementation usually is not required.

> Other nutrients

- ***Antioxidants***

Much attention has been given to antioxidants for their potential role in the prevention and treatment of human cardiac diseases. Reactive oxygen species are a by-product of oxygen metabolism for which the body normally compensates through the production of endogenous antioxidants. An imbalance between oxidant production and antioxidant protection (eg, oxidative stress), however, could increase the risk for cardiac disease **(Figure 11)**. Antioxidants are produced endogenously but also can be supplied exogenously. The major antioxidants include enzymatic antioxidants (e.g., superoxide dismutase, catalase, glutathione peroxidase) and oxidant quenchers (e.g., vitamin C, vitamin E, glutathione, and β-carotene).

Oxidative stress has been implicated in the development of a number of cardiac diseases. Increased oxidative stress has been demonstrated in people with CHF *(Belch et al, 1991; Keith et al, 1998)*. In dogs with heart failure, regardless of the underlying cause, there are increased levels of biomarkers of oxidative stress and a reduction in certain antioxidants, particularly vitamin E *(Freeman et al, 1999; Freeman et al, 2005)*. These alterations suggest an imbalance between oxidant stress and antioxidant protection in dogs with CHF.

Additional research is required to evaluate the effect, but antioxidant supplementation may hold promise in the future for the therapy of animals with cardiac disease.

TABLE 7 - VITAMINS OF GROUP B

Name	Abbreviations
Thiamin	B1
Riboflavin	B2
Pantothenic acid	*(B5*)*
Pyridoxine	B6
Biotin	*(B8*)*
Folic acid	*(B9*)*
Cobalamin	B12
Niacin	PP
Choline	

* *also called*

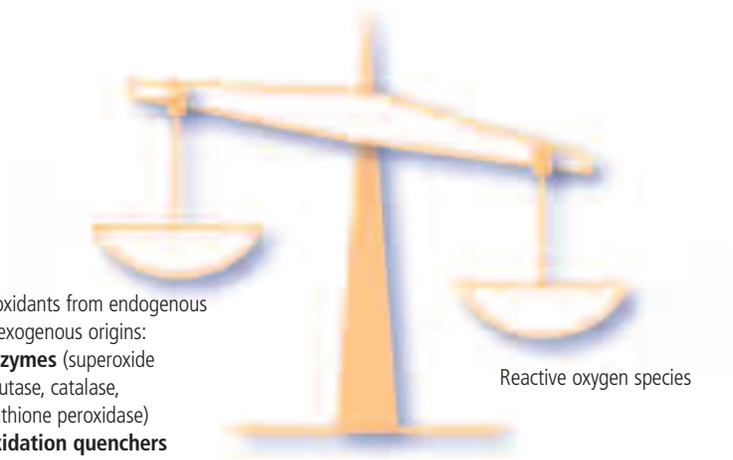
- ***L-Carnitine***

L-Carnitine is a quaternary amine **(Figure 12)** whose major role is in long-chain fatty acid metabolism and energy production. Carnitine deficiency syndromes in people have been associated with primary myocardial disease and, based on this and its high concentrations in cardiac muscle, its role in canine DCM also has been of interest.

L-carnitine deficiency was reported in a family of Boxers in 1991 *(Keene et al, 1991)*. Since that time, L-carnitine supplementation has been used in some dogs with DCM but no blinded prospective studies have been done so a causative role has not been established. In human DCM patients, most studies of L-carnitine have not been well-controlled. However, one randomized, double-blind, placebo-controlled study showed improved three-year survival in human DCM patients receiving 2 gm/day L-carnitine *(Rizos, 2000)*.

One of the difficult aspects of studying L-carnitine in DCM is that one must measure myocardial concentrations since plasma concentrations are often normal even in the face of myocardial deficiency. Therefore, the advancement of knowledge of the role of this nutrient in DCM has been slow. It is not yet clear whether the carnitine deficiency seen in some dogs with DCM is the cause of the disease or merely secondary to the development of CHF. One study of dogs with heart failure induced by rapid pacing showed that myocardial concentrations decreased in normal dogs after the onset of CHF *(Pierpont et al, 1993)*. However, even if L-carnitine deficiency is not the inciting cause of DCM, supplementation may still provide benefits by improving myocardial energy production.

FIGURE 11 - ORIGIN OF OXIDATIVE STRESS



Oxidative stress comes from the imbalance between the production of free radicals and antioxidant defenses.

L-carnitine supplementation has few side effects but it is expensive and this may be a significant deterrent for some owners. The authors offer the option of L-carnitine supplementation to owners of dogs with DCM, especially Boxers and Cocker spaniels, 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 currently recommended dose is 50-100 mg/kg PO q 8 hours.

• *Coenzyme Q10*

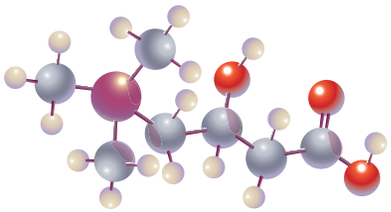
Coenzyme Q10 is a cofactor required for energy production and has antioxidant properties. There are a number of mechanisms by which coenzyme Q10 might play a role in cardiac disease. Some investigators have proposed coenzyme Q10 deficiency as a possible cause for DCM but this has not been proven. Even in dogs with experimentally-induced CHF, serum coenzyme Q10 levels were not reduced *(Harker-Murray et al, 2000)*.

The minimum or optimal dose of L-carnitine necessary to replete a dog with low myocardial carnitine concentrations is not known, but the currently recommended dose is 50-100 mg/kg PO q 8 hours.

The most enthusiasm for coenzyme Q10 has been as a dietary supplement in the treatment of people or dogs with DCM. Coenzyme Q10 supplementation has anecdotally been reported to be beneficial but most of the human studies of coenzyme Q10 supplementation have not been well-controlled and results are conflicting. However, some encouraging results have been found *(Langsjoen et al, 1994; Sacher et al, 1997; Munkholm et al, 1999)*. In one study of dogs with experimentally-induced CHF, coenzyme Q10 supplementation increased serum, but not myocardial, concentrations *(Harker-Murray et al, 2000)*. The bioavailability of coenzyme Q10 varies in different tissues and also depends upon the degree of tissue deficiency in that tissue.

The current recommended dose in canine patients is 30 mg PO BID, although up to 90 mg PO BID has been recommended for large dogs. The purported benefits of supplementation include

FIGURE 12 - CARNITINE MOLECULE



Discovered in 1905, L-carnitine is synthetized in dogs from lysine and methionine, if vitamin C and pyridoxine (vit B6) are present. It is a quaternary amine that acts as a water soluble vitamin. Carnitine can be synthetized in D or L forms, but L-carnitine is the only one of relevance for dogs with cardiac disease.

correction of a deficiency, improved myocardial metabolic efficiency, and increased antioxidant protection. Controlled prospective studies will be necessary to accurately judge the efficacy of this supplement.

5 - General issues in feeding dogs with cardiac disease

Dietary modification in dogs needs to be individualized - not all dogs with cardiac disease will need the same dietary formulation. Patients with cardiac disease vary in terms of their clinical signs, laboratory parameters, and food preferences and these should all affect diet selection. For example, more severe sodium restriction would be required for a dog with DCM and CHF than for a dog with asymptomatic DCM. Dogs with cardiac cachexia require a calorically-dense diet while an overweight dog should be fed a calorically-restricted diet. Dogs with cardiac disease may be hyper-, hypo-, or normokalemic and this will influence the choice of diet.

Concurrent diseases also influence diet choice and, in one study, concurrent diseases were present in 61% of dogs with cardiac disease *(Freeman et al, 2003b)*. For example, a dog with CVD and colitis would need a diet that is sodium restricted but also one that has nutritional modifications to help manage the colitis (eg, reduced fat, increased fiber).

Based on these patient parameters, a diet or diets can be selected for the individual patient. There currently are a number of commercial veterinary diets available that are specifically designed for animals with cardiac disease. Specific characteristics of these foods vary, but they are moderately to severely sodium restricted and generally contain increased levels of B vitamins. Some cardiac diets also may include increased levels of taurine, carnitine, antioxidants, or n-3 fatty acids. In some cases, a "cardiac" diet may not be needed as some over-the-counter diets may have the properties desired for an individual dog. The authors also recommend offering more than one diet that would be appropriate for a dog so that the owner can see which is most palatable to the pet. Having a number of dietary choices is particularly beneficial for more severely affected CHF patients, in which a cyclical or selective loss of appetite is common.

In addition to the dog food(s) selected, one must also give the owner careful instructions on treats and table food. In some cases, dogs may be eating an ideal dog food but are getting large amounts of sodium from treats. In one study, over 90% of dogs with cardiac disease received treats and these dogs were receiving up to 100% of their sodium (median, 25%) from treats *(Freeman et al, 2003b)*.

Therefore, in addition to finding a diet that has the desired nutritional properties and palatability, it also is important to devise an overall dietary plan that meets the owner's expectations. This

includes devising a satisfactory method for administering medications. Most people administering medications to their dogs use foods as a way to administer the medication *(Freeman et al, 2003b)*. Discussing appropriate options for an owner to use for this purpose is necessary, as the foods most commonly used by owners are very high in sodium (eg, cheese, lunch meats, etc). Including all forms of dietary intake in the overall diet plan is important to achieve success with nutritional modification.

In many cases, the desired nutrient modifications can be achieved through diet alone. However, supplementation of certain nutrients may be desirable if they are either not in a particular diet or not at high enough levels to achieve the desired effect. One issue with the administration of dietary supplements is that they should not take the place of standard cardiac medications (eg, ACE inhibitors, diuretics). Dogs with severe CHF may be receiving 10-20 pills per day and it may be difficult for the owner to give supplements on top of this without discontinuing one or more of the cardiac medications. It is important to ask each owner about any dietary supplements being used as this is often not information that is volunteered (ie, dietary supplements are often not considered medications or diet). This will help to determine if any harmful supplements are being given and if the supplements are being given at an appropriate dose. In situations in which pill administration is becoming overwhelming for an owner, the veterinarian can assist the owner in determining which dietary supplements have the least potential benefits and can be discontinued.

There currently are a number of commercial veterinary diets available that are specifically designed for animals with cardiac disease. Specific characteristics of these foods vary, but they are moderately to severely sodium restricted and generally contain increased levels of B vitamins. Some cardiac diets also may include increased levels of taurine, carnitine, antioxidants, or n-3 fatty acids.

Finally, owners should be aware that dietary supplements are not regulated in the same way as drugs. They do not require proof of safety, efficacy, or quality control before they can be sold. Therefore, careful selection of type, dose, and brand is important to avoid toxicities or complete lack of efficacy.

References

Alroy J, Rush J, Freeman L et al - Inherited infantile dilated cardiomyopathy in dogs: Genetic, clinical, biochemical, and morphologic findings. J Med Genetics 2000; 95: 57-66.

Agnoletti L, Curello S, Bachetti T et al - Serum from patients with severe heart failure downregulates eNOS and is proapoptotic. Circulation 1999; 100: 1983-1991.

Alexander JK - The heart and obesity. In: Hurst JW, ed. The heart, 6th ed 1986. New York, McGraw-Hill Book Co; 1452.

Anker SD, Negassa A, Coats AJ et al - Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. Lancet 2003; 361:1077-83.

Association of American Feed Control Officials. Official publication. Oxford, Ind, Association of American Feed Control Officials, 2005; 144-146.

Azuma J, Heart Failure Research with Taurine Group - Long-term effect of taurine in congestive heart failure. In: Huxtable R, Michalk DV (eds) 1994. Taurine in health and disease. New York: Plenum Press; 425-433.

Backus RC, Cohen G, Pion PD et al - Taurine deficiency in Newfoundlands fed commercially available complete and balanced diets. J Am Vet Med Assoc 2003; 223: 1130-1136.

Banning AP, Prendergast B - Intravenous L-arginine reduces VE/VCO_2 slope acutely in patients with severe chronic heart failure. Eur J Heart Failure 1999; 1: 187-190.

Barger A, Ross R, Price H - Reduced sodium excretion in dogs with mild valvular lesions of the heart and in dogs with congestive failure. Am J Physiol 1955; 180:249-260.

Belch JJF, Bridges AB, Scott N et al - Oxygen free radicals and congestive heart failure. Br Heart J1991; 65: 245-248.

Billman GE, Kang JX, Leaf A - Prevention of sudden cardiac death by dietary pure n-3 polyunsaturated fatty acids. Circulation 1999; 99: 2452-2457.

Bocchi EA, Vilella de Moraes AV, Esteves-Filho A et al - L-arginine reduces heart rate and improves hemodynamics in severe congestive heart failure. Clin Cardiol 2000; 23: 205-210.

Boegehold MA, Kotchen TA - Relative contributions of dietary Na^+ and Cl^- to salt-sensitive hypertension. Hypertension 1989; 14: 579-583.

Buchanan JW - Causes and prevalence of cardiovascular disease. In: Kirk RW, Bonagura JD (eds). Current veterinary therapy XI, 1992. Philadelphia: WB Saunders; 647-655.

Charnock JS - Dietary fats and cardiac arrhythmias in primates. Nutrition 1994; 10: 161-169.

Clark MA, Hentzen BTH, Plank LD et al - Sequential changes in insulin-like growth factor 1, plasma proteins, and total body protein in severe sepsis and multiple injury. J Parenter Enteral Nutr 1996; 20: 363-370.

Cobb M, Michell A - Plasma electrolyte concentrations in dogs receiving diuretic therapy for cardiac failure. J Small Animal Pract 1992; 33:526-529.

Comini L, Bachetti T, Agnolitti L et al - Induction of functional inducible nitric oxide synthase in monocytes of patients with congestive heart failure. Eur Heart J 1999; 20: 1503-1513.

COVE Study Group - Controlled clinical evaluation of enalapril in dogs with heart failure: Results of the cooperative veterinary enalapril study group. J Vet Intern Med 1995; 9: 243-252.

Davos CH, Doehner W, Rauchhaus M et al - Body mass and survival in patients with chronic heart failure without cachexia: the importance of obesity. J Cardiac Failure 2003; 9:29-35.

De Belder AJ, Radomski MW, Why HJF et al - Nitric oxide synthase activities in human myocardium. Lancet 1993; 341: 84-85.

De Laforcade AM, Freeman LM, Rush JE - Serum nitrate and nitrite in dogs with spontaneous cardiac disease. J Vet Intern Med 2003; 17: 315-318.

Delaney SJ, Kass PH, Rogers QR et al - Plasma and whole blood taurine in normal dogs of varying size fed commercially prepared foods Anim Physiol Anim Nutr 2003;87:236-244

Edwards NJ - Magnesium and congestive heart failure, in Proceedings of Annual American College of Veterinary Internal Medicine Forum, 1991; 679-680.

Elizarova EP, Orlova TR, Medvedeva NV - Effects on heart membranes after taurine treatment in rabbits with congestive heart failure. Arzneim Forsch/Drug Res 1993; 43: 308-312.

Endres S, Ghorbani R, Kelley VE - Effect of dietary supplementation with n-3 polyunsaturated fatty acid on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. N Engl J Med 1989; 320: 265-271.

Fascetti AJ, Reed JR, Rogers QR et al - Taurine deficiency in dogs with dilated cardiomyopathy: 12 cases (1997-2001). J Am Vet Med Assoc 2003; 223: 1137-1141.

Feng Q, Lu X, Fortin AJ et al - Elevation of an endogenous inhibitor of nitric oxide synthesis in experimental congestive heart failure. Cardiovasc Res 1998; 37: 667-675.

Feng Q, Fortin AJ, Lu X, et al - Effects of L-arginine on endothelial and cardiac function in rats with heart failure. Eur J Pharmacol 1999; 376: 27-44.

Fox PR, Sisson D, Moise NS (eds) - Textbook of canine and feline cardiology, 2nd ed 1999. Phildelphia: WB Saunders.

Freeman LM, Brown DJ, Rush JE - Assessment of degree of oxidative stress and antioxidant concentrations in dogs with idiopathic dilated cardiomyopathy. J Am Vet Med Assoc 1999; 215: 644-646.

Freeman LM, McMichael MA, De Laforcade AM et al - Indirect determination of nitric oxide in cats with cardiomyopathy and arterial thromboembolism. J Vet Emerg Crit Care 2003a; 13: 71-76.

Freeman LM, Roubenoff R - The nutrition implications of cardiac cachexia. Nutr Rev 1994; 52: 340-347.

Freeman LM Rush JE, Brown DJ et al - Relationship between circulating and dietary taurine concentrations in dogs with dilated cardiomyopathy. Vet Therapeutics 2001; 2: 370-378.

Freeman LM, Rush JE, Cahalane AK et al - Dietary patterns in dogs with cardiac disease. J Am Vet Med Assoc 2003b; 223: 1301-1305.

Freeman LM, Rush JE, Kehayias JJ et al - Nutritional alterations and the effect of fish oil supplementation in dogs with heart failure. J Vet Intern Med 1998; 12: 440-448.

Freeman LM, Rush JE, Milbury PE et al - Antioxidant status and biomarkers of oxidative stress in dogs with congestive heart failure. J Vet Intern Med 2005;19:537-541

Gottleib SS, Baruch L, Kukin ML - Prognostic importance of the serum magnesium concentration in patients with congestive heart failure. J Am Coll Cardiol 1990; 16: 827-831.

Gulick T, Chung MK, Pieper SJ et al - Interleukin 1 and tumor necrosis factor inhibit cardiac myocyte-adrenergic responsiveness. Proc Natl Acad Sci USA 1989; 86: 6753-6757.

Hambrecht R, Hilbrich L, Erbs S et al - Correction of endothelial dysfunction in chronic heart failure. J Am Coll Cardiol 2000; 35: 706-713.

Hamlin R, Smith R, Smith C et al - Effects of a controlled electrolyte diet, low in sodium on healthy dogs. Vet Med 1964; 59:748-751.

Harker-Murray AK, Tajik AJ, Ishikura F et al - The role of coenzyme Q10 in the pathophysiology and therapy of experimental congestive heart failure in the dog. J Cardiac Failure 2000; 6: 233-242.

International Small Animal Cardiac Health Council - Recommendations for the diagnosis of heart disease and the treatment of heart failure in small animals. Appendix 1. In: Teilley LP, Goodwin JK eds. Manual of Canine and Feline Cardiology, 3rd ed. Philadephia: WB Saunders Co, 2001: 459-489.

Iseri LT - Magnesium and dysrhythmias. Magnesium Bull 1986; 8: 223-229.

Johnson ML, Parsons CM, Fahey GC et al - Effects of species raw material sources, ash content and processing temperature on amino acid digestibility of animal by-product meals by cecectomized and ileally cannulated dogs. J Anim Sci 1998; 76: 1112-1122.

Kanaya Y, Nakamura M, Kobayashi N et al - Effects of L-arginine on lower limb vasodilator reserve and exercise capacity in patients with chronic heart failure. Heart 1999; 81: 512-517.

Kang JX, Leaf A - Antiarrhythmic effects of polyunsaturated fatty acids. Circulation 1996; 94: 1774-1780.

Katz SD, Khan T, Zeballos GA et al - Decreased activity of the L-arginine-nitric oxide metabolic pathway in patients with congestive heart failure. Circulation 1999; 99: 2113-2117.

Keene BW, Panciera DP, Atkins CE et al - Myocardial L-carnitine deficiency in a family of dogs with dilated cardiomyopathy. J Am Vet Med Assoc 1991; 198: 647-650.

Keith M, Geranmayegan A, Sole MJ et al - Increased oxidative stress in patients with congestive heart failure. J Am Coll Cardiol 1998; 31: 1352-1356.

Kittleson MD, Keene B, Pion PD et al - Results of the multicenter spaniel trial (MUST). J Vet Intern Med 1997; 11: 204-211.

Kittleson MD, Kienle RD - Small animal cardiovascular medicine. St Louis: Mosby 1998.

Kittleson MD. Therapy of heart failure - In Ettinger SJ, Feldman EC (eds). Textbook of veterinary internal medicine, 5th ed 2000. Philadelphia: WB Saunders; 713-737.

Koch J, Pedersen H, Jensen A et al - Short term effects of acute inhibition of the angiotensin-converting enzyme on the renin-angiotensin system and plasma atrial natriuretic peptide in healthy dogs fed a low-sodium diet versus a normal-sodium diet. J Vet Intern Med 1994; 41:121-127.

Kotchen TA, Krzyzaniak KE, Anderson JE et al - Inhibition of renin secretion by HCl is related to chloride in both dog and rat. Am J Physiol 1980; 239: F44-F49.

Kramer GA, Kittleson MD, Fox PR - Plasma taurine concentrations in normal dogs and in dogs with heart disease. J Vet Intern Med 1995; 9: 253-258.

Kubota T, Imaizumi T, Oyama J et al - L-arginine increases exercise-induced vasodilation of the forearm in patients with heart failure. Japan Circ J 1997; 61: 471-480.

Langsjoen H, Langsjoen P, Langsjoen P et al - Usefulness of coenzyme Q10 in clinical cardiology: A long-term study. Mol Asp Med 1994; 15 suppl: S165-S175.

Lubestsky A, Winaver J, Seligmann H et al - Urinary thiamine excretion in the rat: Effects of furosemide, other diuretics, and volume load. J Lab Clin Med 1999; 134: 232-237.

Maguire SM, Nugent AG, McGurk C et al - Abnormal vascular responses in human chronic cardiac failure are both endothelium dependent and endothelium independent. Heart 1998; 80: 141-145.

Mallery KF, Freeman LM, Harpster NK et al - Factors contributing to the euthanasia decision in dogs with congestive heart failure. J Am Vet Med Assoc 1999; 214: 1201-1204.

Maxwell A, Butterwick R, Yateman M et al - Nutritional modulation of canine insulin-like growth factors and their binding proteins. J Endocrinol 1998; 158: 77-85.

Meurs KM, Fox PR, Miller MW et al - Plasma concentrations of tumor necrosis factor-alpha in cats with congestive heart failure. Am J Vet Res 2002; 63: 640-642.

Meydani SN, Endres S, Woods MM - Oral (n-3) fatty acid supplementation suppresses cytokine production and lymphocyte proliferation. J Nutr 1991; 121: 547-555.

Morris M, Patton R, Teeter S - Low sodium diet in heart disease: How low is low? Vet Med 1976; 71:1225-1227.

Muller J - Divergent effects of dietary chloride restriction on aldosterone biosynthesis and the renin-angiotensin system in rats. Acta Endocrinol 1986; 112: 105-113.

Munkholm H, Hansen HH, Rasmussen K - Coenzyme Q10 treatment in serious heart failure. Biofactors 1999; 9: 285-289.

O'Keefe DO, Sisson DD et al - Serum electrolytes in dogs with congestive heart failure. J Vet Intern Med 1993; 7:118.

Pedersen H, Koch J, Bie P et al - Effects of a low sodium diet with a high potassium content on plasma endothelin-1, atrial natriuretic peptide and arginine vasopressin in normal dogs. J Vet Intern Med 1994a; 8:713-716.

Pedersen H, Koch J, Jensen A et al - Some effects of a low sodium diet high in potassium on the renin-angiotensin system and plasma electrolyte concentrations in normal dogs. Acta Vet Scand 1994b; 35:133-140.

Pedersen H - Effects of mild mitral valve insufficiency, sodium intake, and place of blood sampling on the renin-angiotensin system in dogs. Acta Vet Scand 1996; 37:109-118.

Pedersen HD, Schutt T, Sondergaard R et al - Decreased plasma concentration of nitric oxide metabolites in dogs with untreated mitral regurgitation. J Vet Intern Med 2003; 17:178-84.

Pensinger R - Dietary control of sodium intake in spontaneous congestive heart failure in dogs. Vet Med 1964; 59:752-784.

Pierpont MEM, Foker JE, Pierpont GL - Myocardial carnitine metabolism in congestive heart failure induced by incessant tachycardia. Basic Res Cardiol 1993; 88: 362-370.

Pion PD, Kittleson MD, Rogers QR et al - Myocardial failure in cats associated with low plasma taurine: A reversible cardiomyopathy. Science 1987; 237: 764-768.

Pitt B, Zannad F, Remme WJ et al - The effect of spironolactone on morbidity and mortality in patients with severe heart failure. New Engl J Med 1999; 341: 709-717.

Poehlman ET, Scheffers J, Gottlieb SS et al - Increased resting metabolic rate in patients with congestive heart failure. Ann Intern Med 1994; 121: 860-862.

Quamme GA, Dirks JH - Magnesium metabolism - In: Narins RG (ed). Clinical disorders of fluid and electrolyte metabolism, 5th ed. New York: McGraw-Hill, 1994; 373-397.

Rayssiguer Y - Role of magnesium and potassium in the pathogenesis of arteriosclerosis. Magnesium Bull 1984; 3: 226-238.

Resnick L - Intracellular free magnesium in erythrocytes of essential hypertension. Proc Natl Acad Sci 1984; 81: 6511-6515.

Rieck J, Halkin H, Almog S et al - Urinary loss of thiamine is increased by low doses of furosemide in healthy volunteers. J Lab Clin Med 1999; 134: 238-243.

Rizos I - Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration. Am Heart J 2000; 139: S120-S123.

Roudebush P, Allen T, Kuehn N et al - The effect of combined therapy with captopril, furosemide, and a sodium-restricted diet on serum electrolyte concentrations and renal function in normal dogs and dogs with congestive heart failure. J Vet Intern Med 1994; 8:337-342.

Rush JE, Freeman LM, Brown DJ et al - Use of enalapril in feline hypertrophic cardiomyopathy. J Am Anim Hosp Assoc 1998; 34: 38-41.

Rush JE, Freeman LM, Brown DJ et al - Clinical, echocardiographic, and neurohumoral effects of a sodium-restricted diet in dogs with heart failure. J Vet Intern Med 2000; 14: 513-520.

Sacher HL, Sacher ML, Landau SW et al - The clinical and hemodynamic effects of coenzyme Q10 in congestive cardiomyopathy. Am J Therapy 1997; 4: 66-72.

Sanderson SL, Gross KL, Ogburn PN et al - Effects of dietary fat and L-carnitine on plasma and whole blood taurine concentrations and cardiac function in healthy dogs fed protein-restricted diets. Am J Vet Res 2001; 62: 1616-1623.

Seligmann H, Halkin H, Rauchfleisch S et al - Thiamine deficiency in patients with congestive heart failure receiving long-term furosemide therapy: A pilot study. Am J Med 1991; 92: 705-706.

Sisson D - Medical management of refractory congestive heart failure in dogs. In Bonagura JD (ed). Current veterinary therapy XIII 2000a. Philadelphia: WB Saunders; 752-756.

Sisson DD, Thomas WP, Bonagura JD - Congenital heart disease. In Ettinger SJ, Feldman EC (eds). Textbook of veterinary internal medicine, 5th ed 2000b. Philadelphia: WB Saunders; 737-787.

Tsikas D, Boger RH, Sandmann J et al - Endogenous nitric oxide synthase inhibitors are responsible for the L-arginine paradox. FEBS Lett 2000; 478: 1-3.

Wang J, Yi GH, Knecht M et al - Physical training alters the pathogenesis of pacing-induced heart failure through endothelium-mediated mechanisms in awake dogs. Circulation 1997; 96: 2683-2692.

Ware WA, Keene BW - Outpatient management of chronic heart failure. In Bonagura JD (ed). Current veterinary therapy XIII 2000. Philadelphia: WB Saunders;748-752.

Yamamoto S, Tsutsui H, Tagawa H et al - Role of myocyte nitric oxide in beta-adrenergic hyporesponsiveness in heart failure. Circulation 1997; 95: 1111-1114.

EXAMPLES OF HOME-PREPARED THE TREATMENT OF

Example 1

COMPOSITION
(1000 g diet)

Pork, shoulder with skin . . . . . 525 g
Rice, cooked . . . . . 435 g
Wheat bran . . . . . 30 g
Rapeseed oil . . . . . 10 g

Add a low-sodium mineral and vitamin supplement.

ANALYSIS		
The diet prepared in this way contains 30% dry matter and 70% water		
	% dry matter	**g/1000 kcal**
Protein	31	59
Fat	28	55
Available carbohydrate	34	66
Fiber	4	9

INDICATIVE RATIONING			
Energy value (metabolizable energy) 1810 kcal/1000 g diet prepared (5990 kcal/1000 g DM)			
Dog's weight (kg)*	Daily amount (g)**	Dog's weight (kg)*	Daily amount (g)**
2	120	45	1250
4	200	50	1350
6	280	55	1450
10	400	60	1550
15	550	65	1640
20	680	70	1740
25	800	75	1830
30	920	80	1920
35	1030	85	2010
40	1140	90	2100

Key Points

- **Energy concentration** to combat cardiac cachexia
- **Moderated sodium content** to facilitate the work of the heart

**The diet is offered in accordance with the dog's healthy weight. For obesity, the diet must be prescribed in accordance with the ideal weight and not the real weight of the dog.*
*** Dividing the diet into two meals is recommended to promote proper digestion.*

DIETS ADAPTED TO CARDIAC COMPLAINTS

Example 2

COMPOSITION
(1000 g diet)

Tuna ..... 500 g
Rice, cooked ..... 450 g
Wheat bran ..... 25 g
Rapeseed oil ..... 25 g

Add a low-sodium mineral and vitamin supplement.

INDICATIVE RATIONING			
Energy value (metabolizable energy) 1935 kcal/1000 g diet prepared (5180 kcal/1000 g DM)			
Dog's weight (kg)*	Daily amount (g)**	Dog's weight (kg)*	Daily amount (g)**
2	110	45	1170
4	190	50	1260
6	260	55	1360
10	380	60	1450
15	510	65	1540
20	640	70	1630
25	750	75	1710
30	860	80	1800
35	970	85	1880
40	1070	90	1960

ANALYSIS		
The diet prepared in this way contains 37% dry matter and 63% water		
	% dry matter	**g/1000 kcal**
Protein	33	63
Fat	28	54
Available carbohydrate	33	64
Fiber	4	7

Contra-indications

Gestation
Lactation
Growth
State of sodium depletion

Examples of home-made diets are proposed by Pr Patrick Nguyen
(Nutrition and Endocrinology Unit; Biology and Pathology Department, National veterinary School of Nantes)

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The majority of cardiac dogs suffer from systolic failure due either to acquired chronic valvular disease (endocardiosis) or dilated cardiomyopathy (DCM). The former disease very often affects small-breed dogs. DCM is most common in large-breed dogs.

Key Points
to remember:

The role of nutrition in cardiac disease

• One of the main goals of dietetic strategy is to achieve **optimal body weight** whatever the initial situation: obesity (especially in case of a subclinical disease) or cachexia in some severe cardiac diseases. Anorexia is a common phenomenon in cardiac patients that needs to be given due consideration: it is one of the main reasons for the request to euthanize patients with severe cardiac disease. It may be directly linked to respiratory problems, to fatigue accompanying heart failure, to nausea induced by medication or to poor palatability of certain cardiac diets, containing low sodium and protein content.

Selecting a **palatable food**, giving frequent small meals and encouraging the dog to eat are all measures that should not be neglected in therapeutic management.

• Cardiac dogs often suffer from a **deficiency of EPA-DHA**, long-chain n-3 fatty acids. A food with a higher EPA-DHA content facilitates the treatment of cardiac cachexia.

• **Severe sodium restriction has been inappropriately recommended for far too long.** Its application is unwarranted in the initial stages of heart failure, as it risks hastening the progression of the cardiac disease by activating the renin-angiotensin system, especially when angiotensin converting enzyme (ACE) inhibitors are simultaneously prescribed.

A moderate restriction of sodium content (< 80-100 mg/100 kcal) is sufficient for stages I and II of heart failure. Only severe heart failure justifies restricting sodium content to 50 mg/100 kcal.

• **A cardiac dog must receive a normal intake of high quality proteins to combat cardiac cachexia.** Limiting the protein intake is not indicated, except for concomitant hepatic encephalopathy or kidney disease that demands such a restriction. Taurine supplementation is recommended as this sulfated amino acid has positive properties that can prove effective in the prevention and treatment of dilated cardiomyopathy.

• **Arginine is a precursor of nitric oxide** (NO), which has been identified as a relaxation factor for the smooth muscle of blood vessels. Supplementary arginine intake will indirectly help combat hypertension.

• **L-carnitine is concentrated in the striated muscles and the heart** where it plays a key role in providing energy to the cells. L-carnitine deficiency has been suggested in connection with dilated cardiomyopathy. Clinical improvements have been reported after the administration of a supplement, although several months of treatment are necessary to achieve changes that can be detectable by echocardiography.

• Free radicals, which are responsible for oxidation of membranous phospholipids, aggravate cardiac lesions. Oxidative stress is a causal factor of dilated cardiomyopathy. The **daily administration of antioxidants in the food** is one of the main ways of combating the progression of heart failure.

Focus on:

THE IMPORTANCE OF TAURINE INTAKE TO ENCOURAGE OPTIMAL CARDIAC CONTRACTILITY

Taurine accounts for at least 40% of the pool of free amino acids in the heart. This amino acid is normally synthesized in the dog from methionine and cystine. The taurine concentration can be limited in certain conditions such as when the animal receives a food with reduced protein content or when taurine synthesis is insufficient, as is the case in some breeds and some lines. The synthesis of taurine appears to be much less efficient in large-breed dogs (> 35 kg) compared to Beagles *(Ko et al, 2005)*.

A simple blood sample will help determine whether the dog has taurine deficiency. Taurine analysis should be performed on whole blood as taurine is stored predominantly in blood cells. The plasma taurine concentration does not properly reflect the muscular and cardiac storage of taurine.

Taurine is essential to the contractility of the heart muscle.

1. It has a positive or negative inotropic effect depending on whether calcium is abundant or not in the cells; taurine protects the myocytes against the effects of excess calcium *(Satoh & Sperelakis, 1998)*.

2. It has an antiarrhythmic role *(Satoh & Sperelakis, 1998)*.

3. It helps preserve the integrity of cardiac muscle cells: in vitro taurine prevents myocyte hypertrophy induced by angiotensin II *(Takahahsi et al, 1998)*.

It has long been known that taurine deficiency can provoke degeneration of the retina and slow down growth. Only recently has DCM in dogs been associated with extremely low plasma taurine levels.

The correlation has especially been shown in Newfoundland dogs in the United Kingdom *(Dukes-McEwan et al, 2001)*. Positive responses to taurine supplementation have been noted in Boxers suffering from DCM. It is therefore advisable to provide sufficient quantities of taurine in the food to prevent any risk of deficiency.

LATERAL THORACIC RADIOGRAPH OF A LARGE-BREED DOG WITH DILATED CARDIOMYOPATHY

Generalized cardiomegaly during cardiomyopathy with clinical signs.

References

Dukes-McEwan J, Biourge V, Ridyard A et al - Dilated cardiomyopathy in Newfoundland dogs: association with low whole blood taurine level. Proceedings of the British Small Animal Veterinary Association Congress J Small Anim Pract 2001: 500.

Ko K, Backus RC, Berg JR et al - In vivo taurine biosynthesis is greater in small dogs than large dogs. Waltham International Nutritional Sciences Symposium, Sept 15, 2005; Washington DC, USA.

Satoh H, Sperelakis N - Review of some actions of taurine on ion channels of cardiac muscle cells and others. Gen Pharmacol 1998; 30(4): 451-63.

Takahahsi K, Azuma M, Baba A et al - Taurine improves angiotensin II-induced hypertrophy of cultured neonatal rat heart cells. Adv Exp Med Biol 1998; 442: 129-135.

Summary of select publications...

There is a hypothesis associating dilated cardiomyopathy (DCM) in dogs, especially large breeds, with taurine deficiency. This study was designed to evaluate the taurine status of a group of Newfoundland dogs in the United Kingdom. One hundred and four Newfoundlands underwent clinical and echocardiography examinations. The evaluation of taurine status was based on total blood analysis (nmol/mL). In addition, a detailed dietary history was obtained for each dog. The echocardiography examinations permited the classification of dogs as normal, dogs with dilated cardiomyopathy, dogs with a reduction in shortening fraction or dogs presenting with dilatation of the left ventricle.

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A low taurine concentration is considered less than 200 nmol/mL, and a very low taurine level is less than 130 nmol/mL.

COMBINATION OF ECHOCARDIOGRAPHIC RESULTS AND TOTAL BLOOD TAURINE CONCENTRATIONS (AVERAGE NMOL/ML ± STANDARD DEVIATION)

	Total blood taurine concentration		
	Average	< 200 nmol/mL	<130 nmol/mL
Normal dogs (n=49)	247±73	7	3
Dog with a reduction in the shortening fraction (n=39)	215±67	14	4
Dogs with DCM (n=11)	184±62	3	4
Dogs with dilatation of the left ventricle (n=5)	187±116	3	1

The taurine concentrations are significantly lower in dogs with DCM compared with normal dogs (ANOVA p=0.02)

Reference

Biourge V, Dukes-McEwan J, Desprez G et al - Association between low whole blood taurine and Dilated CardioMyopathy (DCM) In Newfoundland dogs. ESVCN 2001, abstract.

A low taurine concentration has been shown in a significant number of Newfoundland dogs. In this study population, the taurine values tended to be lower than in dogs with dilated cardiomyopathy (DCM). The purpose of this study was to test the impact of taurine or methionine supplementation in correcting taurine deficiency.

Forty-eight dogs with a blood taurine value less than 200 nmol/mL were identified. Echocardiography examination enabled the establishment of three categories of dogs: normal, echocardiography anomalies without clinical signs (e.g. reduced contractility or dilatation of the left ventricle) and dogs with clinical DCM.

The dogs with clinical DCM received 1000 mg of taurine by mouth twice a day. The remaining dogs were matched by age and sex and then received 250 mg of taurine or 750 mg of methionine per os twice a day. Four dogs were fed with a specific food for very-large dogs.

The blood and urine taurine concentration, as well as the urine creatinine concentration were measured after three and six months of supplementation and compared with the initial values.

The blood taurine concentration increased in all the dogs. It rose from 144±8 nmol/mL at the start of the study to 324±14 nmol/mL after three months of supplementation and 275±10 nmol/mL after six months of supplementation. No differences could be distinguished with respect to the type or dose of supplementation.

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The urine taurine/creatinine ratio was minimal at the start of the study, increasing significantly with supplementation of methionine or taurine, more makedly with the highest taurine concentration.

These results suggest that 250 mg of taurine or 750 mg of methionine per os twice a day, and a diet providing 1000 mg of taurine/kg normalizes the taurine concentration in taurine deficient Newfoundland dogs. For the dogs in this study, a low taurine status cannot be explained by greater taurine losses or an inability to utilize methionine as a taurine precursor.

Reference

Willitz R, Desprez G, Duke-McEwans J et al - Six months taurine or methionine supplementation in 53 Newfoundland Dogs suffering from low whole blood taurine. ESCVN 2002, abstract.

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Main nutritional imbalances implicated in osteoarticular diseases

1 - Anatomy 371
2 - Consequences of nutritional excesses and deficiencies in developmental orthopedic diseases and/or osteoarticular diseases 372
3 - Developmental orthopedic diseases associated with nutritional excesses 380
4 - Developmental orthopedic diseases due to nutritional deficiencies (nutritional secondary hyperparathyroidism, rickets) 389
5 - Osteoarthrosis 394

Frequently asked questions: nutrition and orthopedic diseases 402
References 403
Royal Canin Nutritional Information 406

Main nutritional imbalances implicated in osteoarticular diseases

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He is president of the International Elbow Working Group, past-president of the European Society for Veterinary Orthopedics and Traumatology, member of the Hereditary Committee of the WSAVA and other specialty groups examining companion animal orthopedics and nutrition.

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Developmental orthopedic diseases and osteoarthritis are common diseases seen in canine practice and account for 25% of patient visits to veterinarians. Of those visits for osteoarticular disorders, 70% are due to diseases of the appendicular skeleton, 20% are probably due to dietary origin and more than 22% occur in dogs under one year of age *(Richardson et al, 1997; Johnson et al, 1994)****. Large breed dogs account for the majority of cases however any size dog can be affected.***

The development of these skeletal diseases may be due in part to dietary management. Nutritional excesses and deficiencies can contribute to canine osteoarticular disorders. In many cases, optimal intake of a balanced diet can prevent or at least diminish the severity of the diseases. For a few diseases, dietary correction alone is sufficient to restore skeletal integrity.

1 - Anatomy

► Bone composition

Bone is a specialized form of connective tissue with a complex chemical and physical composition **(Table 1)**. Apart from its cellular fraction (10%) and the water phase (25%), it is composed of an organic matrix and a mineral phase. The cellular fraction includes osteoblasts (organic matrix-forming cells) and osteoclasts (calcified matrix-resorbing cells). The organic matrix is composed of 90% collagen fibers with a high content of hydroxyproline and 10% aminopolysaccharides, non-collagen proteins and a small quantity of lipid. The mineral phase encompasses about 65% of the bone volume, mainly in the form of hydroxyappatite crystals and amorphous calcium phosphate, as well as small quantities of other elements. Of the total body calcium and phosphorus, 99% and 80%, respectively, are present in the skeleton.

TABLE 1 - COMPOSITION OF BONE AND CARTILAGE

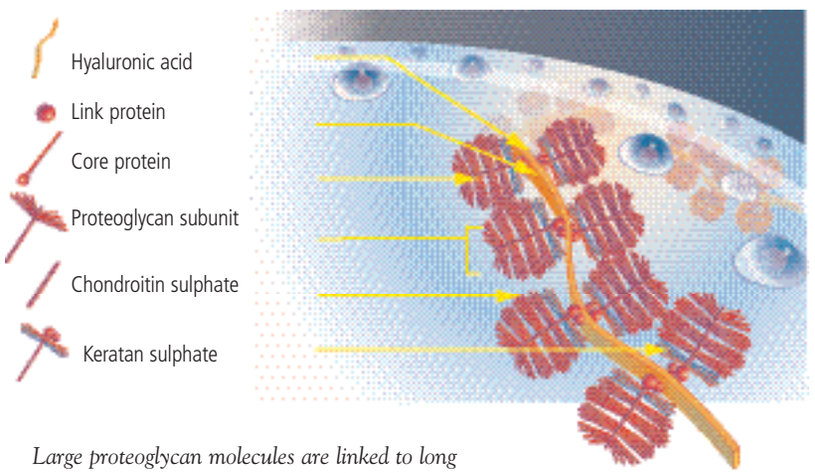
Bone	Cartilage
25% water **10% cells** **- osteoblasts** (organic matrix forming cells) **- osteoclasts** (calcified matrix-resorbing cells) **- osteocytes** (osteoblasts surrounded by matrix) **- extracellular matrix:** collagen (hydroxyproline), aminopolysaccharides, lipids, proteoglycans (low molecular weight) **65% inorganic material** - calcium~phosphate (hydroxy-apatite) - carbonate, Na, K, Mg, Fl	**70% water** **30% cells** **- chondroblasts** (organic matrix forming cells) **- chondroclasts** (organic matrix resorbing cells) **- chondrocytes** (young cells developing into chondroblasts) **- extracellular matrix:** collagen, proteoglycans (glucosaminoglycans, hyaluronic acid, chondroitin sulphate, keratin sulphate)

► Calcium cartilage composition

There are striking differences between the organic and inorganic composition of the main constituents of the skeleton, i.e. bone and cartilage **(Table 1)**. The difference between bone and cartilage is mainly the flexibility (and therefore the water content), the lack of mineral deposition, and the difference in collagen elements. Cartilage contains chondroblasts, proteoglycans, and collagen. The latter are anchored in the subchondral bone in the tide-mark.

Proteoglycans are composed of glycosaminoglycans (GAGs) and a core protein called aggrecan. Aggrecan is an important proteoglycan in cartilage with keratin sulphate and chondroitin sulphate being the most important GAGs. About 200 aggrecan molecules are bound via a glycoprotein to a hyaluran molecule which binds a large quantity of extracellular water **(Figure 1)**.

FIGURE 1 - SCHEMATIC REPRESENTATION OF AGGRECAN WITHIN ARTICULAR CARTILAGE



Large proteoglycan molecules are linked to long chains of hyaluronic acid and stabilized by two or more link proteins to form the large proteoglycan aggregates found in cartilage.

Collagen molecules in cartilage contain large amounts of hydroxyproline and hydroxylysine. The molecules form a triple helix structure, bound to fibrils and these form fibers. Cartilage does not contain blood or lymphatic vessels. With loading, extracellular water is pressed out of the cartilage until the decreased diameter of the pores and the increased negative charge prevents further escape of water, whereas at unloading fresh water and nutrients enter the cartilage.

2 - Consequences of nutritional excesses and deficiencies in developmental orthopedic diseases and/or osteoarticular diseases

TABLE 2 - OSTEOARTICULAR POTENTIAL CONSEQUENCES OF NUTRITIONAL EXCESSES AND DEFICIENCIES IN YOUNG DOGS

Deficiency in energy	Decreased growth rate
Deficiency in calcium	Hyperparathyroidism Pathological fractures
Deficiency in vitamin D	Rickets Bowed legs, pathological fractures
Deficiency in phosphorus	Rickets-like syndrome (very rare)
Excess energy	Hip dysplasia, osteochondrosis, panosteitis, increased risk of osteoarthrosis
Excess calcium	Osteochondrosis, panosteitis, radius curvus syndrome, wobbler syndrome in young dogs
Excess vitamin D	Osteochondrosis, radius curvus syndrome
Excess calcium & phosphorus	Osteochondrosis, radius curvus syndrome

Although most osteoarticular diseases are multi-factorial, the pathophysiology of each disease appears to be influenced by nutrition **(Table 2)**. Excesses of energy and/or calcium contribute to hip dysplasia, elbow dysplasia and osteochondrosis.

► Malnutrition during growth

Slight underfeeding, with respect to energy intake, may slow the growth of puppies but will not influence the adult size of the dog. After a period of inhibited growth due to malnutrition or illness of short duration, the animal will grow at a greater rate than average for its age.

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Rottweiler puppies with an abnormal stance due to carpal laxity. During the period of fast growth, mostly between 1 - 3 months of age, dogs may reveal abnormal angulation of the carpal joint, probably due to a discrepancy between the increase in body weight and the carpal support. Bandaging for 10 days will allow the carpus to gain strength and restore the normal posture of the dog.

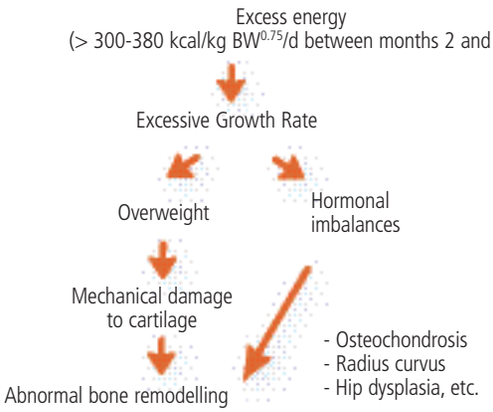
► Overnutrition during growth

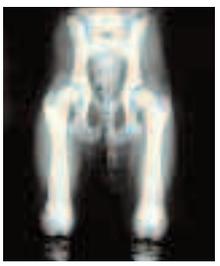
In young animals, unlike adults, excessive energy intake does not cause a substantial increase in fat deposition, but rather, a more rapid rate of growth. As long as there is an adequate protein and essential fatty acid supply, it does not appear to matter for growing dogs if the proportion of energy comes from carbohydrate, fat or protein. If the diet supplies sufficient amounts of specific nutrients, the amount of energy will regulate the rate of growth within the genetic possibilities *(Grøndalen & Hedhammar, 1982)*.

> Pathophysiological consequences of excessive energy intake

Puppies should not be fed to achieve maximum weight gain as this will reduce the period of growth. Overnutrition in growing puppies causes a more rapid growth in bone length and a more rapid gain in body weight, when compared with normal or restricted feeding *(Riser & Shirer, 1964; Hedhammar et al, 1974; Kasstrom, 1975; Tvedten et al, 1977; Lavelle, 1989; Meyer & Zentek, 1991; Kealy et al, 1992)*. Heavy body weight will overload the juvenile skeleton and its support system. This may contribute to the development of a variety of multi-factorial diseases in ad libitum fed dogs including osteochondrosis *(Hedhammar et al, 1974; Lavelle, 1989)*, hip dysplasia *(Hedhammar et al, 1974; Kasstrom, 1975)* and fragmentation and fissures of the coronoid process *(Grondalen & Hedhammar, 1982)* **(Figure 2)**.

Figure 2 - Evolution of osteoarticular complaints related to the over-consumption of energy





Radiograph screening of coxofemoral dysplasia.

The rate of growth is directly influenced by the energy supply. Surplus energy consumption accelerates the attainment of adult weight. The resulting overload on the still immature joints increases the risk of osteoarticular pathology.

High growth rates have been observed in young dogs that are:
- bitch-fed puppies versus hand-reared puppies
- receiving ad libitum palatable commercial food versus meal-restricted energy intake
- fed unrestricted energy enriched diets versus time-restricted food intake.

Not all these studies specifically researched hip joint development or status, but in those where this was the case, a detrimental effect from overnutrition was observed *(Riser & Shirer, 1964; Hedhammar et al, 1974; Kasstrom, 1975; Lavelle, 1989; Kealy et al, 1992)*.

> Clinical consequences of excessive energy intake in large breed puppies

The original study *(Hedhammer et al, 1974)* was performed on 12 pairs of Great Danes raised on food rich in protein, calcium, phosphorus and energy. Skeletal diseases including osteochondrosis and delayed skeletal modeling were observed more frequently in the dogs fed ad libitum, whereas the dogs that received restricted feeding (i.e. 2/3 of the amount of the ad lib group) showed less severe signs.

In a controlled study of Great Danes with high food intake of more balanced commercial foods, the ad libitum fed dogs revealed more frequent osteochondrosis of the shoulder compared to the dogs fed 60% of the ad libitum amount *(Lavelle, 1989)*.

Another study showed overload of the skeleton in puppies by either overnutrition through feeding a basal food enriched with rice ad libitum or by stimulating high body weight through the use of sand belts in the scapular region *(Meyer & Zentek, 1991)*. After 6 months, both the ad libitum fed dogs and the load bearing dogs had skeletal problems. This highlights the adverse effects of excess weight during growth of large breed puppies **(Figure 2)**.

A study, unique in its design and long term follow up has been published by Kealy *et al (1992)*, in which 48 Labrador Retrievers, originating from seven different litters, were divided into two groups at the age of eight weeks. Dogs of one group were allowed to eat a dry dog food ad libitum, whereas sex-matched littermates received 75% of the amount of food consumed by littermates. The pair mates were both housed in the same indoor cage with an outdoor run to standardize other environmental influences, except for 15 minutes during feeding. Other reports, in comparable studies, found that restricted-fed dogs approach the body weight and size of ad libitum fed dogs after 6 months of age *(Hedhammar et al, 1974; Lavelle, 1989)*.

The restricted fed Labrador puppies in Kealy's study had an average body weight of approximately 20kg, being 78.3 ± 5.35% (mean ± SD) of that of the ad libitum fed pair mates, at the age of 30 weeks. The difference in mean body weight of the 2 groups was even more apparent at the age of 2 years.

At 30 weeks of age, measurement of the Norberg angle on radiographs of all dogs revealed statistically significant differences ($p<.0.05$) in joint laxity. These differences were still significant at 2 years of age *(Kealy et al, 1992)*. This long term study with 24 pairs of littermates, raised under the same environmental conditions, demonstrates a considerably higher incidence of HD in the group of overfed dogs when compared with the group fed 25% less.

> Influence of the protein content of the diet

Since a high protein diet (30% DMB) did not increase the frequency or severity of skeletal abnormalities in giant breed dogs (as compared with control dogs fed isoenergetic diets) *(Nap et al, 1993b)*, it may be concluded that it is excess body weight during rapid growth, rather than the high protein content of diet, that can be deleterious for skeletal development. In this study, performed in Great Danes, no differences in occurrence or severity of osteochondrosis occurred when compared with the normal or low protein fed dogs *(Nap et al, 1991)*.

Growth and proteins

The assumption that a high protein content might be harmful for large-breed puppies is wrong. There is no scientific evidence supporting an undesirable effect of proteins for growth and especially, ossification *(Nap et al, 1991)*. On the contrary, a rather high protein content in the diet helps to reinforce the palatability and to restrict the fat content without including a high level of carbohydrates.

The quality of dietary proteins has to be excellent. The quantity to include in the diet depends obviously on their biological value and on the digestibility of protein sources. Generally, the protein-caloric ratio should be higher in a puppy-diet compared to an adult dog diet.

► Overnutrition in adults

In most Western countries, the major nutrition-related clinical problems in canine orthopedics are due to excessive energy intake which will be stored as body fat in the normal dog. Obesity is a common disease and the prevalence in dogs is approximately 28-44% *(Edney & Smith, 1986)*. Osteoarticular disorders are often associated with obesity. It is not clear if the high body weight precedes orthopedic problems including osteoarthrosis, herniated intervertebral disc disease and cruciate ligament rupture. The mechanical effect of increased body weight might cause a shear or tear of stabilizing structures and an overload of the articular cartilage.

There have been a few studies investigating the relationship between ad libitum fed vs restricted fed dogs and osteoarthritis (OA). In two groups of Labradors, litter mates of the same gender were pair fed, i.e. one group ad libitum, the other 75% of the ad libitum amount. Housing, food and maintenance were the same, except for the amount of food and as a consequence the body weight which was an average 32 kg for the ad libitum dogs and 23 kg for the restricted fed dogs. At 5 years of age, 12 of 23 of the ad libitum fed dogs and 3 of 23 of the restricted fed dogs had OA of the hip joints. By 8 years of age, 12 of 23 of the ad libitum fed dogs and 2 of 23 of the restricted fed dogs had OA in multiple joints *(Kealy et al, 1997; Kealy et al, 2000; Smith et al, 2001)*. OA in multiple joints (including hips, elbows and shoulders) was seen more frequently in overweight dogs than in slim litter mates *(Kealy et al, 1997)*.

The pathophysiology behind the high incidence of OA in overweight dogs can be mechanical, but also hormonal as a decreased growth hormone level was demonstrated in these overweight dogs *(Hazewinkel et al, 1999)*.

In Labrador puppies, an appropriate diet during growth helps limit weight gain in the adult dog.

► Insufficient calcium intake

Young animals have a high requirement for calcium to mineralize newly formed cartilage and osteoid. In Great Danes the daily calcium deposited in the skeleton can be as high as 225-900 mg calcium/kg body weight *(Hazewinkel et al, 1991)*. **During growth, the calcium requirement largely depends on the stage of growth (i.e. the age of the puppy) and its growth rate (i.e. the expected adult size and weight).**

In miniature Poodles, 3.3 g calcium per kg diet (DMB) [corresponding to 140 mg per kg BW per day] did not cause any skeletal abnormalities. In comparison, Great Dane puppies receiving 5.5 g calcium per kg diet (DMB) [150-250 mg per kg BW per day] in the same research setting, with the research diet right after weaning, developed severe osteoporosis with pathological fractures *(Hazewinkel et al, 1985; Nap et al, 1993)* with a growth rate exceeding that of the control puppies fed with a diet containing 11 g calcium per kg diet (DMB) [300-500 mg per kg BW per day] **(Figure 3)**.

► Excess calcium intake

> Clinical observations(Figure 3)

The series of studies in Great Danes have demonstrated that daily food intake of calcium rich diets lead to hyperplasia of calcitonin (CT) producing cells, reduced osteoclastic activity and disturbed endochondral ossification *(Nunez et al, 1974; Hazewinkel et al, 1985)*. A decreased remodeling of the proximal femur (i.e. a delayed antetorsion) was observed in a group of Great Danes, a breed not particularly prone to HD, fed an ad libitum diet rich in calcium *(Hedhammar et al, 1974)*.

Others described delayed skeletal maturation in both Great Danes and in Poodles fed a diet with high calcium content (i.e. 3.3% calcium on a dry matter basis) when compared with controls fed a diet according to NRC *(1974)* guidelines *(Voorhout & Hazewinkel, 1987a; Nap et al, 1993a)*.

Great Danes raised on diets with an increased calcium and phosphorus level (3.3 and 3.0% respectively [i.e. 1240 mg calcium per kg BW per day], in comparison with controls on 1.1% and 0.9% respectively [i.e. 400 mg calcium per kg BW per day]) starting at the age of weaning, 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 length of the radius, or due to a severe radius curvus syndrome with disturbed growth in the length of the ulna *(Hazewinkel et al, 1985; Schoenmakers et al, 2000)*. The latter may coincide with an ununited anconeal process or the painful distraction cubiti, and will all lead to OA of the elbow joint.

In another study, Great Danes fed diets differing only in calcium content, the higher calcium diet group showed progressively more severe disturbances of osteochondrosis in the proximal humerus as well as in growth plates of long bones and of non-weight bearing (i.e. ribs) areas *(Hazewinkel et al, 1985)*.

Weber *et al (2002)* found no abnormalities when starting a diet at 2 months of age in Great Dane dogs with a calcium content of 1.5 g per kg diet [i.e 830 mg per kg BW per day].

OSTEOCHONDROSIS OF THE PROXIMAL HUMERUS

1- Scapula
2- Humerus
3- Humeral head
4- Cartilage
5- Cartilage flap

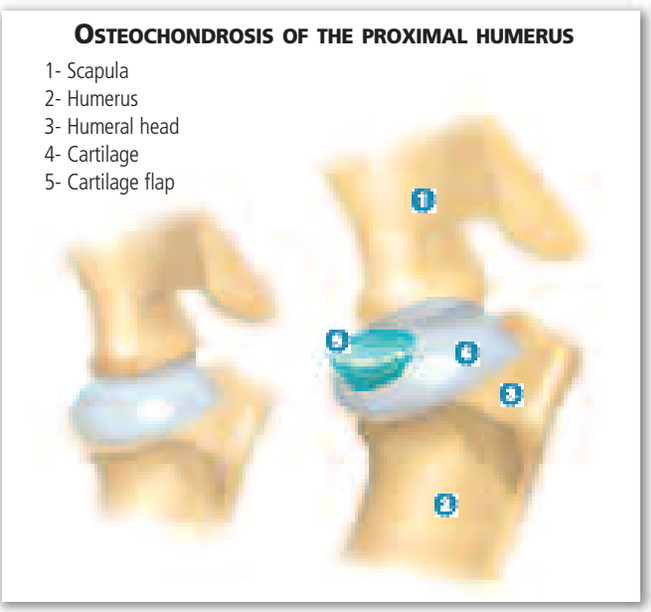


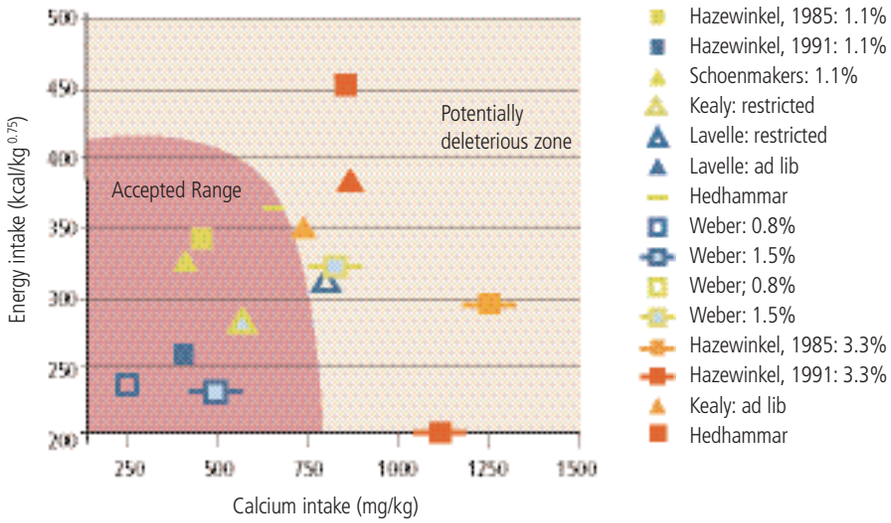
FIGURE 3 - NUTRITIONAL RESEARCH IN LARGE-BREED PUPPIES CONCERNING THE OPTIMUM CALCIUM CONTENT OF FOOD

(From Hedhammar et al, 1974; Lavelle et al, 1989; Hazewinkel et al, 1985 & 1991; Kealy et al, 1992; Schoenmakers et al, 2000; Weber et al, 2000)

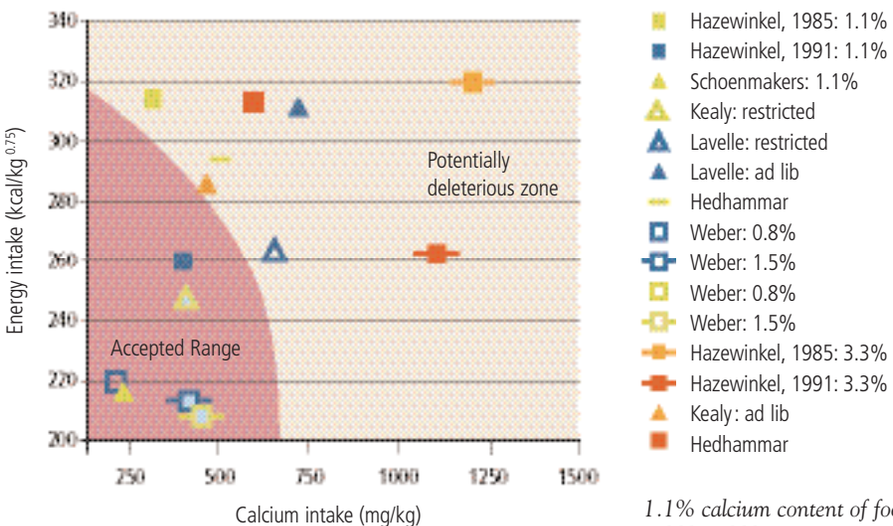
Different research groups have investigated the influence of nutrition on the manifestation of skeletal disease in large and giant breed puppies. These graphs (Royal Canin, 2004), account for the quantity of calcium and energy ingested by puppies at 2 and 5 months in the different studies. Several studies show that high calcium consumption can have deleterious effects on the skeleton, particularly in large breed dogs.

Red and orange shapes: observation of growth problems
Green and blue shapes: no evidence of a link between food and growth problems

• 2 months of age



• 5 months of age



1.1% calcium content of food used
Ad lib: ad libitum consumption
Restriction: rationed consumption

> Pathophysiology of excess calcium

In young dogs, calcium (Ca) is absorbed in the intestine by means of both uncontrolled passive diffusion and active, controlled absorption. Puppies less than 6 months of age are unable to protect themselves from an excess of calcium *(Tryfonidou et al, 2002b)*; during weaning at least 50% of the calcium is absorbed whatever the quantity ingested *(Hazewinkel et al, 1991)* **(Figure 4)**. Great Danes raised on a food according to the NRC *(1974)* recommended 11 g calcium per kg diet (DMB) [0.5 g per kg BW per day] absorbed 45-60% (260-300 mg/kg/d) of the ingested amount of Ca, whereas puppies with triple that amount of in their diet, absorbed 23-43%. Thus puppies fed the high calcium diet absorbed considerably higher amounts of calcium (345-645 mg/kg/d), even if the rate of absorption is lower.

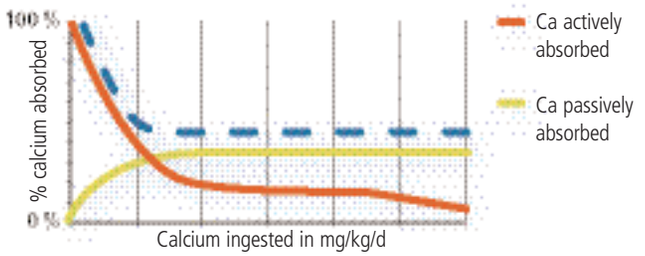
Intake of food, and especially of Ca, causes the release of gastrointestinal hormones, some of which will cause calcitonin (CT) release from the thyroid glands. In the growing animal, chronic high calcium intake will cause chronic hypercalcitoninism *(Hedhammar et al, 1974; Hazewinkel et al, 1985)* which prevents calcium release from the skeleton by decreasing bone resorbing osteoclastic activity. Remodeling of the skeleton cannot occur. The calcium absorbed will be routed to the skeleton without influencing the concentration of calcium in the extracellular fluid at each meal.

Although it is not fully understood if calcium plays a direct role in disturbing chondrocyte maturation, or if it is mediated by CT and/or a relative deficiency of other minerals at a cellular level, there is little doubt on the deleterious effect of high calcium intake on endochondral ossification, with osteochondrosis as a consequence.

The recommended calcium allowance for a growing puppy according to NRC 2006 is 3.0 grams of calcium/ 1000 kcal Metabolizable Energy (ME) or 0.5 g of calcium/ kg of body weight/ day. The NRC 2006 minimum calcium requirement for growing puppies is 2 g/1000 kcal or 0.37 g of calcium / kg body weight / day. This should be appropriate for all breeds and sizes. Compilation of the previously mentioned studies suggests that there is a safety zone for calcium intake at which osteoarticular diseases do not develop. This safety zone would be 260-830 mg of calcium/ kg / day for puppies at 2 months of age. The range would narrow slightly at 5 months of age to 210-540 mg of calcium /kg/ day *(Weber et al, 2000; Royal Canin, 2004)* **(Figure 5)**.

FIGURE 4 - FRACTION OF CALCIUM ABSORBED PASSIVELY OR ACTIVELY ACCORDING TO THE LEVEL OF CALCIUM CONSUMED (IN 3-MONTH-OLD PUPPIES OF VARIOUS BREEDS)

(from Tryfonidou et al, 2002)



The dog balances the small quantity of ingested calcium (e.g. all-meat diet) with a very large active absorption (red line). When the calcium content in the diet increases too much, active absorption decreases but the puppy continues to passively absorb at least 30-40% of the calcium ingested (green line). Finally, when the puppy is fed a very high-calcium diet, total absorption represent 40-50% of the calcium ingested (blue line).

FIGURE 5 - SYNOPSIS OF STUDIES THAT HAVE HELPED TO DETERMINE THE OPTIMAL CALCIUM RECOMMENDATION FOR A 2 MONTH OLD PUPPY

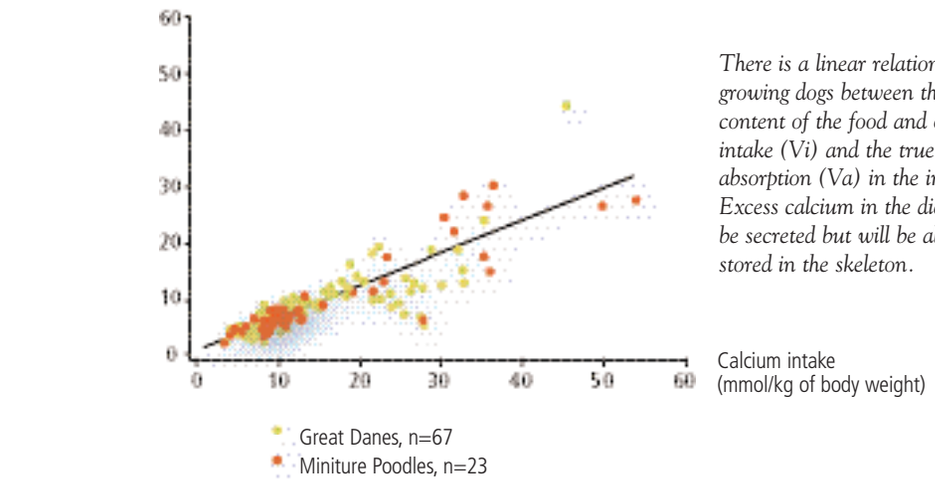
(Hazewinkel et al,1985-1991; Shoenmakers et al, 2000; Weber et al, 2000)

There is no ideal calcium content relative to age, but there is a safety zone.
To feed a 2 month-old large-breed puppy as safely as possible, it is advisable to give it between 260 and 830 mg of calcium/kg/day.

At 5 months, the calcium safety zone should be lowered: between 210 and 540 mg of calcium/kg/day.

CALCIUM METABOLISM AND SKELETAL DEVELOPMENT IN YOUNG DOGS

FIGURE 6 - LINEAR ABSORPTION OF CALCIUM
(From Tryfonidou & coll, 2002)



There is a linear relationship in young growing dogs between the calcium content of the food and of calcium intake (Vi) and the true calcium absorption (Va) in the intestine. Excess calcium in the diet will not be secreted but will be absorbed and stored in the skeleton.

1. In adult dogs and puppies calcium absorption takes place not only via an active mechanism, but also via a process of passive diffusion **(Figure 6)**, dependent on the concentration gradient. In puppies, passive absorption is however more important than in the adult dog, where it is a minor phenomenon. As a consequence, there is higher calcium absorption from higher biologically available calcium diets, both in small and large breed dogs.

2. Even calcium excess at the time of partial weaning (i.e. from 3-6 weeks of age) causes hypertrophy of the calcitonin producing cells with consequences in later life. All large breed dogs with higher calcium intakes as weaning puppies developed enostosis at the age of 3-4 months.

3. Excess calcium as well as excess calcium and phosphorous, starting at the age of weaning (6 weeks of age) caused severe signs of osteochondrosis as well as radius curvus syndrome in large breed dogs.

4. Excess calcium starting at 3 weeks of age caused hypercalcemia, hypophosphatemia, and very low concentrations of parathyroid hormone. The skeleton revealed signs of hypophosphatemic rickets, i.e. widened growth plates and thin cortices.

5. Calcium deficiency occurs sooner in large than in small breed dogs: 0.55% Ca [i.e. 250 mg Ca per kg BW per day] DMB caused nutritional secondary hyperparathyroidism (NSHP) in 2 months-old Great Dane puppies but not in Miniature Poodles fed at 0.33% [i.e. 170 mg Ca per kg BW per day] Ca DMB. NSHP in Poodles was seen under 0.05% Ca [i.e. less than 25 mg Ca per kg BW per day] DMB.

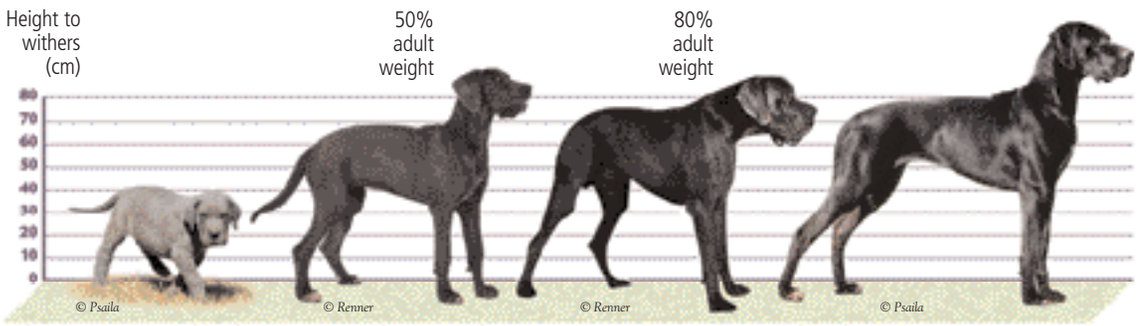
6. In calcium deficiency, the proportion of ingested calcium which is actively absorbed versus passively diffused increases, although the total amount of calcium which is absorbed may still be less than required. In order to keep plasma calcium concentration constant, osteoclasts start to remove bone. Chronic calcium deficiency causes NSHP with severe calcium resorption of the skeleton and eventually pathological fractures (i.e. greenstick and compression fractures).

7. Vitamin D deficiency, even with adequate dietary content of calcium and phosphorus, leads to rickets.

8. Excessive vitamin D intake does not lead immediately to increased calcium absorption due to metabolic adaptations of vitamin D in the body, but it may cause osteochondrosis and radius curvus syndrome in young dogs of large breeds.

Influence of two levels of calcium on growth and skeleton development in large-breed puppies

Male Great Dane at different stages of growth



2-month puppy: 42 cm, 12 kg | 5 months: 70 cm, 36 kg | 8 months: 75 cm, 58 kg | Adult: 80 cm, 70 kg

The bones grow primarily during the first few months. The second phase corresponds to muscular development, which continues until adult weight has been reached.

Osteoarticular diseases are particularly common in large-breed and giant-breed puppies. Calcium excess (3.3%) and deficiency (0.55%) have in turn been incriminated as factors promoting skeletal developmental problems. The object of this study was to evaluate the influence of these two calcium levels, by remaining within the regular calcium-value range in puppy food.

Six Great Dane bitches (GD) and six giant Schnauzers (GS) were split into two groups (3GDs + 3 GSs) from the age of 9 weeks. These two groups were raised on two foods composed of the same ingredients (C08 and C15); the only difference was the calcium (0.8% vs 1.5%)and phosphorus (0.6% vs 1.23%) content in C08 and C15 respectively (identical metabolizable energy (ME) value: 3800 kcal/kg).

Between 10 and 40-46 weeks parameters including body weight, height to withers, length of ulna and tibia, serum calcium and phosphate concentrations, alkaline phosphate levels and IGF-1 were measured.

Skeletal radiographs and orthopedic examinations were also conducted regularly to evaluate the position of the legs and the conformation and to identify any lameness.

Energy ingested was identical for all the dogs. Energy intake increased gradually from 1400 kcal ME/day in week 10 to 3500 kcal ME/day in week 46 for the GDs versus 610-1800 kcal ME/day for the GSs. The calcium consumption was respectively 400 and 200-250 mg/kg/day in the puppies that receive the C15 and C08 diet.

No difference was observed in bodyweight or body condition between the two groups of puppies. Within the two breeds the differences in tibia and ulna length according to dietary group, were not significant. There was no significant difference between the groups with respect to the size of the GDs (from 40 cm in wk 10 to 77 cm in wk 46), or in the GSs (from 33 cm to 58 cm in wk 46).

The serum calcium, phosphate, alkaline phosphate, and IGF-1 values did not vary between the groups. In the GDs the median IGF-1 value during the study ranged between 254±61 and 406±40 ng/mL, while in the GSs these values ranged between 92±43 and 417±82 ng/mL.

No particular health problems were revealed. Orthopedic examinations did not provide any evidence of clinical difference between the dogs. No painful areas or biomechanical problems were detected. Mild osteochondrosis lesions were transiently shown in the two groups.

This study concluded that there were no skeletal developmental abnormalities detected in giant-breed puppies when they consumed a diet containing 0.8% or 1.5% calcium.

Weber M, Martin L, Dumon H et al - Calcium in large breed growing dogs: a safety range? 4th Conference of the European Society of Veterinary and Comparative Nutrition, April 2000; Amsterdam, The Netherlands.

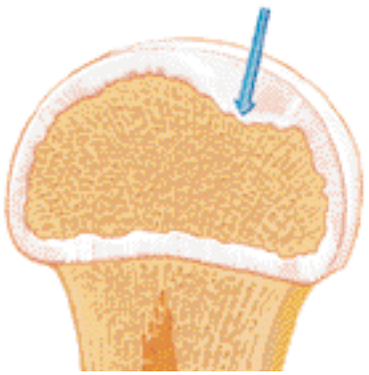
3 - Developmental orthopedic diseases associated with nutritional excesses

► Osteochondrosis

Osteochondrosis is a disturbance of endochondral ossification, characterized by an abnormal maturation of chondrocytes and therefore a delay in cartilage mineralization **(Figures 7 & 8)**. If the disturbance in endochondral ossification occurs in articular cartilage, osteochondritis dissecans (OCD) may be a consequence. In OCD, part of the articular cartilage becomes detached and may be fragmented, mineralized or even ossified together with inflammation of both the joint and the endochondral bone in the area of the cartilage lesion.

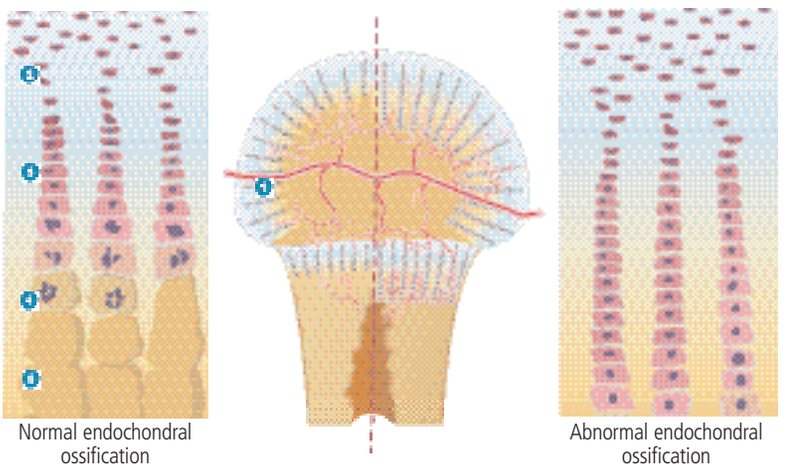
The disturbance in endochondral ossification can also occur in growth plate cartilage, with irregular growth plates, enlarged cartilage cores and decreased growth in length as a consequence. In addition, the disturbance in endochondral ossification can manifest in a delay in ossification of the secondary ossification centers. Disturbances in growth plates which lead to clinical manifestations of osteo-

FIGURE 7 - OSTEOCHONDROSIS LESION



Osteochondrosis is the result of an anomaly in the development of growing cartilage: the ossification process is altered and we see cartilage retention and thickening. (The arrow points to a zone of abnormally thick cartilage.) Osteochondrosis may develop into osteochondritis dissecans when a fragment of cartilage is freed in the joint. Osteochondrosis is stimulated by a chronic excess of calcium in the diet.

FIGURE 8 - NORMAL (LEFT) AND ABNORMAL (RIGHT) PROCESS OF ENDOCHONDRAL OSSIFICATION IN THE GROWTH PLATES AND GROWING ARTICULAR CARTILAGE



Normal endochondral ossification

Abnormal endochondral ossification

1- Epiphyseal vessels
2- Germinal cells
3- Zone of growth
4- Zone of cartilage transformation
5- Zone of ossification

The intercellular material between the columns of cartilage cells mineralizes when a certain stage of maturity is reached. Chondrocytes are then sealed off from their nutritional resources (i.e. synovia in articular cartilage and epiphyseal vessels in growth plate cartilage) and then die and disintegrate. Now endothelial cells of the capillaries invade the non-calcified horizontal septa between the chondrocytes and the lacuna of the disintegrated chondrocytes. Osteoblasts align themselves along the partially resorbed cartilaginous cores and deposit osteoid. Primary spongiosa, i.e. mineralized cartilage surrounded by mineralized osteoid, can be eroded by osteoclasts to become cancellous bone (more oriented osteoid fibers without a cartilaginous core). When present in the metaphyseal area of growing bone, it may be eroded locally to become the medullary cavity. In osteochondrosis due to a disturbance of cartilage-cell maturation, mineralization of the intercellular substance is delayed. Therefore the cascade of events, including chondrocyte death, capillary ingrowth, osteoblast introduction and bone formation, will not take place. This causes elongated cartilage columns in the articular cartilage as well as in the growth plate cartilage. This thickened cartilage is vulnerable to microtrauma.

chondrosis (including bilateral radius curvus syndrome or rear leg exorotation) are seen predominately in giant breed dogs. Detachment of the anconeal process of the ulna or the supraglenoid process of the scapula can also occur.

> Diagnosis

Dogs with osteochondrosis, without detachment of cartilage, will not be clinical. However with OCD, dogs may exhibit lameness, pain upon hyperextension and flexion of the affected joint and joint effusion. The joints most commonly affected are shoulder, elbow, stifle and hock. Dogs will also not be clinical in cases of osteochondrosis in the growth plate when the retained cartilage core is small or temporary. In longitudinal radiological studies of the distal growth plate of the ulna of Great Danes, a slight flattening or indentation could be seen at five months of age. However, when a severe flattening of the metaphyseal area develops, or a deep cartilage core can be seen, impaired growth in length of the radius and ulna can be expected **(Figure 9)**. This can result in radius curvus syndrome (short ulna, curved radius and valgus deformation of the feet).

With clinically suspected OCD, a thorough clinical and radiographic investigation will suffice in most cases. Radiographs may reveal subchondral sclerosis bordering an indentation of the articular surface. Some cases may require additional diagnostics such as arthrocentesis, contrast arthrogram, arthroscopy, other imaging techniques and/or exploratory surgery of the joint for definitive diagnosis.

> Epidemiology

Osteochondrosis is primarily seen in large breeds of dogs (i.e. more than 25 kg adult body weight), and more frequently in male and fast growing female dogs. The disease is seen in a variety of breeds with Great Dane, Labrador, Golden Retriever, Newfoundland and Rottweiler being the breeds at highest risk *(Milton, 1983; Slater et al, 1991; Van Bree, 1991)*.

Osteochondrosis appears to have a predisposition for specific locations in each breed. OCD lesions are seen most commonly in:
- the shoulder and stifle joints of Great Danes
- the shoulder, elbow and hock joints of Labradors and Golden Retrievers
- the elbow joints of Newfoundlands
- the shoulder and hock joints of Rottweilers *(Slater et al, 1991)*.

In one study, 66% of the dogs with OCD had more than one joint affected; in 5% three joints were affected *(Slater et al, 1991)*. Although histologically osteochondrosis can be diagnosed also in non-weight bearing growth plates like that of the rib, microtrauma may play a significant role in causing the fissures as can be concluded from the fact that osteochondrosis dissecans is mostly seen on convex, weight bearing areas.

> Pathophysiology

Osteochondrosis is a multifactorial disease common in large breeds in which heredity and nutrition play a significant role. A variety of studies have been performed to elucidate the role of nutrition in the manifestation of osteochondrosis **(Table 2)**. These studies support the conclusion that chronic intake of excess energy or of a food enriched with calcium, with or without changes in other nutrients, plays a significant role in the development and manifestation of osteochondrosis in dogs of large breeds. Minor changes of endochondral ossification, without clinical significance, have also been demonstrated in miniature Poodles raised on a food with high calcium content. Please refer to sections: **Overnutrition in growth and Excess calcium intake; for further information.**

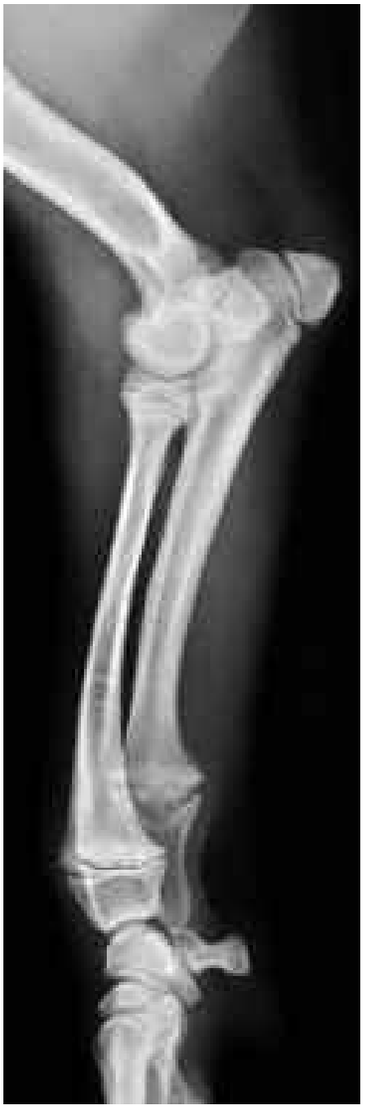


Figure 9 - *A mild retained cartilage core may disappear spontaneously.*

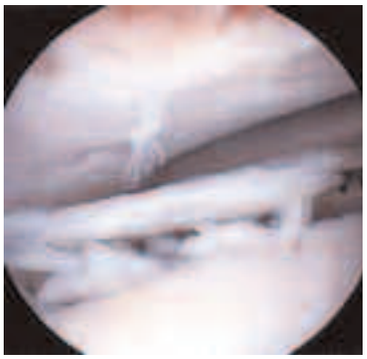


Figure 10 - *Arthroscopic removal of a cartilage flap from the humeral head.*

> Therapy

Dietary correction at an early stage may positively influence the spontaneous resolution of disturbed endochondral ossification *(Voorhout & Hazewinkel, 1987a)*. Osteochondrosis in cartilage and growth plates could disappear, but dietary modification will not normalize cases of OCD in which there is severe detached cartilage, or where a more severe curvature of the radius exists *(Olsson, 1982)*. Surgical correction will be indicated in most of these cases **(Figure 10)**.

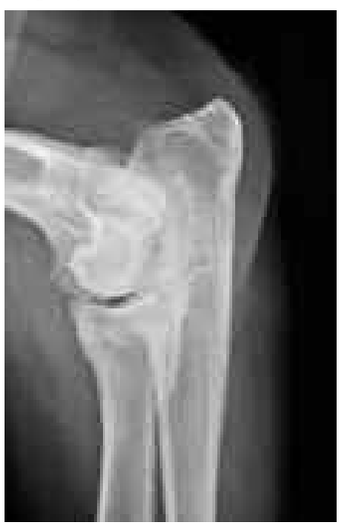
Dietary correction entails a decrease in intake of energy, calcium and vitamins to the recommended levels for dogs. Fast growing puppies should be weighed and have their body condition score assessed frequently (every 2-4 weeks) to monitor their growth. If a puppy is growing too quickly or becoming overweight, its energy intake will need to be decreased without unbalancing the other nutrients. No pharmacological or other medications are known to support the nutritional management.

Osteochondrosis will not develop into OCD in all cases. Based on controlled studies where both shoulder joints were radiographed, it can be concluded that, although 45-65% of the dogs had radiographically detectable abnormal contours of the humeral head, only 3-5% were clinically affected on both sides *(Van Bree, 1991)*. When detached, the period of lameness can be shortened as well as most probable the secondary changes of the joint minimized with surgical or arthroscopic treatment.

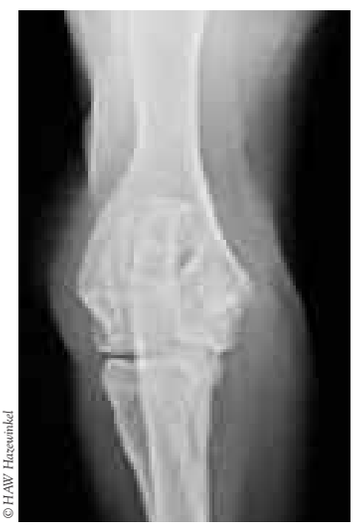
► Elbow Dysplasia (ED)

ED 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).

Figure 11 - Elbow joint of an 8-month-old Bernese Mountain Dog with severe osteoarthrosis (OA)
(A) Notice osteophytes at the radial head, anconeal process and medial epicondyle and osteosclerosis in the semilunear notch. (B) The craniocaudal view shows that the radial head does not run parallel with the distal humerus indicating elbow incongruity as well as an indication of a fragmented coronoid process (FCP). The final diagnosis is: elbow incongruity and FCP with severe OA.



A



B

> Diagnosis

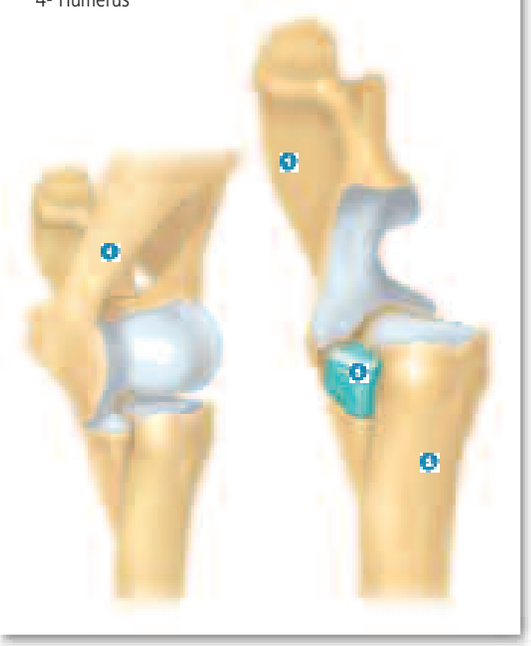
The typical age of the patient suffering from ED is 4 -10 months of age, although there is an increasing frequency of dogs with elbow pain (without any signs of OA on radiographs) seen at more than 3 years of age. Upon examination in almost 50% of the cases the paw of the affected leg is externally rotated and slightly abducted. On palpation the elbow is often effusive. The range of motion (ROM) of the elbow joint can be decreased in advanced cases. Subtle crepitation can be appreciated at an early stage. In an UAP, there is crepitation and pain on firm hyperextension of the elbow joint. In FCP and/or OCD, crepitation and pain reaction can be evoked at prolonged hyperextension, especially when the radius and ulna are externally rotated at the same time (i.e. supination).

Diagnosis of ED can be confirmed by radiography. Bony union between the anconeal process and the olecranon should be complete at the age of 16-20 weeks *(Sjöström et al, 1995)*. When a radiolucent area is present at an older age it is suggestive of an anconeal process which is not united, i.e. an UAP. This may be due to a partial or complete separation in the cartilage between the anconeal process and olecranon, which is preferentially demonstrated on a mediolateral flexed radiographic view. Sclerosis at the fracture site and osteophytes at the margins of the joint can be visible at a later stage. For grading OA of the elbow joint, see the web page of the International Elbow Working Group: *www.iewg-vet.org*.

OCD of the medial humeral condyle is best assessed on anterior posterior medial oblique (APMO) views *(Voorhout & Hazewinkel, 1987b)*. In a small number of cases a calcified flap can be seen located near the indentation of the medial condyle. In FCP, the fragment can only be seen on high quality films when the coronoid process is displaced cranially (as in Bernese Mountain Dogs), whereas the cranial alignment of the ulna at the level of the medial coronoid can give an indication of fragmentation. Secondary signs such as osteophytes and sclerosis of the semilunar notch can help to confirm the clinical diagnosis. Small osteophytes are especially visible on mediolateral views of the flexed elbow at the dorsal margin of the anconeal process. Extended views help to visualize osteophytes at the radial head, and AP views demonstrate irregularities at the medial aspect of the humerus as well as the ulna **(Figure 11)**.

FRAGMENTATION OF THE MEDIAL PORTION OF THE CORONOID PROCESS

1- Ulna
2- Radius
3- Medial coronoid process
4- Humerus



Most entities of ED occur bilaterally in 30-70% of the cases, and therefore both elbow joints should be investigated, even in case of unilateral lameness. In case there are no radiographic abnormalities visible 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.

> Epidemiology

Certain breeds appear to be at risk for ED **(Table 3)**. Depending on the specific sub-population and the method of investigation, elbow dysplasia is seen in 46-50% of the Rottweilers, 36-70% of the Bernese Mountain Dogs, 12-14% of the Labradors, 15-20% of the Golden Retrievers, 30% of Newfoundland dogs, and 18-21% of German Shepherds *(Swenson et al, 1997; Remy et al, 2004)* but also in Great Danes, St Bernards, Irish Wolfhound, Pyrenean Mountain Dogs, Bloodhounds, Bouviers, Chow Chows and chondrodystrophic breeds *(Hazewinkel et al, 1988b; Sjöström et al, 1995)*. According to the Orthopedic Foundation for Animals (OFA) statistics, in breeds having had at least 100 evaluations between January 1974 and December 2003, elbow dysplasia has been registered in the USA in the following breeds in descending order: Chow Chows, Rottweilers, Bernese Mountain Dogs, Chinese Shar Pei, Newfoundland, Fila Brasileiro, and German shepherds. There are 64 breeds ranked according to frequency of elbow dysplasia on the OFA website *www.offa.org*.

TABLE 3 - BREEDS AT RISK FOR ELBOW DYSPLASIA

Elbow Dysplasia	Breeds at risk
Fragmented coronoid process (FCP)	Labradors, Bernese Mountain Dogs, Rottweilers, German Shepherds
OCD of medial humeral condyle	Retrievers, Newfoundlands
Incongruities of elbow joint (INC)	Bernese Mountain Dogs, chondrodystrophic breeds
Ununited anconeal process (UAP)	German Shepherd, Bloodhounds, Bassets Hounds, St Bernards, Great Danes

> Surgical therapy

Early surgical intervention has the best prognosis for the future status of the joint in lame dogs. In a study, with a follow-up period ranging from 0.5-8 years (mean 2.7 years) the success rate was 78% in a group of 64 Retrievers (with 67.8% males) operated at a young age. Only 33% of the conservatively treated dogs with a FCP (i.e. low body weight and controlled activity but no surgery), were not lame *(Meij et al, 1996)*. This stresses the importance of an early diagnosis and surgical treatment. Results with arthroscopy are comparable, depending on availability of the equipment and the skills of the surgeon.

Elbow incongruity (INC) due to a short radius is frequently seen in Bernese Mountain dogs (BMD), but also other breeds (Retrievers, Napolitan Mastiff) and dogs raised on food supplemented with minerals may be affected. A random study in the Dutch BMD population revealed that

72% of the dogs had INC *(Hazewinkel et al, 1995)*. The joint surface supporting the humerus is decreased in the case of a short radius. This leads to an increased pressure on the remaining joint surface, e.g. the lateral and medial coronoid process. Congruity is restored after the removal of the FCP at the same surgical intervention.

> The role of nutrition in ED

A combination of FCP and OCD has been explained by Olsson *(1993)* as a disturbance of endochondral ossification and as such expressions of the same disease. Osteochondrosis is seen more frequently in certain breeds and sub-populations and can be aggravated by high food intake and excessive calcium intake *(Hazewinkel, 1993)* as well as by oversupplementation of balanced food with vitamin D *(Tryfonidou et al, 2002a)*. Please refer to sections: Overnutrition in growth and Excess calcium intake; for further information. **The frequency and severity of osteochondrosis can thus be prevented by dietary management, including a food with adequate and appropriate calcium to energy ratio, a quantitative restriction of food intake, and without adding vitamin D to a balanced diet.**

► Hip Dysplasia (HD)

Hip dysplasia is a common, heritable developmental orthopedic disease. Studies have shown that dysplastic dogs are born with normal hips, but develop HD as a result of the disparity between the development of the bony part of the hip joint and its supporting soft tissues; ligaments, joint capsule and muscles *(Alexander, 1992)*. This occurs during the first six months of life, during which time the tissues are soft and plastic with an elastic limit.

> Diagnosis

A diagnosis of HD is made on the basis of the history and the clinical signs, including stiffness on rising, "bunny hopping", pain and lameness of the rear limbs, and pain reaction or crepitation upon manipulation of the hip joints. Clinically, the dog may show pain at different stages of development of HD. In the immature dog, stretching of the joint capsule and microfractures of the cartilage will elicit pain, whereas in the mature dog overuse of the arthritic joint will result in general signs of arthrosis. Such signs include pain upon rising, warming out during exercise (initial stiffness which improves with walking), decreased range of movement and worsening of signs after rest following heavy exercise *(Hazewinkel, 1992)*. Laxity of the hip joint can be tested by abduction of the proximal femur, preferably in a non-weight bearing position:
(1) using one hand as a fulcrum, medial to the proximal femur with the dog in lateral recumbency, and medial pressure of the stifle joint;
(2) adducting the stifle with the dog in dorsal recumbency, with the femur perpendicular to the table top (Barden sign) *(Hazewinkel, 1992)*.
Subluxation of the hip joint can be diagnosed by putting medially-directed force on the greater trochanter.

Radiographs in extension **(Figure 12)**, as well as more specific views related to the acetabular rim *(Slocum & Slocum, 1992)* or joint laxity *(Smith et al, 1990)* can be conclusive in diagnosing joint laxity, incongruency, subchondral sclerosis and osteophyte formation.

Rottweiler, German Shepherd, Golden Retriever, and Labrador Retriever (top to bottom) are breeds predisposed to coxo-femoral dysplasia. They are also the breeds most likely to be screened for this disease.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> Epidemiology

HD is a hereditary abnormality commonly seen in certain breeds (i.e. St Bernards, Rottweilers, Newfoundlands, Bernese Mountain Dogs, German Shepherd, Labrador and Golden Retrievers) and infrequently in other breeds (i.e. Afghan Hounds, Shetland Sheepdogs, Malamutes and Huskies) *(Corley, 1992)*.

There are 136 breeds ranked according to frequency of hip dysplasia on the Orthopedic Foundation for Animals (OFA's) website: *www.offa.org*. These breeds have had at least 100 evaluations between January 1974 and December 2003. The results of a retrospective study using the OFA data base have shown that there has been improvement in the hip joint phenotype of dogs in the United States. Certain breeds have shown an increase in the percentage of dogs classified as having excellent hip joint phenotype and there has been a decrease in the percentage of dogs classified as having HD. German Shepherds, Golden Retrievers, Labrador Retrievers and Rottweilers have shown the greatest increase in percentage of dogs classified as having excellent hip joint phenotype and the greatest submission screening rate. Rottweilers have shown the greatest improvement *(Morgan et al, 2000)*. Even if these figures are biased by the tendency to pass on the best hips for official judging and not to offer the bad ones, it will help to use only the best dogs with the best hips as breeding stock.

Environmental factors, which are believed to influence the development of HD, have yet to be elucidated. Research has shown that diet has both quantitatively and qualitatively, a significant effect on the development of HD *(Kealy et al, 1992)*. Diet will not cure HD or alter the genetic status of the offspring in this respect, but it can influence the phenotypic expression of HD by optimizing the development of the hip joints of those animals potentially at risk. Diet can also play a role in conservative treatment in those dogs where HD has already developed. Good control of body weight will alleviate clinical signs.

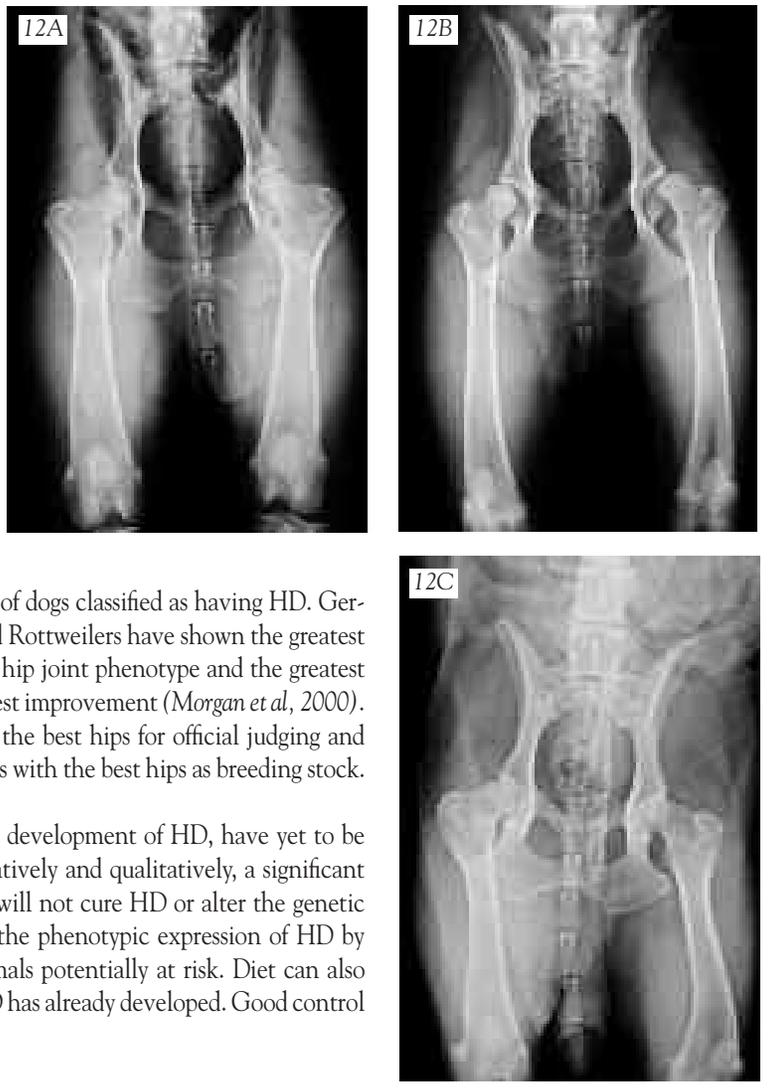


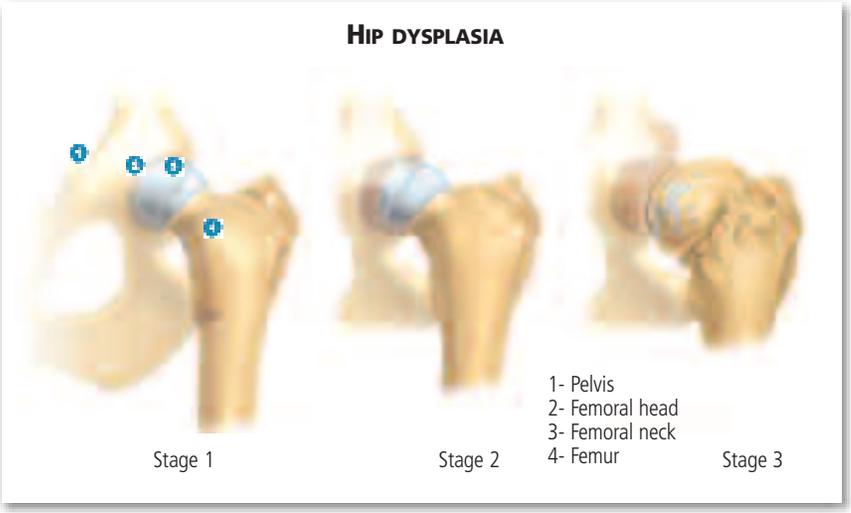
Figure 12 - Radiographs of hip joints of three different dogs
(12A) Normal hips
(12B) Subluxation and flattening of the femoral heads
(12C) Severe osteophytes around the femoral heads and flattening of the acetabuli.

> Pathophysiology

In the canine hip joint, both the femoral head and the acetabulum are mainly cartilaginous at birth. Bone formation, and a change in position of the femoral head in relation to the femoral shaft, will take place via endochondral ossification and osteoclastic activity respectively. In HD, joint laxity results in an incongruent hip joint where the dorsomedial part of the femoral head and the acetabular rim are in contact, while supporting almost half the body weight when walking. This causes microfractures and deformation of the acetabular rim, erosions of the cartilage and deformation of the subchondral bone *(Fox et al, 1987)*. The associated pathological changes are joint effusion, stretching and thickening of the joint capsule and the round ligament, as well as osteophyte formation.

There are several dietary factors which play a role in hip joint development and hip joint overload, both of clinical significance in canine HD. Excess energy intake has been previously discussed. Heavy body weight will cause overloading of the cartilaginous skeleton, including the hip joints. This could be a significant factor, which may help to explain the increased frequency and severity of HD in overweight dogs.

Increased calcium intake has also been previously discussed. It can be concluded that excessive dietary calcium intake decreases maturation of the hip joint conformation as well as of the vulnerable cartilaginous template of the skeleton. This may coincide with overloading of the hip joint



which is too immature in its development for the age and size of the dog and therefore, may play a significant role in deformation of the hip joint at an early age.

In the field of canine nutrition, there is now sufficient evidence to suggest that, within the range of nutrient levels normally encountered in practice, it is not the calcium to phosphorus ratio, but the absolute calcium amount in the daily ration which determines the occurrence of skeletal abnormalities *(Hazewinkel et al, 1991; Nap, 1993)*. A high dietary phosphorus content may bind more calcium in the intestine to form non absorbable complexes, but this is possibly only the case with non-absorbable phytates. A highly absorbable salt (as is present in bone meal) will cause the same skeletal effects as excessive calcium alone *(Hazewinkel et al, 1991)*.

Electrolytes are present in body fluids including synovia. Differences in circulating cations (Na^+, K^+, Ca^{++} and Mg^{++}) and anions (Cl-, $H_2PO_4^-$ and the SO_4^- present in amino acids) influence acid-base balance. The influence of electrolytes on the osmolality of body fluids as well as on acid-base balance may play a role in the development of HD in young dogs.

Mean osmolality in synovial fluid from normal hip joints was significantly lower than that of synovia of hip joints of dysplastic retrievers *(Olsewski et al, 1983)*. Whether this difference reflects the cause of joint laxity or the result of hyperperfusion of the joint capsule of the arthritic joint needs to be elucidated.

In another study *(Kealy et al, 1993)*, the dietary content of Na+, K+ and Cl- ions differed (increased, increased and decreased, respectively) in the diets of three groups of dogs (n=177) of five breeds (St Bernards, German Shepherds, Coonhounds, English Pointers and Labrador Retrievers) originating from 27 litters. In these dogs, joint laxity was observed by the measurement of the Norberg angle on radiographs taken at 30 and 105 weeks of age. However, the acid-base balance and electrolyte content of body fluids were not measured. It was found that the dogs on the dry dog food (moisture <10%) with the low Na (0.32-0.43%), low K (0.39-0.70%) and high Cl (0.66-0.81%) content had a slight but statistically significant improvement in the Norberg angle when compared with the other groups. Only the retrievers revealed a low Norberg angle of the hip joint, irrespective of the diet. The clinical significance of these findings, the sensitivity and reproducibility of the radiographic procedure *(Smith et al, 1990; Heyman et al, 1993)*, the influence of other electrolytes playing a role in acid-base balance and osmolality *(Lemann & Lennon, 1972)* must all be further investigated before the optimum electrolyte content of the food can be established. The detrimental effects of prolonged dietary-induced acidosis on skeletal mineral content *(Ching et al, 1989)*, however, imply that further studies in this area would be valuable.

Although not proven in research, vitamin D could play a role in the development of HD. Although an increased vitamin D intake will not cause an increased absorption of calcium (see section on Vitamin D), hypervitaminosis D has a detrimental effect on the process of endochondral ossification *(Tryfonidou et al, 2003b)* and as such on the growth and development of the hip joint. Disturbances in cartilage differentiation may decrease the resistance of cartilage to physiological loading of the joint and lead to deformation of both femoral head and acetabular rim.

HD can develop in young, overfed dogs, even under conditions of relatively restricted activity. This is most likely due to overstressing the elasticity of the periarticular tissues and the resulting pathological cartilaginous and subchondral bone changes.

> Therapy

Overnutrition should be prevented by feeding to meet the dog's energy requirements. The energy intake should be determined based on individual needs of the pet which are influenced by age, breed, body weight and activity. Since excess calcium intake can be detrimental to hip joint development, puppies should be fed diets with an appropriate calcium level for their size and age. Commercial balanced diets are available which will satisfy the special energy and calcium requirements of a fast growing puppy. These diets should never be supplemented with vitamins and minerals as excesses may occur.

Rest *per se* and weight loss can improve the clinical signs of HD in young and adult dogs, as was observed by force plate measurements before and after a period of 3 months cage rest *(Hazewinkel, 1992)*.

In selected cases, development of the hip joint in young growing dogs can be surgically optimized. In dogs of 8-13 weeks of age, symphysiodesis is advocated by some researchers. They claim that the bottom of the pelvis does not grow in width, whereas the dorsal aspect including the acetabular roof is not hindered. As a consequence, the covering of the femoral heads will improve after thermocauterization of the symphysis pelvis. Myectomy of the pectineus muscle is indicated in dogs with contraction of these muscles, causing adduction of the hind paws even to a degree that the feet are crossing. This can be seen in young and adult dogs. Short-term results may be spectacular, whereas long term effects in regards to the development of OA are not known.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In the non surgical treatment of HD, both dietary measures and activity restriction should be employed.

Other surgeries **(Table 4)** that can be performed when indicated include triple pelvic osteotomy (TPO), hip prosthesis and excision arthroplasty (i.e. removal of the femoral head and neck). TPO can be performed in dogs with severe hip laxity but without deformation of the head and socket. Dogs with severe hip dysplasia or severe deformation of head and/or acetabulum due to OA or trauma are potential candidates for hip prosthesis. Excision arthroplasty is indicated in cases of severe joint deformation and pain. The result of surgery is mainly dependent on the creation of smooth surface between the femur and acetabulum, the weight of the dog (<20 kg), the musculature of the dog (poorer with muscle atrophy), and early training (swimming).

TABLE 4 - PREVENTION AND TREATMENT OF DIFFERENT STAGES OF HIP DYSPLASIA

Stage of HD	Therapeutic modalities
Prevention	- Breed with proven HD negative parents - Prevent obesity - Prevent over-use, do not supplement a completed and balanced diet, chondroprotective agents (symphysiodesis)
Treatment - young dogs	Adapt life style and body weight, NSAIDs, chondroprotective agents, triple pelvic osteotomy or myectomy
Treatment - adult dogs	Adapt life style and body weight, NSAIDs, chondroprotective agents, myectomy, hip prosthesis, excision arthroplasty

► Orthopedic diseases due to decreased skeletal remodeling

Decreased skeletal remodeling may occur in two separate entities: canine wobbler syndrome and enostosis, which are seen either alone or in conjunction with osteochondrosis.

> Diagnosis

Ataxia, non coordinated gait of the rear legs, delayed proprioceptive reflexes and pain reaction upon extension of the neck are all signs which can be seen in young dogs of large breeds, with **canine wobbler syndrome**. These signs appear at the age of 6 months, unlike the unrelated ataxia in Doberman Pinchers which appears at the age of 6 years. Although not pathognomonic, the presence of the crossed extensor reflex is of great help in making the diagnosis. The other findings of a neurologic examination depend on the location of the lesion.

Figure 13 - *Disproportionate widening of the spinal canal causing compression of the spinal cord.*

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Shifting lameness in dogs under two years of age is suggestive of enostosis (**eosinophilic panosteitis**). This occurs due to the fact that all long bones are affected, but will vary in their degree of painfulness at any given time.

Plain radiographs are the initial diagnostic test. Often additional imaging techniques such as myelography and CT need to be performed to determine the exact location of the lesion in cases of canine wobbler syndrome **(Figure 13)**. Positive pain reactions upon deep palpation of bones, together with radio-opaque areas in the medullary cavities, which arise close to the nutrient foramina, are conclusive for enostosis.

> Epidemiology

Canine wobbler syndrome has an increased incidence in Great Danes, Mastiffs and Irish Wolfhounds and is unrelated to the spondylolisthesis and consequent ligamentous hypertrophy seen in the aged Doberman Pinscher. Enostosis occurs in a variety of dog breeds at a young age, particularly in the German Shepherd Dog.

> Pathophysiology

The etiology may be multifactorial, but the influence of diet has been demonstrated in rapidly growing dogs of large breed *(Hedhammar et al, 1974; Hazewinkel et al, 1985)*. Skeletal growth occurs in two ways: growth in length and modeling in shape. The latter includes an adaptation to changes in body size, muscle-pull and body weight. The load of hydroxyapatite crystals may cause a shift in electrons which can influence osteoblastic and osteoclastic activity. This and other still unexplained mechanisms may form the basis of Wolff's law which states that "bone is laid down where it is needed". However, the integrity of the skeleton is subordinate to calcium homeostasis, which includes the strict regulation of calcium concentration in the extracellular fluid.

As previously discussed in the section on Excess calcium intake, a chronic excessive calcium intake will cause high calcium absorption in young dogs, especially of large breeds **(Figure 6)**. Calcium is not significantly excreted in the urine or via the endogenous fecal pathway, but is mainly routed to the bone in these dogs. Nutritional hypercalcitoninism-induced decreased osteoclastic activity occurs with a high calcium intake and bone remodeling is diminished. As a result adaptation of the diameter of foramina to the proportional growth of the spinal cord or blood vessels may be delayed and certain forms of canine wobbler syndrome or enostosis may occur.

Great Danes fed a diet with high calcium content (i.e. 2-3 times the recommended amount) displayed a delayed expansion of the cervical vertebral canal in proportion to the growth of the spinal

cord. Compression of the spinal cord causes myelin degeneration of both the ascending and descending tracts, the extent of which is related to the severity of clinical and imaging signs *(Hedhammar et al, 1974; Hazewinkel et al, 1985)*.

In dogs fed high calcium diets, a decreased endosteal osteoclastic resorption, together with an increase in new periosteal bone formation has been observed *(Hedhammar et al, 1974)*. The nutrient canals and foramina of the cortex are often abnormal in shape; this may cause edema formation, and eventually fibrosis in the medullary cavity. Edema may also extend through the cortex and underneath the periosteum, causing a loose periosteal attachment and/or excessive lamellar bone formation **(Figure 14)**.

Enostosis was radiologically confirmed in research animals at the age of 3-4 months given a gruel in their period of partial weaning (i.e: 3-6 weeks of age) with an elevated calcium content, together with the bitch milk. On the contrary, none of the control puppies (raised on a diet with 1% Ca DMB) first as a gruel (3-6 weeks) and eventually as their sole food, revealed any clinical or radiological sign of enostosis *(Hazewinkel et al, 2000)*.

> Therapy

Early dietary correction may halt the process of disproportionate remodelling of the skeleton. Commercial diets providing an adequate amount of calcium and energy for the weight and age of the dog should be instituted.

In canine wobbler syndrome, surgical decompression of the spinal cord may prevent further degeneration. Enostosis can be very painful and recurrent. Non-steroid anti-inflammatory drugs (NSAIDs) can be prescribed. Enostosis will heal without long term effects however, relapses may occur until the dog is 2 years of age.

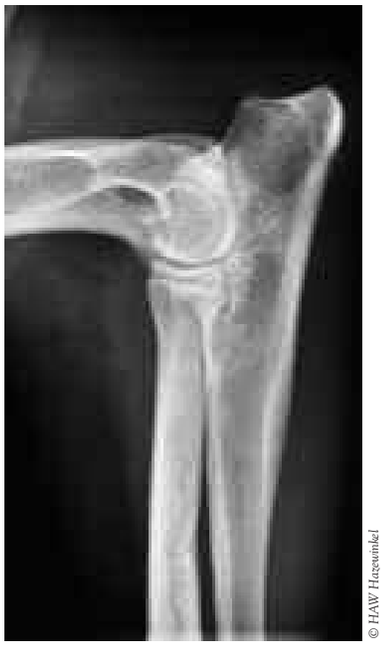


Figure 14 - Enostosis
This 8-month-old Labrador with shifting lameness revealed pain reactions on deep palpation of the long bones including the right radius. The radiograph shows mineralization of the medullary cavity of the radius typical of enostosis and a slight thickening of the dorsal cortex of the ulna.

4 - Developmental orthopedic diseases due to nutritional deficiencies (nutritional secondary hyperparathyroidism, rickets)

Pathological fractures, including folding of the cortical bones, compression of the cancellous bone spiculae and deformation of flat bones can occur secondary to nutritional deficiencies of calcium (nutritional secondary hyperparathyroidism NSHP) or vitamin D (rickets in young dogs and osteomalacia in mature dogs). Along with pathological fractures, other clinical signs of the rarely seen rickets or hypovitaminosis D can include lethargy, muscle weakness and bulging metaphyseal areas of radius-ulna and ribs. Chronic progressive demineralization of skeletal bone with resultant loss of teeth and/or pathological and/or compression fractures can be the consequences of NSHP. As well, due to constant muscle pull on the pelvic bones, calcaneus, scapula and other prominences, the weakened bone can become misshaped. In some locations this can be seen or palpated.

► Diagnosis

Developmental orthopedic diseases secondary to nutritional deficiencies may be suspected based on dietary history and physical examination. The most practical and inexpensive diagnostic technique is radiographic investigation of the long bones and axial skeleton *(Riser & Shirer, 1964; Voorhout & Hazewinkel, 1987a)*. Although it has been demonstrated that under standardized conditions, a mineral loss of at least 30% is required before NSHP lesions are noticeable radiographically, the abnormal alignment due to greenstick and compression fractures, as well as bowing of bones due to the constant pull, is obvious. In addition, the growth plate has a normal width and the metaphyseal area is usually more radio-opaque than the rest of the bone **(Figure 15)**. Radiographic

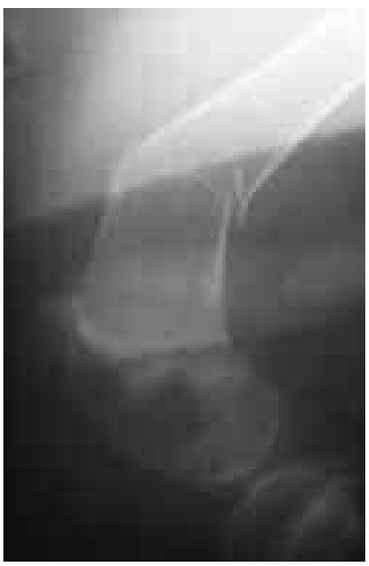


Figure 15 - Nutritional secondary hyperparathyroidism
Radiograph of a dog suffering from nutritional hyperparathyroidism showing thin cortex, greenstick fracture and a normal growth plate bordered by white metaphyseal area.

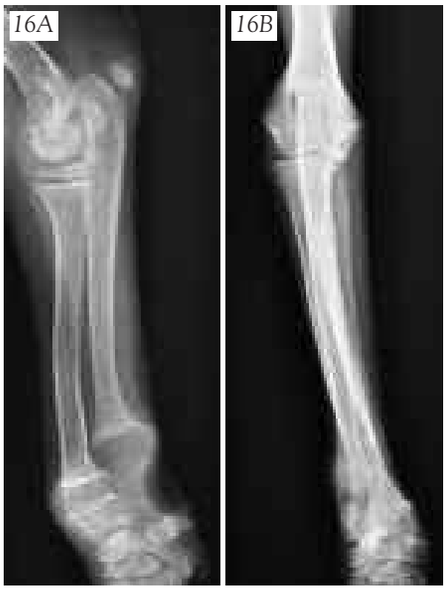


Figure 16 - Hypovitaminosis D (rickets)
(16A) Thin cortex, large diameter of medullary cavity and increased width of the growth plates are typical for hypovitaminosis D (rickets). (16B) Six weeks later, the radiograph shows good mineralization of both the cortices and the growth plates.

changes of the radius and ulna can be diagnostic for rickets. Typical findings include a thin cortex, larger diameter of the medullary cavity, bowed long bones and an increase in width of the growth plates **(Figure 16)**.

Diagnosis can also be supported by the measurement of vitamin D metabolites and parathyroid hormone (PTH). With rickets, levels of vitamin D, 25-OH vitamin D and 24,25-OH_2 vitamin D will be low, whereas the 1,25 OH_2 vitamin D metabolite will be in the low to normal range. In contrast, elevated PTH, increased 1,25 OH_2 vitamin D and low 25-OH vitamin D may occur with NSHP. Serum biochemistry panels may also show some abnormalities with these diseases. Serum phosphate concentrations are strongly influenced by nutritional intake and this factor must be considered in the interpretation of the value. Alkaline phosphatase, abundantly available in osteoblasts and liver cells, will be markedly elevated whenever there is increased bone cell activity (including growth). Even with a low dietary calcium intake, serum calcium concentrations are kept constant. However with hypovitaminosis D, serum calcium concentrations can be in the low to normal range and serum phosphorus concentrations can be low with concurrent increased urinary phosphorus. The latter can be explained by hypocalcemia induced hyperparathyroidism, which will decrease the maximal tubular reabsorption of phosphorus.

► Epidemiology

A major risk factor for development of these diseases appears to be diet. Rickets or hypovitaminosis D, rarely seen in puppies, can occur when a dog has been raised on lean meat immediately after weaning. Home-made meat-rich diets, especially those prepared from cardiac and skeletal muscle can be deficient in phosphorus and calcium resulting in NSHP. In addition, NSHP may also be induced when the diet meets all other requirements but is deficient only in its calcium content, and cannot therefore support proper skeletal mineralization. Poor availability of calcium due to complex formation with phytic acid, oxalate, high phosphate content of the food or inadequate vitamin D may cause the same symptoms.

Other risk factors may be breed and breed size. Under experimental conditions, pathological fractures may occur in small breed dogs when fed a diet with extremely low calcium content, whereas Great Danes may exhibit pathological fractures when the dietary calcium content is 50% of the recommended amount. In adult dogs, Krook et al (1971) described severe hyperparathyroidism in adult Beagles fed 1.2 g calcium per kg diet (DMB), whereas in adult Golden Retrievers fed a diet with 1 g calcium per kg diet *(Hedhammar et al, 1980)* and adult mongrels fed a diet with 1.3 g per kg diet did not develop clinical signs of osteoporosis *(Gershoff et al, 1958)*.

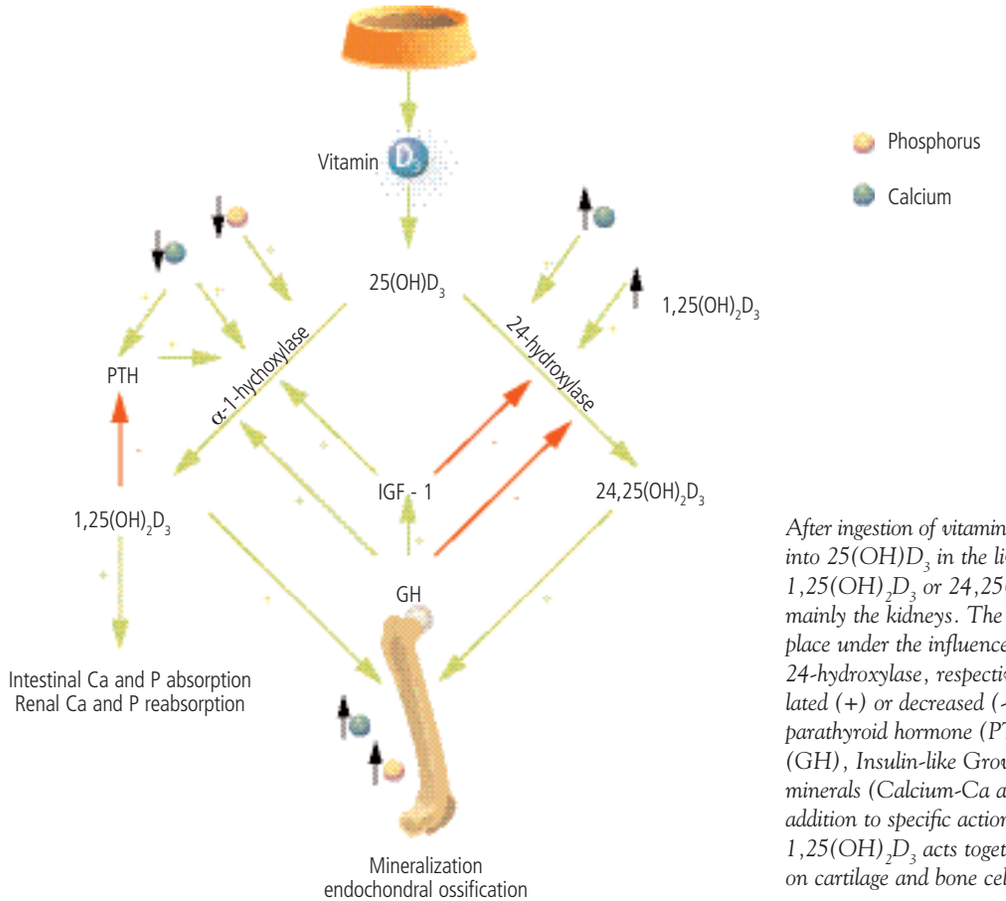
► Pathophysiology

Up to 95% of ingested c*alcium may be absorbed following long term feeding of a calcium deficient diet (Gershoff et al, 1958; Hazewinkel et al, 1991)*. This increase in absorption efficiency is achieved by an increase in formation of the most active metabolite of vitamin D. This metabolite is formed in the kidney under the influence of PTH **(Figure 17)**.

A low calcium uptake stimulates PTH synthesis and secretion. Both elevated vitamin D3 levels and hyperparathyroidism will increase the number, as well as the activity, of the bone resorbing osteoclasts *(Hazewinkel et al, 1987a)*. Osteoclasis will be augmented at the sites where osteoclasts are normally active in young growing bone, i.e. at the medullary aspect of cortical bone and at the periphery of the cancellous bone spiculae. The circulating calcium level is kept constant and is sufficient not to disturb other process in the body, including mineralization of the newly formed cartilage of growth plates.

FIGURE 17 - VITAMIN D METABOLISM

(modified after Hazewinkel & Tryfonidou 2002)



After ingestion of vitamin D3 in food, it is hydroxylated into 25(OH)D_3 in the liver and subsequently to 1,25(OH)$_2D_3$ or 24,25(OH)$_2$ D_3 in various organs, mainly the kidneys. The second hydroxylation takes place under the influence of 1-α-hydroxylase and 24-hydroxylase, respectively, whose activity is stimulated (+) or decreased (-) by a variety of hormones: parathyroid hormone (PTH), Growth Hormone (GH), Insulin-like Growth Factor (IGF-I) and minerals (Calcium-Ca and Phosphorus-P). In addition to specific actions on intestine and kidneys 1,25(OH)$_2D_3$ acts together with 24,25 (OH)$_2D_3$ on cartilage and bone cells.

Vitamin D metabolites stimulate calcium and phosphate absorption in the intestine and reabsorption in the renal tubules as well as stimulate osteoclasts and are necessary for mineralization of the newly formed osteoid and cartilage. Vitamin D is absorbed in the intestine as one of the fat soluble vitamins, transported to and hydroxylated in the liver and then further hydroxylated in the kidney to 24,25 OH_2 vitamin D or 1,25 OH_2 vitamin D *(Fraser, 1980)*. It has been demonstrated that dogs do not synthesize adequate vitamin D in their skin when radiated with ultraviolet B-light, unlike herbivores and other omnivores **(Table 5)**. Under experimental conditions, young dogs developed the signs of rickets when fed a vitamin D deficient diet with adequate

TABLE 5 - ROLE OF VITAMIN D IN CANINE NUTRITION

In general	All dogs need vitamin D in their diets, since dogs are not able to synthesize adequate vitamin D in their skin under the influence of sunlight. The vitamin D content of balanced dog foods is enough to treat (and prevent) hypovitaminosis D in dogs.
Young dogs	Vitamin D deficiency (even when the calcium and phosphorus content of the diet is adequate) will cause rickets: bowed legs, increased width in the growth plates, thin cortices
	Vitamin D excess (100 x the recommended content of 500 IU/kg food) does not increase absorption of calcium and phosphorus in the intestine, but causes severe disturbances in endochondral ossification (osteochondrosis)
Adult dogs	Vitamin D intoxication causes increased absorption and bone resorption and thus increased calcium and phosphorus blood levels, with mineralization of lungs and kidneys and eventually death.

Table 6 - Main natural sources of vitamin D

Ingredients	Vitamin D3 (IU/100 g)	Vitamin D3 (µg/100 g)
Fish liver oil	8 000 - 24 000	200 - 600
Fishes	200 - 4000	5 - 100
Liver	80 - 200	2 - 5
Butter	100	2,5
Egg yolk	160- 280	4 – 7
Milk	4 - 8	0.1– 0.2
Recommended allowance for growth* (NRC 2006)	**55**	**1.38**

**Energy density of 4000 kcal/kg of Dry Matter (DM)*

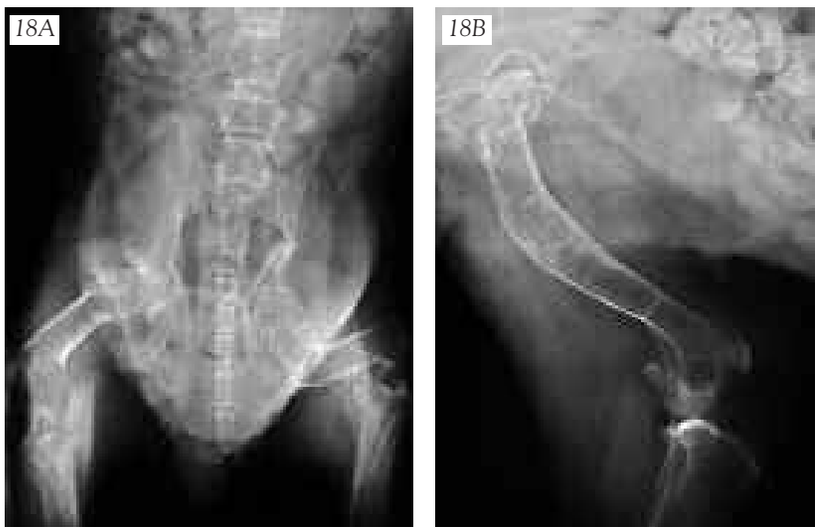


Figure 18 - Greenstick fracture
(18A) Ventrodorsal view of the pelvis and femurs of a 7 month old crossbred dog raised on a home made diet based on chicken meat, revealing folding fractures of the long bones and the pelvis and compression fractures of the sixth lumbal vertebra. (18B) The mediolateral view of the left femur shows the abnormal alignment, the thin cortex and wide medulla and the poor contrast when compared with the surrounding soft tissues.

amounts of calcium, phosphorus and other constituents according to the NRC 1974 guidelines. Daily exposure with ultraviolet B-light did not prevent or heal the hypovitaminosis D *(Hazewinkel et al, 1987b)*.

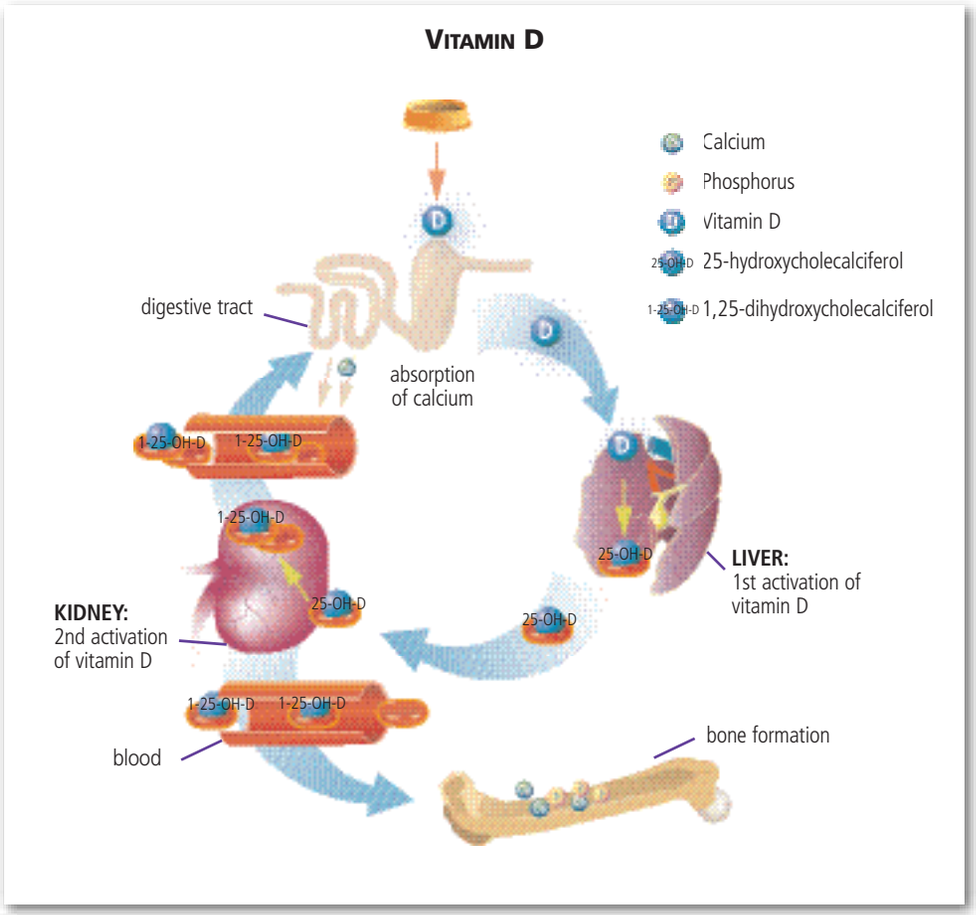
Therefore, dogs rely on the vitamin D in foodstuffs including liver, fish, egg, milk and commercial available dog foods to meet their requirements **(Table 6)**. Synthesis of the most active metabolite (1,25-OH_2 vitamin D) is stimulated by the influence of PTH, low serum calcium and phosphorus levels and during growth, pregnancy and lactation.

► Nutritional therapy

Developmental orthopedic diseases secondary to nutritional deficiencies are highly responsive to nutritional intervention. Nutritional therapy should be begun immediately and usually involves feeding a commercial dog food. Commercial dog foods contain adequate amounts of calcium and phosphate and are well above the recommended allowance of vitamin D (i.e. 3.4 µg or 136 IU/ 1000 kcal *-NRC 2006*). In hypovitaminosis D, after 3 weeks of dietary therapy, mineralization of the growth plates should be almost normal and there should be an improvement in mineralization of cortical and cancellous bone, as well as callus formation around pathological fractures. Mineralization will be complete after several more weeks. If mineralization has not improved within the first 3 weeks, then the diagnosis should be reevaluated: collagen diseases like osteogenesis imperfecta or an inability to hydroxylate vitamin D metabolites should be considered. Vitamin D injections carry the risk of over supplementation and are not recommended when dietary measures are employed *(Hazewinkel et al, 1987b)*. Corrective surgery should be postponed until mineralization of the skeleton is complete.

In the acute phase of NSHP, therapy involves good nursing care and feeding a diet which fulfils the dog's nutritional requirements for its age and size without any injections of calcium or vitamin D. Commercial dog foods would be appropriate and contain adequate calcium content if chosen for correct age and size. The amount of calcium needed exceeds the amount which can be safely injected by 1000 fold. The 1,25 OH_2 vitamin D level is expected to be elevated and vitamin D injections would not be beneficial **(Figure 18)**.

In the acute phase, affected bones cannot withstand the load of a splint or cast and will form another greenstick fracture just proximal to its margin. Compression of the vertebrae with compression of the spinal cord, especially in the lumbar area can occur and cause posterior paralysis in severe cases.



INFLUENCE OF INCREASED VITAMIN D INTAKE IN PUPPIES

Under normal circumstances with a vitamin D3 intake of 500-1000 IU per kg food, the 24,25(OH)vitamin D3 plasma concentration is 10 times higher in small breed dogs than in large breed dogs of the same age (70 μg/L vs. 7 μg/L), due to excess growth hormone (GH) and insulin-like growth factor (IGF-I) in large breed dogs *(Hazewinkel & Tryfonidou, 2002)*. The 1,25(OH) vitamin D3 plasma concentration in large breed dogs is higher than in small breed dogs (250 pmol/L vs 200 pmol/L) when raised on the same food *(Tryfonidou et al, 2002a)*, mainly due to a lower activity of 24-hydroxylase in large breed dogs.

However, with high vitamin D3 intake, increased hydroxylation occurs in the liver with conversion into the 25(OH) vitamin D3 form. The high plasma concentration of 25(OH) vitamin D3 stimulates both the activity of 24-hydroxylase and 1alpha-hydroxylase. As a consequence more 1,25 $(OH)_2$ vitamin D3 will be synthesized but immediately further hydroxylated into 1,24,25(OH) tri-hydroxy-vitamin D3 and other products of oxidation. This results in an increased 24,25$(OH)_2$ vitamin D3 plasma concentration and a decreased 1,25$(OH)_2$ vitamin D3 plasma concentration *(Tryfonidou et al, 2002)*. These changes do not alter the absorption rate of is calcium or phosphate, but it does cause severe abnormalities in cartilage maturation, known as osteochondrosis, in Great Danes less than 6 months of age. The latter is probably the result of an imbalance between 24,25$(OH)_2$ vitamin D3 and the available 1,25$(OH)_2$ vitamin D3 at the site of the growth plate *(Tryfonidou et al, 2003; Boyan et al, 2001)*.

Therefore excessive vitamin D intake for a long period should be avoided **(Table 5)**, since it might have deleterious effect on cartilage development in young dogs. Some dog foods may have high vitamin D levels, due to both the ingredients and additional pre-mixture with a standard amount of vitamin D and minerals *(Kallfelz & Dzanis, 1989)*.

Vitamin D intoxication due to vitamin D over supplementation or cholecalciferol poisoning will cause an increase in serum calcium levels by reabsorption of calcium and increased osteoclastic activity.

As a consequence of the increased serum calcium, PTH levels will decrease. There will be an increased threshold for phosphate in combination with phosphate derived from osteoclasia. An increased plasma phosphate level will also be seen with vitamin D intoxication. Calcium phosphate will precipitate in the stomach, lungs, and kidneys with severe clinical consequences.

The long bones may be abnormally shaped and need surgical correction after mineralization is completed, to allow for normal use. Although the prognosis should be guarded, posterior paralysis may disappear two weeks after installation of therapy. Abnormal alignment of the pelvic bones may cause repetitive obstipation which will continue after restoration of the mineralization status of the skeleton. Fracture treatment or corrective osteotomies must be postponed till the skeleton is firmly mineralized.

5 - Osteoarthrosis

Osteoarthrosis (OA) is the largest problem in companion animal orthopedics since most if not all joint diseases eventually result in OA and OA is the main cause of euthanasia in orthopedics.

► Diagnosis

Clinical signs of OA can include decreased weight bearing of the affected leg, pain upon rising, warming out during exercise (initial stiffness which improves with walking) and worsening of signs after rest following heavy exercise. Physical examination may reveal palpably swollen and sometimes painful joints, crepitation and decreased range of motion depending on the chronicity of the OA. OA can be divided in primary OA, often associated with aging, whereas secondary OA has a primary cause **(Table 7)** like disturbances in development, trauma, and septic or non-septic osteoarthritis.

TABLE 7 - PRIMARY CAUSES OF SECONDARY OSTEOARTHROSIS IN DOGS

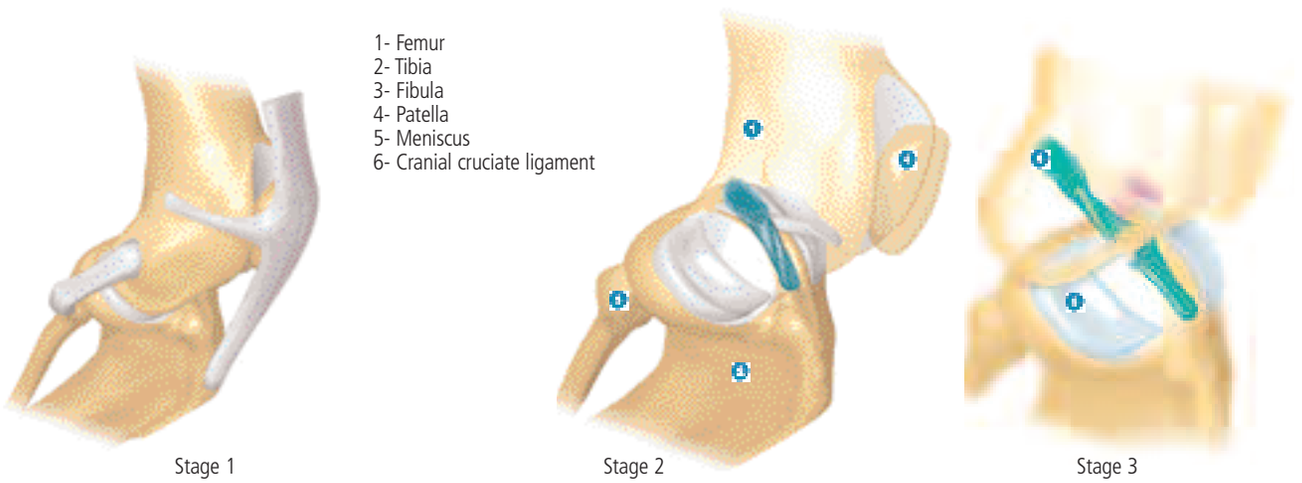
Osteoarthrosis in forelimbs	Osteoarthrosis in hindlimbs
Shoulder joint - Osteochondritis dissecans (OCD)	**Hip joint** - Hip dysplasia - Avascular femoral head necrosis - Trauma (luxation, fracture)
Elbow joint - Elbow dysplasia (OCD, UAP, FCP, INC) - Luxation - Fracture	**Stifle joint** - Cranial cruciate ligament rupture (figure 19) (with medial meniscus damage) - OCD - Patella luxation with cartilage damage - Trauma (other ligament ruptures, fractures)
Carpal joint - Hyperextension with ligament rupture - Immune mediated disease	**Hock joint** - OCD - Immune mediated disease - Trauma (instability)
Digits (both front and hind leg) - Sesamoid bone fractures, - Trauma (subluxation, avulsions)	

The history and clinical findings of OA are so typical, that localization of the diseased joint may almost lead to the diagnosis; however radiographs should be performed to rule out other less likely causes. Joint effusion, osteophytes at the joint margins, and sclerosis of subchondral bone are the main radiographic findings; narrowing of the joint space and specific findings like a mineralized flap in case of OCD, cranial displacement of the tibia in case of cruciate ligament rupture **(Figure 19)** and other findings may be noticed. In some

TABLE 8 - DIAGNOSTIC TESTS FOR THE DIAGNOSIS OF OSTEOARTHROSIS

History	Pain upon raising, normal general health
Examination & palpation	Swollen joints, new periarticular tissue formation
Passive motions	Specific findings in specific diseases; for example: drawer sign and Barden sign
Radiographs	Plain, 2 views: distended joint, osteophytes, subchondral sclerosis, no lytic lesions
Arthrocentesis	Additional diagnostics such as arthrocentesis may be required in certain cases; cytology to classify arthritis; bacterial culture and sensitivity
Laboratory investigation	Additional diagnostics such as serology, CBC, biochemistry panel may be required; leukocyte count, total protein, protein electrophoresis, specific antibodies (ANA, SLE), serological titers for infectious organisms
Additional imaging techniques	Bone scintigraphy, MRI, CT-scanning, arthroscopy, arthrotomy

Figure 19 - Cranial cruciate ligament fracture



cases, additional diagnostics such as arthrocentesis, blood work, and other imaging modalities may be necessary **(Table 8)**.

► Epidemiology

The age of 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)*.

It is plausible to imagine that the activity of the dog (like pulling a sled, running races, and jumping fences for police dog training) may advance degeneration of joint cartilage, even without any primary cause including subluxation, shear and tear injuries, and avulsions or fatigue fractures. Although not yet proven, there is reason to suggest that some breeds are more vulnerable for OA than others. It is the author's experience that Retrievers suffer more from OA than Rottweilers, and some breeds suffer more from immune mediated OA (Shar-Pei, Boxer) than others.

Gender in secondary OA may also be a risk factor for disease. Gender differences in OA are related to the primary cause. An example is fragmented coronoid process, seen in a 3:1 ratio of males to females, and so too is the secondary OA. Another example is cranial cruciate ligament ruptures which are seen more frequently in castrated females than in any other gender (probably due to obesity), and so too is the secondary OA of the stifle joint.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Overloading of the joint, either due to obesity or to over-use, is the main cause for increased complaints in dogs with OA. Although the genotypical factors can not be regulated by the owner of a specific dog, the phenotype (i.e. suffering from OA) can partially be influenced. Increased food intake *(Hedhammar et al, 1974; Kasstrom, 1975; Lavelle, 1989; Kealy et al, 2000)*, and increased calcium intake *(Hazewinkel et al, 1985; Schoenmakers et al, 2000)* may increase the frequency and severity of OA in individual dogs at an older age.

In these dogs a discrepancy in growth hormone and insulin-like growth factor concentrations were demonstrated in the plasma, similar to human patients with OA *(Hazewinkel et al, 1999)*. A previously unidentified humoral factor harvested from arthritic joints has been identified that can cause OA *in vitro* as well as *in vivo (Wastacott et al, 1997; van Bilsen et al, 2002)*.


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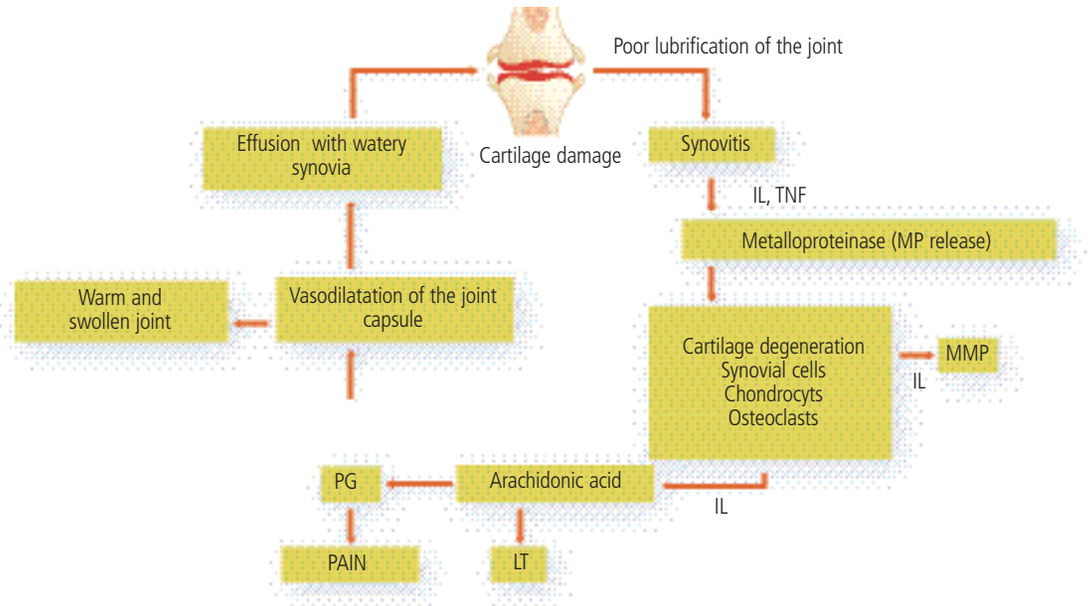
Large breed dogs generally exhibit signs of osteoarthrosis at an earlier age compared with small breed dogs.

► Pathophysiology

Osteoarthrosis (OA) is a vicious cycle. Cartilage damage (primary or secondary) will cause synovitis with the release of mediators of inflammation including interleukins (IL) and Tumor Necrosis Factor (TNF) which release metalloproteinases (MMPs) that cause further degeneration of cartilage **(Figure 20)**. As a consequence, arachidonic acid will be metabolized into prostaglandins and leukotrienes, causing a decrease in pain threshold, vasodilatation of the joint capsule, and thus a swollen and warm joint.

These elements are characteristic for OA. The joint is not lubricated and the cartilage is not receiving enough nutrients with more cartilage damage as a consequence. This vicious cycle should be broken by eliminating the cause, changing the breakdown pathways of arachidonic acid, decreasing the influence of inflammatory mediators and/or increasing the regenerative capacity of cartilage.

FIGURE 20 - PERPETUATING CYCLE OF OSTEOARTHRITIS



Due to cartilage damage, synovitis develops with the release of a variety of enzymes which further degenerate cartilage and synovial cells. Destruction of the cell walls liberate arachidonic acid which may be enzymatically broken down into leukotrienes or prostaglandins ***(see Figure 21)****, which cause the clinical signs of osteoarthrosis, i.e. painful, warm and swollen joint. The joint is effusive with less mucin and more plasma transudate which, as a consequence, poorly lubricate and nourish the cartilage, with more cartilage damage as a result.*

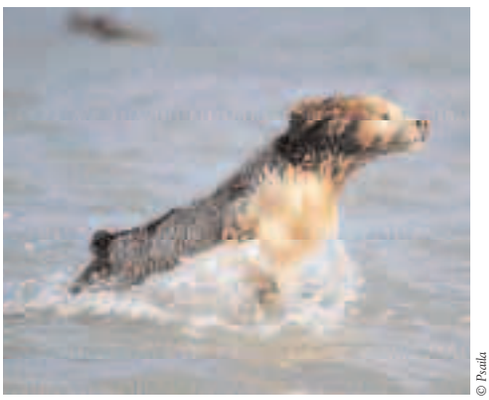
During aging, the length of GAGs and proteoglycan content decrease, and thus so does the water content and the flexibility of the cartilage to withstand loading **(Figure 1)**. Reactive oxygen species (ROS), free radicals, trauma, infection and irradiation may also damage GAGs. Proteolytic enzymes, including metalloproteinase (MMPs) and lysosomal enzymes may degenerate cartilage. Regeneration can occur in cases of micro trauma, by proliferation of undamaged chondrocytes, and de novo synthesis of proteoglycans and collagen. Severe cellular damage will lead to a scar without cells; lesions of the tide mark cause inflammation and sclerosis of the subchondral bone, and possibly the formation of a fibrotic cartilage scar with a low content of proteoglycans.

Under normal circumstances MMPs will be suppressed by tissue inhibitors (TIMPs). However, in cases of OA, MMPs will be formed by mast cells and synovial cells under the influence of the cytokines, interleukin-I (IL-I) and tumour necrosis factor (TNF-α), released by synovial cells, monocytes, macrophages and T-cells. These cytokines 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 such as PGE_2 and leukotriene B4 from chondrocytes and synovial membrane.

The expression and activity of IL-I, TNF-α and cyclooxygenase ($COX\text{-}_2$) can be reduced in presence of omega-3 fatty acids. Fish oil supplementation can specifically affect regulatory mechanisms involved in chondrocyte gene transcription *(Curtis et al, 2000)*.

► Treatment

Weight loss in overweight dogs and loss of any excess weight gained during times of decreased mobility should be the primary goal. A significant improvement has been recorded by Impellizeri *et al (2000)* in dogs with HD, following a decrease in body weight by 11-18%. Weight reduction protocols are discussed in **Chapter 1**.



© Psalla

Swimming is a good activity for overweight dogs with osteoarthrosis.

> Life style

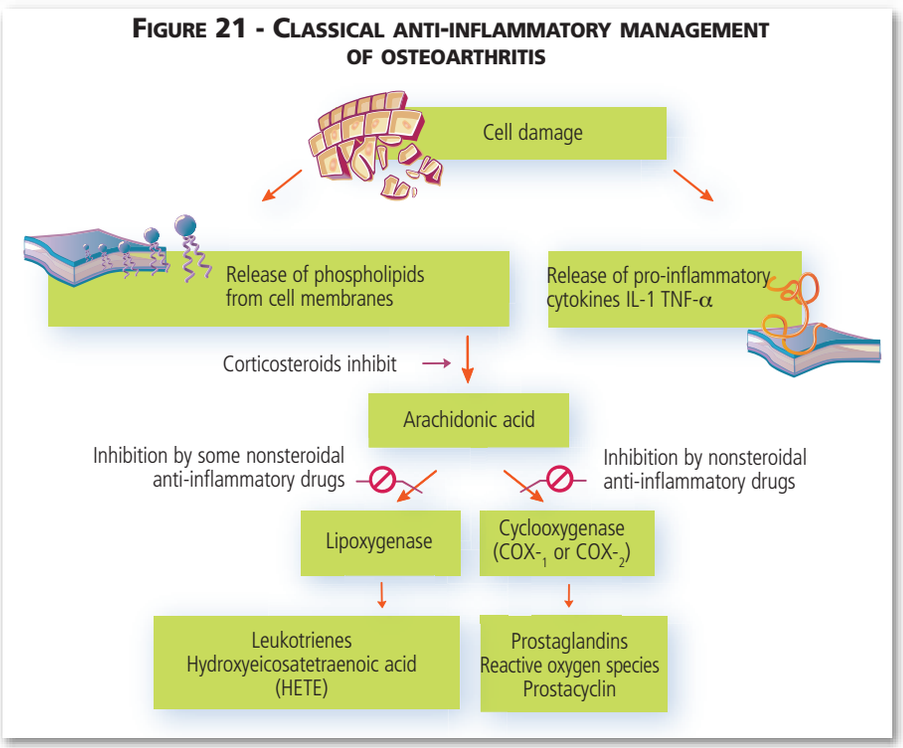
The amount and kind of activity will need to be tailored to the degree of arthritis and the joint involved. For example, a dog with a cruciate ligament rupture is best exercised by leash walks rather than zigzagging through the field and frequently rotating the unstable joint. Swimming is a great activity for overweight dogs with arthrosis. Dogs with HD should be prevented from jumping and climbing. The amount of activity should be divided over several walks during the week rather than one large bout of exercise once a week (i.e. during the weekends). If the dog becomes lamer after a period of rest following the exercise, the amount of activity will have to be reduced.

> Medical treatment

Nonsteroid anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX) enzymes; COX_1 stimulate the production of prostaglandins (PGs) which protect the body, whereas COX_2 stimulate the production of PGE_2 which is responsible for clinical signs like pain and hyperemia (warm joint, overproduction of joint fluid) **(Figure 21)**. NSAIDs are often prescribed in cases of OA for a prolonged period, not to mask pain but to improve the metabolic condition of the diseased joint.

Corticosteroids suppress phospholipase activity **(Figure 21)**, and as a result stabilize blood vessel walls and lysosomes. Clinically, the 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 dosage is contraindicated.

FIGURE 21 - CLASSICAL ANTI-INFLAMMATORY MANAGEMENT OF OSTEOARTHRITIS



> Nutritional treatment

Dietary supplements are another aspect that can be incorporated in the management of OA **(Table 9)**. Chondroprotective agents protect cartilage from degeneration by enhancing the metabolism of chondrocytes and synoviocytes, inhibiting degradative enzymes and inflammatory mediators and preventing thrombi formation in blood vessels *(Beale, 2004; Bui & Taylor, 2000)*. Some chondroprotective products are classified as nutraceuticals. The definition by the NAVNC (*North American Veterinary Nutraceutical Council*) defines a nutraceutical as "a substance that is produced in a purified or extracted form and administered orally to patients to provide agents required for normal body structure and function and administered with the intent of improving the health and well being of animals". There are a variety of these dietary supplements (glucosamine, chondroitin sulfate, polyunsaturated fatty acids, antioxidants and green lipped mussel products) that are used in the management of canine and human OA. However many of these products are lacking controlled clinical trials to show their efficacy in dogs.

Table 9 - Dietary supplements used for the treatment of osteoarthritis

Supplement	Nature	Effect on joints
Glucosamine	Major glycosaminoglycan precursor (represents 50% of hyaluronic acid composition).	- Boosts cartilage regeneration (stimulates synthesis): - through increased collagen synthesis (indirect stimulation); - through increased chondrocyte activity (proteoglycan and hyaluronic acid synthesis); - Slows osteo-arthritic evolution (slow-acting molecule).
Chondroitin Sulfate	One of the major glycosaminoglycans that are essential cartilage components	- Promotes chondrocyte activity (glycosaminoglycan synthesis); - Inhibits the degradative enzyme action, which is at the origin of cartilage destruction
EPA and DHA	Long-chain omega 3 fatty acids (C20/5 and C22/6 respectively)	- Modulates inflammation by stimulating the production of less inflammatory eicosanoids - Affect regulatory mechanisms involved in chondrocyte gene transcription
Antioxidants	Vitamins E & C, lutein, polyphenols…	- Protects cells from free radicals attack
Green lipped mussel (GLM)	Extract from *Perna Canaliculi* (New Zealand)	Anti-inflammatory properties

In articular cartilage one of the predominant GAGs synthesized by chondrocytes is chondroitin sulfate. Chondroitin sulphate increases in vitro the production of proteoglycans and as such the regeneration of cartilage *(Basleer et al, 1998)*. Chondroitin sulfate has also been shown to reduce or inhibit the production of metalloproteinases. These enzymes are known to cause degradation of the cartilage. When given to rabbits prophylactically, chondroitin sulfate has been shown to prevent synthesis of MMPs by IL-3 and thus cartilage damage.

Chondroitin sulfate is partially digested before absorption yet it appears to be therapeutically effective after oral administration *(Bui & Taylor, 2000)*.

Glucosamine is a precursor to GAGS and stimulates synthesis of GAGs, prostaglandins and collagen by chondrocytes *in vitro (Bassler et al, 1992)*. Normal chondrocytes can synthesize glucosamine but it is the rate limiting step in the production of GAGs and proteoglycans *(Bui & Taylor, 2000)*. As well chondrocytes in osteoarthritis may have decreased ability to synthesize glucosamine *(Beale, 2004)*. Thus exogenous administration of glucosamine may be beneficial in chondroprotection. Glucosamine administered orally is absorbed almost completely (87% of intake) and rapidly absorbed from the gastrointestinal tract *(Setnikar et al, 1986; Bui & Taylor, 2000)*. Besides

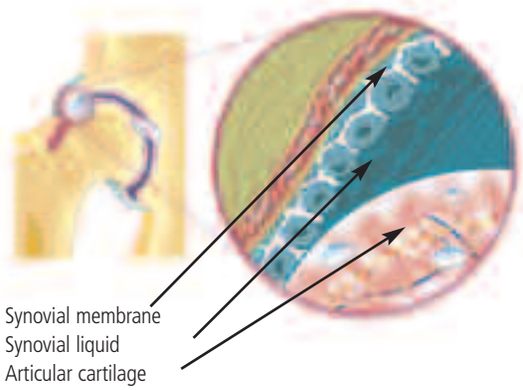
its chondroprotective effects, glucosamine has been shown to have mild anti-inflammatory effects *(Setnikar et al, 1991; Bui & Taylor, 2000)*.

There have been some clinical and in vitro trials to support its use in dogs and other species. Substitution of glucosamine in the medium of chondrocytes resulted in an increase in the mRNA content for aggrecan, a decrease in MMPs, and an increased synthesis of proteoglycan *(Reginster et al, 2001)*.

In rabbits with a cranial cruciate ligament rupture, 120 mg/ kg body weight of prophylactic glucosamine decreased the amount of chondropathy in comparison with controls *(Conrozier, 1998)*. In a study using the cranial cruciate ligament (CCL) rupture as a model, Altman et al *(1989)* demonstrated less cartilage swelling, less total and active metalloproteinase (MMP) and lower pathologic scores in dogs injected with 4 mg/kg BW glucosaminoglycan polysulfuric acid (GAGPS) twice weekly for 4-8 weeks, starting 4 weeks after the CCL rupture. It is suggested that GAGPS suppressed proteoglycan breakdown by MMPs or by directly inhibiting MMP in cartilage, rather than by increasing synthesis of proteoglycans by chondrocytes *(Altman et al, 1989)*.

Another study demonstrated in a clinical double-blind, placebo controlled trial that 4.4 mg/kg GAGPS (I.M. every 3-5 days) coincided with an improvement in lameness score, range of motion and joint pain without side-effects in dogs with hip dysplasia after 8 injections, with only a small improvement in the placebo group of dogs *(De Haan et al, 1994)*.

FIGURE 22 - STRUCTURE OF A JOINT



The joint is protected by a capsule covered on the inside by the synovial membrane. This membrane secretes the synovial fluid essential to the nutrition of the cartilage. After oral administration, glucosamine and chondroitin are concentrated in the synovial fluid.

The combination of chondroitin sulfate and glucosamine may be synergistic since each has a different mechanism of action *(Bui & Taylor, 2000)* **(Figure 22)**. Hulse *(1998)* reported that a combination given to dogs with OA, subjectively allowed for more normal locomotion and joint movement than untreated controls. As well this combination given prophylactically decreased inflammation in dogs with induced arthritis *(Canapp et al, 1999)* possibly due to modulated metabolism of the articular cartilage as was demonstrated in dogs with CCL ruptures *(Johnson et al, 2001)*.

Polyunsaturated fatty acids (PUFA) are often added in diets or given orally to help with the management of OA. Omega 6 and omega 3 fatty acid precursors are desaturated into arachidonic acid (AA; 20:4n-6) and eicosapentaenoic acid (EPA; 20:6n-3), respectively which compete for incorporation into cell membrane phospholipids. With cell damage, AA and EPA are released from the cell membranes and broken down into prostaglandins and leukotrienes. AA forms the proinflammatory series 2 eicosanoids including prostaglandin E_2 and leukotriene B_4. EPA is converted

to the anti-inflammatory or less inflammatory series 3 eicosanoids including prostaglandin E_3 and leukotriene B_5. By altering the amounts of omega 6 and omega 3 fatty acids in dietary intake, production of anti-inflammatory mediators is favored. Gamma linolenic acid (GLA) is an omega 6 dietary PUFA that converts into anti-inflammatory or less inflammatory mediators *(Bui & Taylor, 2000)*.

In vitro, catabolic processes of articular cartilage chondrocytes treated with interleukin 1, are affected by supplementation with omega-3 fatty acids. Supplementation with omega-6 fatty acids does not provide the same results *(Curtis et al, 2002)*.

In joints with OA the LTB_4 content is increased *(Herlin et al, 1990)*. In dogs with experimentally induced synovitis, the clinical signs of synovitis, especially joint effusion, reduced when an inhibitor of the formation and the effects of LTB_4 was given *(Hansen et al, 1990)*. These studies demonstrate the consequence of LTB_4 in a joint affected by OA.

In 36 dogs with elbow OA due to ED a double blind efficacy study was performed by feeding increased omega 3 content (omega 3 of 4%, and omega 6 of 20%) or a high omega-6 content (omega 3 of 0.8%, and omega 6 of 38%) diet. Feeding the increased omega 3 content (omega 3 of 4%, and omega 6 of 20%) diet caused a significant increase in plasma LTB_5 concentrations, although ground reaction forces did not differ between both groups of dogs *(Hazewinkel et al, 1998)*.

Free radicals and toxic oxygen radicals are theorized to play a role in the pathogenesis of OA. Supplemental antioxidants may decrease the damage of synovial cells by radical oxygen scavengers. In human studies there is some evidence to suggest that vitamin C, vitamin E, beta carotene, selenium, and zinc supplementation may be advantageous in reducing the risk of progression of arthritis and/or management of arthritis *(Bui & Taylor, 2000)*. Manganese, silicon and pyridoxine play a role in normal cartilage formation and supplementation may be beneficial with OA.

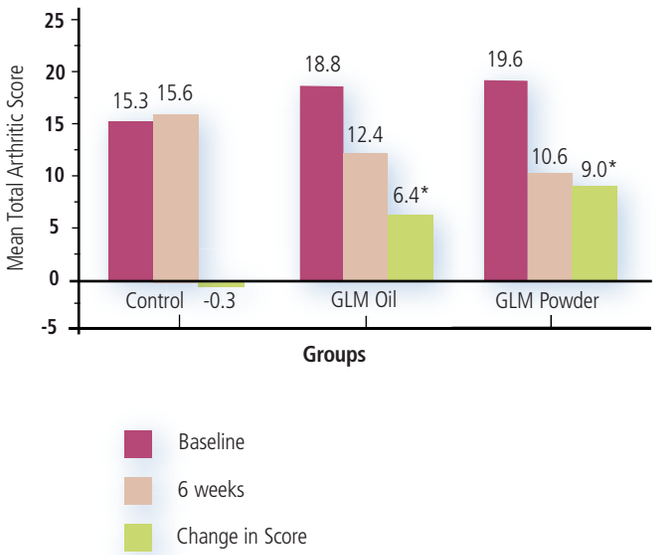
> Role of New Zealand green lipped mussel

New Zealand green lipped mussel (*Perna canaliculus*) contains anti-inflammatory components and other nutrients that may promote joint health *(Bui & Taylor, 2000; Bui & Bierer, 2001; Bierer & Bui, 2002)*. The fatty acid content of the powder (i.e. separated from the shell) of the green-lipped mussel (GLM) is 34.6% saturated, 18.4% mono-unsaturated, and 47% poly-unsaturated. Of the latter, 41% is omega 3 fatty acids (mainly eicosapentaenoic and docosahexaenoic acid (EPA and DHA), and a small amount of eicosatetraenoic acid (ETA, 0.3%), as well as 5.2% omega 6, with a ratio of omega 6: omega 3 of 1: 10. ETA is a dual inhibitor of both the lipoxygenase and cyclooxygenase pathways thus decreasing the production of inflammatory mediators *(Bui &Taylor, 2000; Bui & Bierer, 2001; Bierer & Bui, 2002)*. In addition GLM powder contains chondroitin and glutamine (a glycosaminoglycan precursor), in a concentration of 6.9% and 0.0005% respectively. The combination of omega 3 poly-unsaturated fatty acids, the GAGs chondroitin and precursor glutamine, together with anti-oxidant micronutrients (including zinc, copper, and selenium) may have the synergistic potential to limit the progression of OA.

Green Lipped Mussel (Perna canaliculi) *from New Zealand.*

FIGURE 23 - INFLUENCE OF GLM ON THE TOTAL ARTHRITIC SCORE AFTER 6 WEEKS OF TREATMENT IN DOGS

(Bierer & Bui, 2002)



The influence of GLM extracts on mean total arthritic score after 6 weeks of treatment in dogs. Bar graph includes mean score for each group at each timepoint and mean change in score. A positive value on change inscores indicates improvement. A negative value indicates worsening.

Seven of 14 (50%) dogs in the GLM main meal group demonstrated a 30% or greater reduction in total arthritic scores, including four dogs (29%) that exhibited a 40% or greater improvement and one dog (7%) that showed a 50% or greater improvement after week 6 of treatment. In the Control group, none of the dogs demonstrated 30% or greater improvement after week 6 of treatment.

** Represents a significant difference in mean change as compared to the control group at $p<0.05$. Control, n=15; GLM oil, n=15; GLM powder, n=17.*

Bierer and Bui *(2002)* reported their findings in a double blind, randomized, controlled trial in 17 dogs given GLM supplement powder and 15 dogs given GLM supplement oil (both in a daily dosage of 1000 mg when BW>34 kg; 750 mg when BW 34-25 kg; 450 mg when BW<25 kg) and compared with 15 controls, all with OA. A subjective score of arthritic signs grading from no signs to severe 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-oil supplemented group were only significantly different in joint pain and crepitus scores **(Figure 23)**.

The highest anti-inflammatory activity in GLM was found in the poly-unsaturated free fatty acid fraction of the powder, possibly the ETA by blocking both the COX as well as the lipoxygenase pathway. No gastrotoxic effects or platelet aggregation have been found in *in vivo* studies with GLM, therefore it is thought that the action is less directed to COX_1 than to COX_2. The GAGs in GLM may help to regenerate cartilage or to decrease proteoglycan breakdown *(Altman et al, 1989)*.

Frequently asked questions: nutrition and orthopedic diseases

Q	A
Is it better to feed an adult maintenance diet to fast growing puppies because of the lower protein content?	**No** – high protein diets have not be implicated as the cause of osteoarticular disease during growth in large breed puppies. Young fast growing dogs have a much higher requirement for protein for new tissue formation and development of their immune system than adult dogs. They need the high quality and quantity of protein in their daily diet. By eating an adult maintenance diet, they will not meet their protein requirements. Signs of protein deficiency can be poor body conformation and increased susceptibility to infections.
Is it ok to supplement with extra minerals for the development of strong bones?	**No** – supplementation of commercially available balanced dog foods should be prevented. Adding minerals to the food will unbalance the diet and provide the dogs with excesses. Puppies less than 6 months of age are unable to protect themselves from an excess of calcium. During weaning at least 50% of the calcium is absorbed whatever the quantity ingested. This excess calcium intake will lead to decreased skeletal modeling (enostosis, wobbler syndrome, possibly HD) and osteochondrosis (OCD, radius curvus syndrome, elbow incongruity). During evolution dogs, living in a poor-calcium environment, did not develop a system to defend themselves against excessive calcium intake.
Is it appropriate to advise owners to add fat to their puppy's diet if the puppy is underweight?	By adding fat to the diet you will increase the caloric density. However, if the diet is already complete and balanced for a growing puppy by adding fat you are unbalancing the diet and may be creating nutritional deficiencies. Thus the puppy will now be consuming an unbalanced diet and over time may exhibit signs of nutritional deficiency. Instead, advise the owner to change to a more palatable, more energy dense puppy food tailored for the requirements of that puppy's life stage and size.
Since enostosis can be caused by high calcium intake, should I advise the owners of young puppies to feed an adult food instead?	**No** – adult dog food per energy content has a higher calcium content and generally a lower caloric density than a puppy food. Puppies eat until they satisfy their energy requirements. Thus they need to ingest more of an adult maintenance diet to meet their energy requirements and in the process consume more calcium. Adult maintenance dog foods are not balanced in proteins and other nutrients to meet a growing dog's requirements. The best option is to recommend a diet tailored to meet the nutritional requirements of fast growing dogs.
In my practice I have many dogs from the same breeder with OCD in their elbow joints. Should I advise the owners to change diets?	OCD is a highly hereditary disease. The breeder should be counseled on selective breeding to reduce the incidence of this genetic disease in their dogs. To decrease the occurrence of OCD in animals at risk, feed an appropriate diet formulated for the dog's lifestage and breed. When both quality and quantity of the daily food is optimal, there is no reason to change diets.
What can I recommend to my clients with young dogs which are likely to develop hip dysplasia besides preventative surgery?	Research has shown that diet has both quantitatively and qualitatively, a significant effect on the development of HD. Owners of puppies at risk for HD should feed a high quality diet that has adequate energy and calcium for that breed and age; avoid energy and/or calcium and mineral excesses. The amount of food consumed should be limited to meet the energy requirements of the puppy and nothing more. In addition the training and activity schedules should be tailored to meet the vulnerability of young dogs' skeletons. Surgery might be indicated in certain cases based on strict criteria- joint laxity and conformation - to prevent HD from developing into a clinical disease.

References

Alexander JW - The pathogenesis of canine hip dysplasia. Vet Clin North Am Small Anim Pract 1992; 22: 503-511.

Altman RD, Dean DD, Muniz OE et al - Therapeutic treatment of canine OA with glucosaminoglycan polysulfuric acid ester. Arthritis Rheum 1989; 32(10): 1300-7.

Audell L - Hereditary of elbow dysplasia: can elbow dysplasia be controlled by judicious breeding? In Proceedings of the 57th meeting of Amer Anim Hosp Assoc Meeting 1990: 730-733.

Bardet JF- Arthroscopy of the elbow joint to diagnose and treat FCP and OCD in dogs Meeting Int Elbow Working Group 2002; Granada, Spain (www.iewg-vet.org).

Bassleer C, Rovati L, Franchimont P - Stimulation of proteoglycan production by glucosamine sulfate in chondrocytes isolated from human osteoarthritic articular cartilage in vitro. Osteoarthritis Cartilage 1998; 6(6): 427-34.

Bauer JE -The potential for dietary polyunsaturated fatty acids in domestic animals. Aust Vet Journ 1994; 71: 342-345.

Beale BS - Use of nutraceuticals and chondroprotectants in osteoarthritic dogs and cats. Vet Clin North Am Small Anim Pract 2004; 34: 271-289.

Belfield WO - Chronic subclinical scurvy and canine hip dysplasia. Vet Med Small Anim Clin 1976; 71(10):1399-1403.

Bienz HA - Klinsche und Radiologische Untersuchungen über den Fragmentierten Processus Coronoideus Medialis Im Ellenbogengelenk des Berner Sennenhundes und der andere Sennenhunde Rassen. Inaug Dissertation Zürich (Switzerland), 1985.

Bierer TL, Bui LM - Improvement of arthritic signs in dogs fed green-lipped mussel (Perna canaliculus). J Nutr 2002; 132, 6(Suppl 2): 1634S-1636S.

Boyan BD, Sylvia VL, Dean DD et al - 24,25 $(OH)_2D_3$ regulates cartilage and bone via autocrine and endocrine mechanisms. Steroids 2001; 66: 363-374.

Bui LM, Bierer TL - The influence of green lipped mussels (Perna canaliculus). Vet Ther 2001; 2: 101-111.

Bui LM, Taylor F - Nutritional management of arthritis in dogs. Waltham Focus- Advances in clinical nutrition 2000; 10: 64-69.

Canapp SO Jr, McLaughlin RM Jr, Hoskinson JJ et al - Scintigraphic evaluation of dogs with acute synovitis after treatment with glucosamine hydrochloride and chondroitin sulfate. Am J Vet Res 1999; 60(12): 1552-7.

Ching SV, Fettman MJ, Hamar DW et al - The effect of chronic dietary acidification using ammonium chloride on acid-base and mineral metabolism in the adult cat. J Nutr 1989; 119: 902-915.

Conrozier T - Anti-arthrosis treatments: efficacy and tolerance of chondroitin sulfates (CS 4&6)] Presse Med 1998; 21, 27(36):1862-5.

Corley EA - Role of orthopedic foundation for animals in the control of canine hip dysplasia. Vet Clin North Am Small Anim Pract 1992: 22: 579-593.

Curtis HL, Hughes CE, Flannery CR et al - n-3 fatty acids specifically modulate catabolic factors involved in articular cartilage degradation. J Biol Chem 2000; 275 (2): 721-724.

Curtis CL, Rees SG, Cramp J et al - Effects of n-3 fatty acids on cartilage metabolism. Proc Nutr Soc 2002; 61 (3): 381-389.

De Haan JJ, Goring RL, Beale BS - Controlled double-blinded clinical study of polysulfated GAGs (Adequan) for treatment of hip dysplasia in adult dogs. Vet Comp Orthop Traum.1994; 7: 58.

Edney ATB, Smith PB - Study of obesity in dogs visiting veterinary practices in the United Kingdom. Vet Rec 1986; 118: 391-6.

Fox SM, Burns J, Burt J - Canine hip dysplasia. Veterinary Medicine: Small Animal Clinic 1987; 82: 683-693.

Fraser DR - Regulation of the metabolism of vitamin D. Physiological Reviews 1980; 60: 551-613.

Gershoff SN, Legg MA, Hegsted DM - Adaptation to different calcium intakes in dogs. J Nutr 1958; 64: 303-312.

Goedegebuure SA, Hazewinkel HAW - Nutrition and bone metabolism. Tijdschr Diergeneesk 1981; 106: 234-242.

Greenwald RA - Oxygen radicals, inflammation and arthritis: pathophysiological considerations and implications for treatment. Rheum 1991; 20: 219-240.

Grøndalen J, Hedhammar Å - Nutrition of the rapidly growing dog with special reference to skeletal disease. In: Nutrition and Behaviour in dogs and cats (1982); Anderson RS Ed, Pergamon Press: 81-88.

Hansen ES, Fogh K, Hjortdal VE et al - Synovitis reduced by inhibition of leukotriene B4. Carrageenan-induced gonarthritis studied in dogs. Acta Orthop Scand 1990; 61: 207-212.

Hazewinkel HAW - Diagnosis and conservative treatment of hip dysplasia in young dogs. Tijdschrift voor Diergeneeeskunde 1992; S117: 33-34.

Hazewinkel HAW - Nutrition in orthopedics. In: Disease Mechanisms in Small Animal Surgery (1993); Bojrab MS ed (2nd ed), Philadelphia (USA). Lea & Febiger: 1117-1128.

Hazewinkel HAW, Goedegebuure SA, Poulos PW et al -Influences of chronic calcium excess on the skeletal development of growing Great Danes. J Am Anim Hosp Assoc 1985; 21: 337-391.

Hazewinkel HAW, Hackeng,WHL, Bosch R et al - Influences of different calcium intakes on calciotropic hormones and skeletal development in young growing dogs. Front Horm Res 1987a; 17: 221-232.

Hazewinkel HAW, How KL, Bosch R et al - Inadequate photosynthesis of vitamin D in dogs. In: Nutrition, malnutrition and dietetics in the dog and cat (1987b); Edney ATB Ed, Waltham Centre Press: 66-68.

Hazewinkel HAW, Kantor A, Meij BP - Fragmented coronoid process and osteochondritis dissecans of the medial humeral condyle. Tijdschrift Diergeneesk 1988; 113: 41S-47S.

Hazewinkel HAW, Kantor A, Meij BP (b) - Loose anconeal process. Tijdschrift voor Diergeneesk 1988; 113: 47S-49S.

Hazewinkel HAW, Kealy RD, Mol JA et al - Change in GH-IGF-1 axis in obese dogs with possible consequences for osteoarthritis. Comp Cont Ed Pract Vet 1999; 21: 51-51.

Hazewinkel HAW, Meij BP, Nap RC et al - Radiographic views for elbow dysplasia screening in Bernese Mountain Dogs. Annual Meeting International Elbow Working Group, Constance (Germany) 1995, 29-32.

Hazewinkel HAW, Nap RC, Schoenmakers I et al - Dietary influence on development of enostosis in young dogs Vet Surg 2000; 29 (3): 279.

Hazewinkel HAW, Theyse LFH, Wolvekamp WTh et al - The influence of dietary omega-6: Omega -3 ratio on lameness in dogs with osteoarthrosis of the elbow joint in: 1998 Iams Nutrition Symposium Proceedings, Recent Advances in Canine and Feline Nutrition vol II (ed G.A. Reinhart & D.P. Carey)

Orange Frazer Press, Wilmington (OH), 1998: 325-336.

Hazewinkel HAW, Tryfonidou MA - Vitamin D3 metabolism in dogs. Molecular and cellular endocrinology 2002; 197: 23-33.

Hazewinkel HAW, Van den Brom WE, Van 't Klooster ATh et al - Calcium metabolism in Great Dane dogs fed diets with various calcium and phosphorus levels. J Nutr 1991; 112: S99-S106

Hazewinkel HAW, Van den Brom WE, Theijse LFH et al -. Reduced dosage of ketoprofen for the short-term and long-term treatment of joint pain in dogs. Vet Rec 2003; 152: 11-14.

Hedhammar A, Krook L, Schryver H et al - Calcium balance in the dog. In: Nutrition of the dog and cat (1980); Anderson A Ed, Pergamon Press (Oxford): 119-127.

Hedhammar A, Wu F, Krook L et al - Overnutrition and skeletal disease; an experimental study in growing Great Dane dogs. Cornell Vet 1974; 64 (Suppl 5), 1: 59.

Herlin T, Fogh K, Hansen ES et al - 15-HETE inhibits leukotriene B_4 formation and synovial cell proliferation in experimental arthritis. Agents Actions 1990; 29: 52-3.

Heyman SJ, Smith GK, Cofone MA - Biomechanical study of the effect of coxofemoral positioning on passive hip joint laxity in dogs. Am J Vet Res 1993; 54: 210-215.

Hulse D -. Treatment methods for pain in the osteoarthritic patient. Vet Clin North Am Small Anim Pract 1998; 28(2): 361-75.

Impellizeri JA, Tetrick MA, Muir P - Effect of weight reduction on clinical signs of lameness in dog with hip osteoarthritis. J Am Vet Med Assoc 2000; 216: 1089-1091.

Johnson JA, Austin C, Breur GJ - Incidence of canine appendicular musculoskeletal disorders in 16 veterinary teaching hospitals from 1980-1989. Vet Comp Ortho Trauma 1994; 7: 56-69.

Johnson KA, Hulse DA, Hart RC et al - Effects of an orally administered mixture of chondroitin sulphate, glucosamine hydrochloride and manganese ascorbate on synovial fluid chondroitin sulphate $3B_3$ and $7D_4$ epitope in a canine cruciate ligament transaction model of OA. Osteoarthritis Cartilage 2001; 9: 14-21.

Kallfelz FA, Dzanis DA - Overnutrition: an epidemic problem in pet animal practice? North Am Small Anim Pract 1989; SAP, 19: 433-446.

Kasstrøm H - Nutrition, weight gain and development of hip dysplasia. Acta Radiol 1975; Suppl 344: 135.

Kealy RD, Lawler DF, Ballam JM et al - Five-year longitudinal study on limited food consumption and development of osteoarthritis in coxofemoral joints of dogs. J Am Vet Med Assoc 1997; 210: 222-225.

Kealy RD, Lawler DF, Ballam JM et al - Evaluation of the effect of limited food consumption on radiographic evidence of osteoarthritis in dogs. J Am Vet Med Assoc 2000; 217: 1678-80.

Kealy RD, Lawler DF. Monti KL et al - Effects of dietary electrolyte balance on subluxation of the femoral heads in growing dogs. Am J Vet Res 1993; 54: 555-562.

Kealy RD, Olsson SE, Monti KL et al - Effects of limited food consumption on the incidence of hip dysplasia in growing dogs. J Am Vet Med Assoc 1992; 201: 857-863.

Krook L, Lutwak L, Henrikson F et al - Reversibility of nutritional osteoporosis; physicochemical data on bones from an experimental study in dogs. J Nutr 1971; 101: 233-246.

Kurz B, Jost B, Schunke M - Dietary vitamins and selenium diminish the development of mechanically induced osteoarthritis and increase the expression of antioxydant enzymes in the knee joint of mice. Osteoarthritis Cartilage 2002; 10: 119-126.

Lafond E, Breur GJ, Austin CC - Breed susceptibility for developmental orthopedic diseases in dogs. J Am Anim Hosp Assoc 2002; 38(5): 467-77.

Lavelle RB - The effect of the overfeeding of a balanced complete commercial diet to a young group of Great Danes. In: Nutrition of the dog and cat (1989); Burger IH & Rivers JPW Ed, Cambridge Univ Press: 303-315.

Lemann J, Lennon EJ - Role of diet, gastrointestinal tract and bone in acid-base homeostasis. Kidney Int 1972; 1: 275-27.

Meij BP, Geertsen KMK, Hazewinkel HAW - Results of FCP treatment in Retrievers: a follow-up study at the Utrecht Universtity Small Animal Clinic. Veterinary and Comparative Orthopaedics and Traumatology 1996; 9(2): 64-65.

Meyer-Lindenberg A, Staszyk C, Gasse H et al - Caudomedial approach for removal of an ununited anconeal process and assessment of the medial coronoid process of the ulna. J Vet. Med 2002 A. 49, 277-280.

Meyer-Lindenberg A, Fehr M, Nolte I.Der isolierte Processus anconeus des Hundes-Vorkommen, Behandlung und Ergebnisse. Kleintierpraxis 1991; 36, 671-679.

Meyer H, Zentek J - Energy requirements of growing Great Danes. J Nutr 1991; 121: S35-S36.

Milton JL -. Osteochondritis dissecans in the dog. Vet Clin North Am Small Anim Pract 1983; 13: 117-134.

Moreau M, Dupuis J, Bonneau NH et al - Clinical evaluation of a neutraceutical, carprofen and meloxicam for the treatment of dogs with osteoarthritis Vet Rec 2003; 152: 323-329.

Morgan JP, Wind A, Davidson AP - Hereditary bone and joint diseases in the dog. Schlütersche Verlag, Hannover, 2000.

Nap RC - Nutritional influences on growth and skeletal development in the dog. Thesis University Utrecht 1993: 1-144.

Nap RC, Hazewinkel HAW, Van den Brom WE - Ca^{45} kinetics in growing miniature Poodles challenged by four different levels of calcium. J Nutr 1993; 123:1826-1833.

Nap RC, Hazewinkel HAW, Voorhout G et al - Growth and skeletal development in Great Dane pups fed different levels of protein intake. J Nutr 1991; 121: S107-113.

National Research Concil of the National Academies (NRC) - Nutrient requirements of dogs (1974). The National Academies Press, Washington D.C.

National Research Council of the National Academies – Nutrient requirements of dogs and cats (2006 in press). The National Academies Press, Washington D.C.

Nunez EA, Hedhammar A,Wu FM et al - Ultrastructure of the parafollicular (C-)cells and the parathyroid cells in growing dogs on a high calcium diet. Lab Invest 1974: 31: 96-108.

Olsewski JM, Lust GL, Rendano VT et al - Degenerative joint disease: multiple joint involvement in young and mature dogs. Am J Vet Res 1983; 44: 1300-1308.

Olsson SE - Pathophysiology, morphology, and clinical signs of osteochondrosis in the dog. In: Disease Mechanisms in Small Animal Surgery 1993; Bojrab MS Ed, Philadelphia (USA). Lea & Febiger: 777-796.

Patronek GJ, Waters DJ, Glickman LT - Comparative longevity of pet dogs and humans: implications for gerontology research. J Gerontol A Biol Sci Med Sci 1997, 52; B171-178.

Piermattei D, Greely RG -An atlas of surgical approaches to the bones of the dog and cat (1979); Philadelphia (USA), Saunders WB Comp.

Read RA, Armstrong SJ, Black AP et al - Relationship between physical signs of elbow dysplasia and radiography score in growing Rottweilers. J Am Vet Med Assoc 1996; 209: 1427-1430.

Reginster JY, Deroisy R, Rovati LC et al - Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet 2001; 357: 251-256.

Remy D, Neuhart L, Fau D et al - Canine elbow dysplasia and primary lesions in German shepherd dogs in France. J Small Anim Pract 2004; 45: 244-248.

Richardson DC, Toll PW - Relationship of nutrition to developmental skeletal disease in young dogs. Vet Clin Nutr 1997; 4: 6-13.

Riser WH, Shirer JF - Radiographic differential diagnosis of skeletal diseases of young dogs. J Am Vet Radiol Soc 1964; 5: 15-27.

Roy RG - A retrospective long-term evaluation of ununited anconeal process excision on the canine elbow. Vet Comp Orthop Traumat 1979; 7: 94-97.

Royal Canin - The growth of large breed and giant breed puppies. Latest nutritional breakthroughs. Aniwa publishing (Ed); 2004: 19.

Schoenmakers I, Hazewinkel HAW, Voorhout G et al - Effect of diets with different calcium and phosphorus contents on the skeletal development and blood chemistry of growing great danes. Vet Rec 2000; 147: 652-660.

Setnikar I, Giachettti C, Zanolo G - Pharmacokinetics of glucosamine in the dog and man. Arzneimittel-Forschung 1986; 36: 729-735.

Setnikar I, Pacinic MA, Revel L - Antiarthritic effects of glucosamine sulphate studied on animal models. Arzneimittel-Forschung 1991; 41: 542-545.

Sjöström L, Käsström H, Källberg M - Ununited anconeal process in the dog. Pathogenesis and treatment by osteotomy of the ulna. Vet Comp Orthop Traumat 1995; 8: 170-176.

Slater MR, Scarlett JM, Kaderley RE et al - Breed, gender and age as risk factors for canine osteochondritis dissecans. Vet Comp Ortho Trauma1991; 4: 100-106.

Slocum B, Slocum TD - Pelvic osteotomy for axial rotation of the acetabular segment in dogs with hip dysplasia. Vet Clin North Am Small Anim Pract 1992; 22: 5-682.

Slocumb B, Devine T - Pelvic osteotomy in: Canine orthopedics 2nd ed., Whittick WG ed. Philadelphia, Lea & Febiger, 1990 : 471-480.

Smith GK, Biery DN, Gregor TP - New concepts of coxofemoral stability and the development of a clinical stress-radiographic method for quantitating hip joint laxity in the dog. J Am Vet Med Assoc 1990; 196: 59-70.

Smith GK, Mathew PD, Kapatkin AS et al - Evaluation of risk factors for degenerative joint disease associated with hip dysplasia in German Shepherd Dogs, Golden Retrievers, Labrador Retrievers, and Rottweilers. J Am Vet Med Assoc 2001; 219(12): 1719-24.

Swenson L , Audell L, Hedhammar A - Prevalence and inheritance of and selection for elbow arthrosis in Bernese Mountain Dogs and Rottweilers in Sweden and benefit:cost analysis of a screening and control programme. J Am Vet Med Assoc 1997; 210: 215-221.

Tryfonidou MA, Oosterlaken-Dijksterhuis MA, Mol JA et al - 24-hydroxylase: potential key regulator in hypervitaminosis D_3 in growing dogs. Am J Physiol-Endocrinol Metab 2003a; 284: E505-E513.

Tryfonidou MA, Stevenhagen JJ, Buurman CJ et al - Dietary 135-fold cholecalciferol supplementation severely disturbs the endochondral ossification in growing dogs. Domest Anim Endocrinol 2003b; 24(4): 265-85.

Tryfonidou MA, Van den Broek J, Van den Brom WE et al - Intestinal calcium absorption in growing dogs is influenced by calcium intake and age but not by growth rate. J Nutr 2002; 132: 3363-3368.

Tvedten HW, Carrig CB, Flo GL - Incidence of hip dysplasia in Beagle dogs fed different amounts of protein and carbohydrate. J Am Anim Hosp Assoc 1977; 13: S95-98.

Ubbink GJ, Hazewinkel HAW, Wolvekamp WTC et al - Preliminary results of the genetic analysis of the ED (elbow dysplasia) program of the Dutch seeing eyes dog. VCOT 1998; 11: 76-79.

Van Bilsen JH, Wagenaar-Hilbers JP, Boot EP et al -Searching for the cartilage-associated mimicry epitope in adjuvant arthritis. Autoimmunity 2002; 35(3): 201-10.

Van Bree HJJ - Positive shoulder arthrography in the dog: the application in osteochondrosis lesions compared with other diagnostic imaging techniques. Thesis University Utrecht 1991: 1-173.

Voorhout G, Hazewinkel HAW - A radiographic study on the development of the antebrachium in Great Dane pups on different calcium intakes. Vet Radiol 1987a; 28: 152-157.

Voorhout G, Hazewinkel HAW - Radiographic evaluation of the canine elbow joint with special reference to the medial humeral condyle and the medial coronoid process. Vet Radiol 1987b; 28(5): 158-165.

Weber M, Martin L, Dumon H - Growth and skeletal development in two large breeds fed 2 calcium levels. J Vet Intern Med 2000; 388.

Wind AP - Elbow incongruity and developmental elbow diseases in the dog; part 2. J.Am Anim Hosp Assoc 1986; 22: 711-724.93)

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The growth phase of large-breed and giant-breed puppies is an important period: the puppy multiplies its birth weight eighty to a hundredfold in less than 2 years and most bone growth occurs in the first few months.

Key Points
to remember:

Role of nutrition in osteoarticular diseases

• The daily weight gain is at a maximum between 3 and 5 months of age in a large-breed puppy, although it does continue to be rapid until 8 months. It is advisable to closely monitor the puppy's weight development, which must not exceed 50% of estimated adult weight at 5 months of age. If it does, the ration will have to be reduced and/or a less energy dense diet will have to be chosen. There is a significant correlation between energy overconsumption and a heightened incidence of osteoarticular complaints.

• Before 6 months a puppy is unable to protect itself from calcium excess: it passively absorbs at least 50% of the calcium ingested. The calcium content in the food can be compared on the basis of its energy density. The quantity of calcium consumed per kg of body weight is the only reliable value. There is no ideal calcium content for a given age, but there is a safety zone: at 5 months the optimal calcium content for a large-breed puppy is 210-540 mg/kg/day. Excess calcium is a factor that promotes osteochondrosis.

• Vitamin supplements should not be prescribed when the puppy consumes a complete food for growth. An excess of vitamin D does not promote skeletal growth, but increases bone resorption and leads to severe cartilage maturation abnormalities with a heightened risk of osteochondrosis.

• Glucosamine and chondroitin belong to the family of glycosaminoglycans (GAG), which are natural cartilage components. After oral administration these molecules concentrate in the synovial fluid. Their role is to promote regeneration and to curb enzymatic degradation of the cartilage. Glucosamine and chondroitin participate in maintaining the cartilage's water absorption capacity, an essential requirement to fulfill its role in shock absorption.

• Green-lipped mussel extract (GLM) exhibits interesting properties within the framework of prevention and treatment of arthrosis.

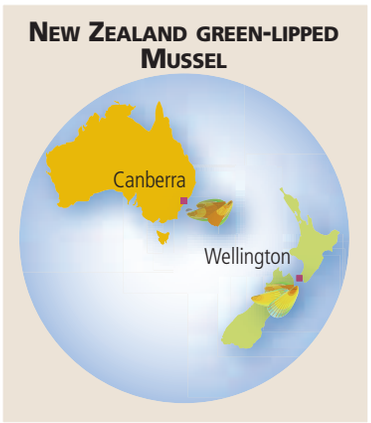
It helps limit inflammation, preserve the integrity of the cartilage and combat oxidative lesions.

The effects appear to be due to synergy between the different components of GLM including GAGs, omega 3 fatty acids, glutamine, antioxidants and trace elements. Several clinical studies show a reduction in pain and an improvement in joint mobility in arthritic dogs during administration of GLM.

Omega-3 fatty acid supplementation causes a decrease in degradative aspects of chondrocyte metabolism, which may have a beneficial effect in degenerative joint diseases.

Focus on:

GREEN LIPPED MUSSEL EXTRACT (GLM)



Origin and composition

The GLM powder used by Royal Canin is an extract of Perna Canaliculi or New Zealand green lipped mussel. It is obtained from the mussel's flesh in a procedure carried out at low temperature (< 30°C) to protect the quality of the components.

The Royal Melbourne Institute of Technology University (RMIT University) in Australia has been studying the lipidic fraction of Perna Canaliculi for 15 years to isolate the fatty acids. Eight to ten different sterols of marine origin are present, as well as at least 10 different essential fatty acids.

GLM is a concentrated source of omega 3 fatty acids, which inhibit some inflammatory mediators. Omega 6 fatty acids account for 5.2% of the polyunsaturated fatty acids (PUFA) and omega 3 fatty acids 41%. The omega 6/omega 3 ratio is therefore 0.1. The two main PUFA of the long-chain omega 3 series are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which account for 35% of the PUFA.

The mussels harvested along the New Zealand coast benefit from a permanently renewed supply of marine nutrients brought by ocean currents. The mussels act as a seawater sieve, tending to retain essential nutrients. That is why GLM contains a large number of substances that are potentially active in the fight against arthritis:

- **Glycosaminoglycans (GAG) (e.g. chondroitin)**

Natural components of cartilage and synovial fluid that participate in the lubrication of joints and preserve the integrity of cartilage.

- **Eicosatetraenoic acid (ETA)**

Omega 3 fatty acid exclusively found in GLM, which is able to inhibit the cascade of metabolites with inflammatory properties derived from arachidonic acid.

COMPOSITION OF GLM POWDER:	
Moisture	6.1%
Protein	40.7%
Fats	10.7 % including: PUFA: 47%
Minerals	16.1% including: - Calcium: 0.98% - Phosphorus: 0.62% - Sodium: 3.5%

- **Glutamine (amino acid)**

Glutamine is a precursor of glucosamine (GAG)

- **Antioxidants (vitamins E and C)**

These vitamins play a role in combating oxidative stress caused by free radicals.

Epidemiological Basis

The mussels of New Zealand were traditionally an integral part of the coastal Maori population's basic diet. It has been known for a long time that there were more cases of arthrosis among the island's interior population than among the coastal population, which had been consuming fresh, raw mussels for generations.

In 1970 American researchers started studying the question and the anti-inflammatory properties of the mussel were soon revealed. It also became clear that the conditions under which the mussel's flesh was harvested and transformed were critical. The lipidic fraction is highly sensitive to oxidation, so extreme precautions are necessary to preserve the therapeutic qualities.

The New Zealand green lipped mussel is now widely used throughout the world.

References

Couch RA, Ormrod DJ, Miller TE et al - Anti-inflammatory activity in fractionated extracts of the green-lipped mussel. N Z Med J 1982; 95(720): 803-6.

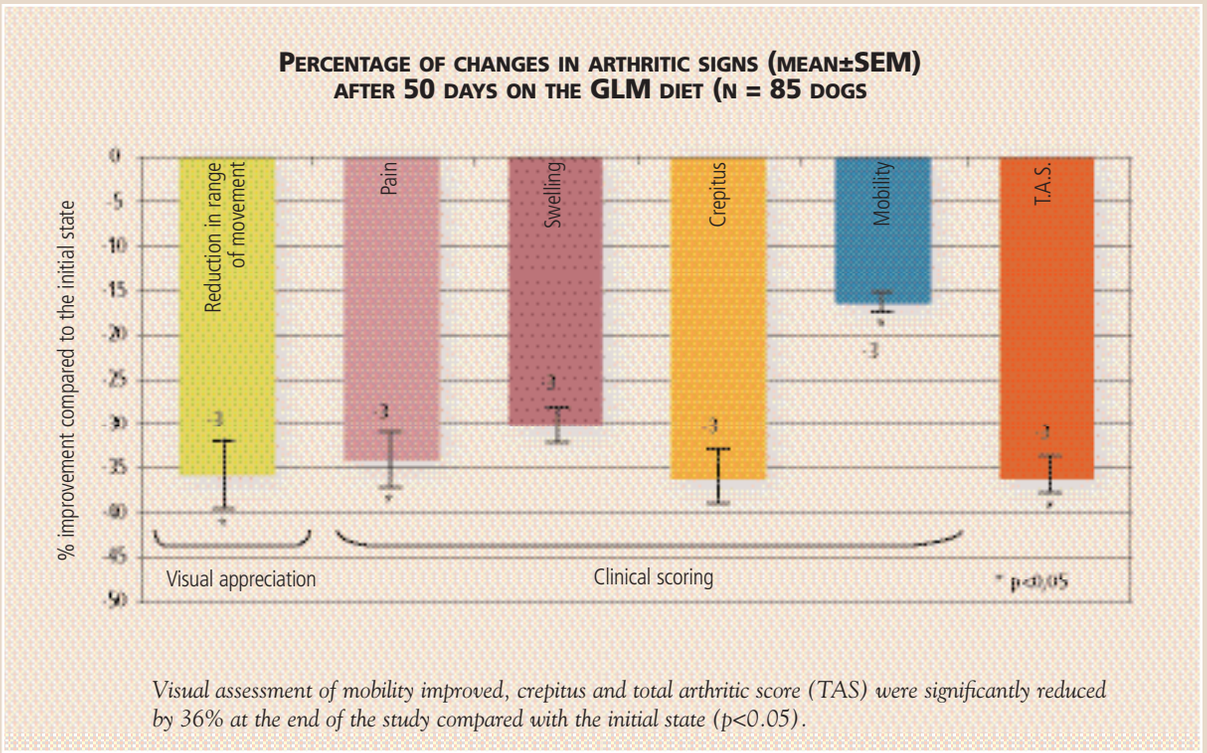
Miller TE, Ormrod D - The anti-inflammatory activity of Perna canaliculus (NZ green lipped mussel). N Z Med J 1980; 92(667): 187-93.

Multicentric trial

Royal Canin recently conducted a study to validate, in field conditions, the efficacy of a GLM-supplemented diet in osteoarthritic dogs.

85 clinically-confirmed arthritic and privately owned adult dogs, seen at 25 veterinary clinics, completed the multicenter trial. All sizes of dog were represented: 7 giant (>45kg), 46 large (26-45kg), 20 medium (11-25kg) and 12 small (<10kg) breed dogs. The dogs did not suffer from any other disease and were not overweight.

Dogs were fed the GLM diet for 50 days. Evaluation of osteoarthritic signs were carried out at day 0 (baseline) and at day 50 by veterinarians. All parameters were scored from 0 to 3 (0: no sign; 1: slight ; 2: moderate; 3: severe). An initial score was given for the dog's general mobility during walking, trotting and climbing steps. Individual joints of each limb were clinically scored for degree of pain, swelling, crepitus and reduction in range of movement. Summation of the previous scores provided a Total Arthritic Score (T.A.S.) for each dog. Statistical comparisons between the initial and final arthritic states were made using a repeated-measure ANOVA Test.



Visual assessment of mobility improved, crepitus and total arthritic score (TAS) were significantly reduced by 36% at the end of the study compared with the initial state ($p<0.05$).

Reference

Servet E, Marniquet P, Biourge V - Dietary intervention can improve clinical signs in osteoarthritic dogs. Proceedings of Waltham International Nutritional Sciences Symposium, Washington 2005; Innovations in Companion Animal Nutrition: 41.

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Canine nutrition and oral health

1 - Anatomy and physiology 413
2 - Periodontal disease and oral hygiene 415
3 - Role of food in oral hygiene 418

References 421
Royal Canin Nutritional Information 422

Canine nutrition and oral health

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A graduate of the National Veterinary School of Toulouse in 1988, Philippe Hennet conducted a research project in canine endodontics with the dental faculty at Toulouse in 1987-1989, which led to a veterinary doctoral thesis in 1990. He continued his research as part of a clinical residency at the Dentistry Section of the University of Pennsylvania Veterinary School at Philadelphia in 1990-1992. Philippe now specializes in oral and ENT diseases at his practice in Paris. He has been a dentistry assistant at the National Veterinary School of Alfort since 1993. He has also been the scientific co-organizer of the dentistry course at the European School for Advanced Veterinary Studies (ESAVS) in Luxembourg since 1995. A diplomate of the American Veterinary Dentistry College (AVDC) since 1993, and of the European Veterinary Dentistry College (EVDC) since 1998, he is the author of many publications in English and in French.

Periodontal disease is the most common disease of the oral cavity in dogs. Every dog is affected during its life to some degree. Curiously, compared with other diseases it's often neglected, although it can be treated or even prevented with care. In oral hygiene, the benefit of any therapeutic intervention is of short duration if it isn't prolonged with daily care by the owner.

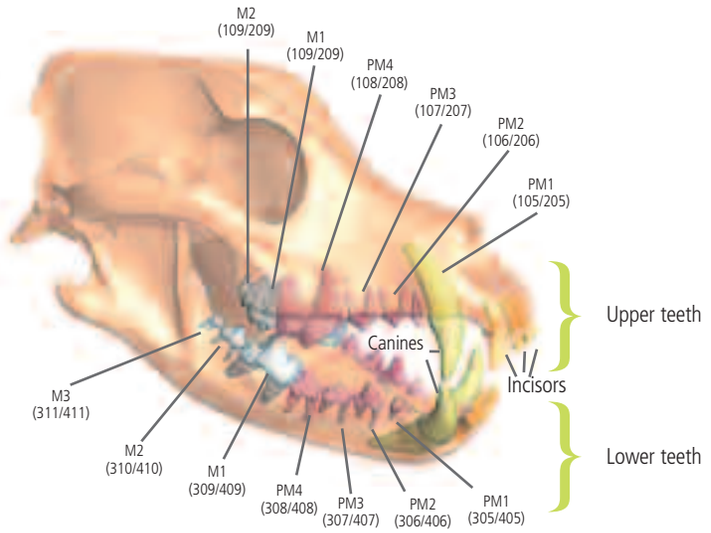
The aim of this care is to fight dental plaque. While brushing is accepted as the most effective means of protection, there are alternatives – both physical and chemical – to help control plaque.

1 - Anatomy and physiology

► Teeth

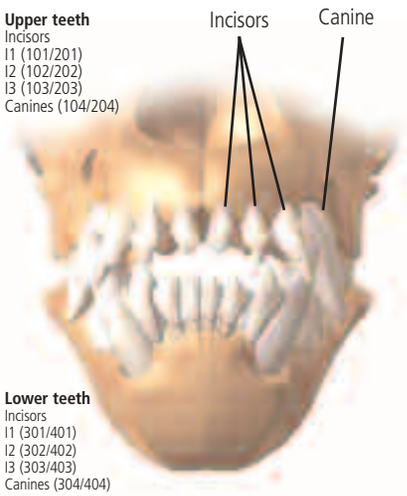
(Figures 1 and 2)

Figure 1 - Lateral view of the denture of the dog



The adult dog has 42 teeth. The dental formula by demi-jaw is: I 3/3; C 1/1; PM 4/4; M 2/3.

Figure 2 - Frontal view of the denture of the dog



The incisors, which are much larger in the upper jaw, are (from the middle of the denture): frontal, central and corner incisors.

The first primitive mammals that appeared 250 million years ago during the Mesozoic era already possessed two hemi-mandibles connected ventrally by a symphysis and joined to the squamosal's glenoid cavity by a condyle (temporomandibular articulation). The enamel-covered teeth were divided into cutting incisors, rounded canines and grinding or hacking molars, implanted in the alveolar borders of the maxilla and the mandible. Present-day mammals retain these essential anatomical characteristics, with modifications depending on diet *(Lavergne et al, 1996)*.

The carnivores are diphyodonts (having two successive sets of teeth, deciduous and permanent) and heterodonts (having different types of teeth with different functions). The incisors – prehensile cutters that number three per hemi-jaw – only have one root. The conical canines are tearing teeth adapted to the diet of a carnivore.

The premolars have two roots, with the exception of the first premolar, which is regressive and has a crown formed by three cusps in a line. There is alternate occlusion of the crowns of the maxillary and mandibular premolars with the necessity of diastema between the teeth.

Occlusion of permanent teeth in dogs
Note the regular alternation of maxillary and mandibular premolars: the main cuspid of maxillary premolars is lodged in the middle of the interdental space of the two mandibular premolars. The mandibular canine is lodged in the corner maxillary canine interdental space, thus forming a powerful triad. In mesocephalic and dolichocephalic dogs, and in certain brachycephalic dogs, the incisors have a scissor bite (the cuspid of the mandibular incisors in contact with the cingulum of the maxillary incisors).

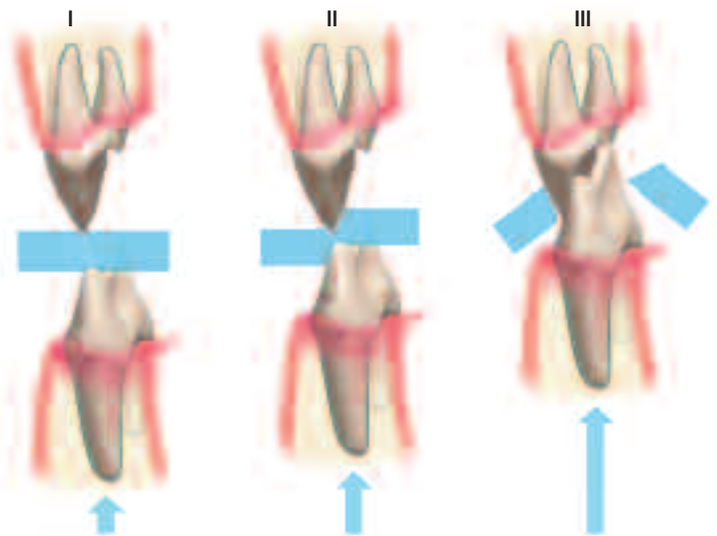
► Jaws

In the carnivore specialization, temporomandibular articulation is located in the extension of the occlusal plane. It consists of a deep transversally-oriented, hemi-cylindrical mandibular fossa, bordered ventrally by a powerful retro-articular process into which an elongated mandibular condyle fits transversally. This mechanism principally permits the raising and lowering of the mandible as well as the lateral movements in dogs that are essential for ripping through prey *(Lafond, 1929 ; Gaspard, 1967)*.

► Physiology of manducation

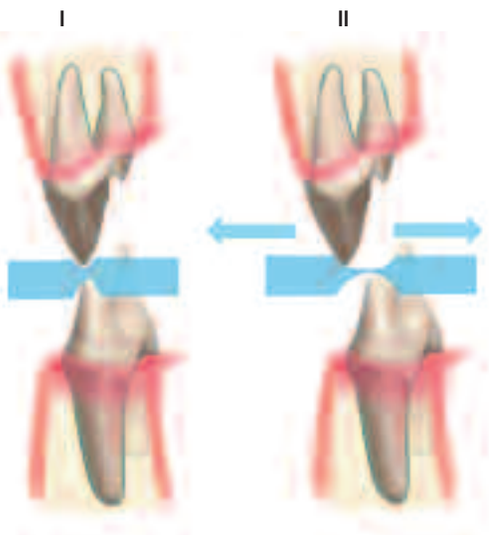
The term manducation designates all the actions involved in eating, including prehension, mastication, insalivation and deglutition *(Verchère et al, 1992)*. Contrary to humans, carnivores do not chew their food. They divide them into scraps that are not completely crushed and scarcely insalivated, but that are quickly swallowed. Manducation principally consists in breaking up large pieces of food. In the wild, the canids capture their prey with their powerful canines. The incisors serve to cut and tear large pieces, which are then introduced deeper into the oral cavity. This action may be supplemented with jerks of the head driven by the muscles in the nape. The piece of food – a muscle mass for instance – is cut by the scissors formed by the cuspids of the mandibular and maxillary carnassials **(Figure 3)**. To enable this, the vestibular surface of the mandibular carnassials must come into contact with the lingual surface of the upper carnassials through an opening of the symphysis and an external torsion of the mandibular body *(Gaspard, 1967)*.

FIGURE 3 - CUTTING EFFORT
(From Gaspard, 1967)



Mandibular biomechanics allow an alignment of the cuspids of the mandibular and maxillary carnassials (I), to exercise a shear force (II) that breaks the food when the mouth is closed (III).

FIGURE 4 - BREAK BY EXTENSION
(From Gaspard, 1967)



Snagged by the cuspids of the carnassials, the food is elongated by a lateral movement that results in its breaking.

Only one mandibular branch works at any one time *(Lafond, 1929)*. When the piece is soft and less voluminous the canid can lock its jaws without bringing its carnassials together. This is also what happens when it works simultaneously with the two hemi-mandibles. Here the piece breaks due to an extension associated with shearing. The deformation is accompanied by lateral movements. Carnivores rip the elastic body and tear the fibrous tissues by laceration, which consists of violently moving the mandibular teeth across the maxillary teeth. The food is violently stretched, which results in it breaking at the point of least resistance **(Figure 4)**.

When faced with a long, rigid body like a bone, the canid immobilizes it between its forepaws by pressing one extremity against the ground and energetically seizing the other extremity in its mouth. It then revolves its head from one side to the other to subject the body to flexion and torsion. The body ultimately breaks at the point of the carnassials. Thus, the body is squeezed then crushed between the first upper molar and the crushing talon cusp of the lower carnassial. These food fragmentation techniques and the major forces developed explain the powerful chewing muscles that allow carnivores to lock their jaws.

2 - Periodontal disease and oral hygiene

Unlike in humans, dental caries is very rare in dogs. A study of 435 dogs presented at a practice specialized in veterinary dentistry reported that only 23 dogs (5.3%) presented with caries *(Hale, 1998)*. The most common oral malady in dogs is periodontal disease, and most of this chapter is devoted to it.

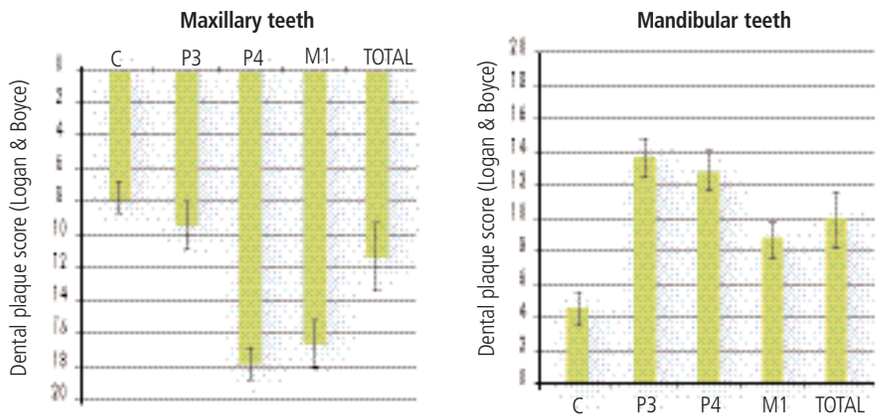
► Periodontal disease

Periodontal disease is the result of a fight at tissue level (periodontium = gingiva, alveolar bone, periodontal ligament and cementum) between bacteria that accumulate on the dental crowns (bacterial dental plaque) and the individual's defense system **(Figure 5)**.

> Epidemiology

Periodontal disease affects every dog in the course of its life, although prevalence varies depending on the breed and the individual. The accumulation of bacterial dental plaque on the dental crowns along the gingiva leads to an inflammatory reaction in this gingiva known as gingivitis. Traditionally, the external surfaces (vestibular) of the teeth are more severely affected than the internal surfaces (palatines or lingual), and the maxillary teeth are more affected than the mandibular teeth *(Isogai et al, 1989; Rosenberg et al, 1966; Harvey et al, 1994)* **(Figure 6)**.

FIGURE 6 - COMPARISON OF DENTAL PLAQUE ON THE TEETH OF SMALL DOGS *(Hennet et al, 2004)*



Four-month study on 18 small dogs (<10 kg), 1-8 years old.
Dental plaque is generally very common on the fourth premolar and the first upper molar.

• *Influence of the size of the dog*

Small dogs (weighing less than 8 kg) suffer earlier and more severely, particularly on the incisors and the internal surfaces of the teeth *(Harvey et al, 1994)*. The smaller the dog, the greater the volume of the teeth in the jaw. As a result, in the event of periodontitis, the gradual destruction of the alveolar bone along the root may threaten the very solidity of the jaw. It has been shown that the ratio [height of the mandible / height of the first molar] in dogs decreases significantly in conjunction with the size of the dog *(Gioso et al, 2001)* **(Figure 7)**.

The loss of a few millimeters of bone in a Yorkshire Terrier has greater consequences than it has for a large dog. The jaw may become so fragile that fractures occur. In Yorkshire Terriers, oral disease represents the primary reason for veterinarian consultation among all age groups *(Veterinary Medical Data Base, 1979-1999)*.

FIGURE 5 - PERIODONTAL DISEASE

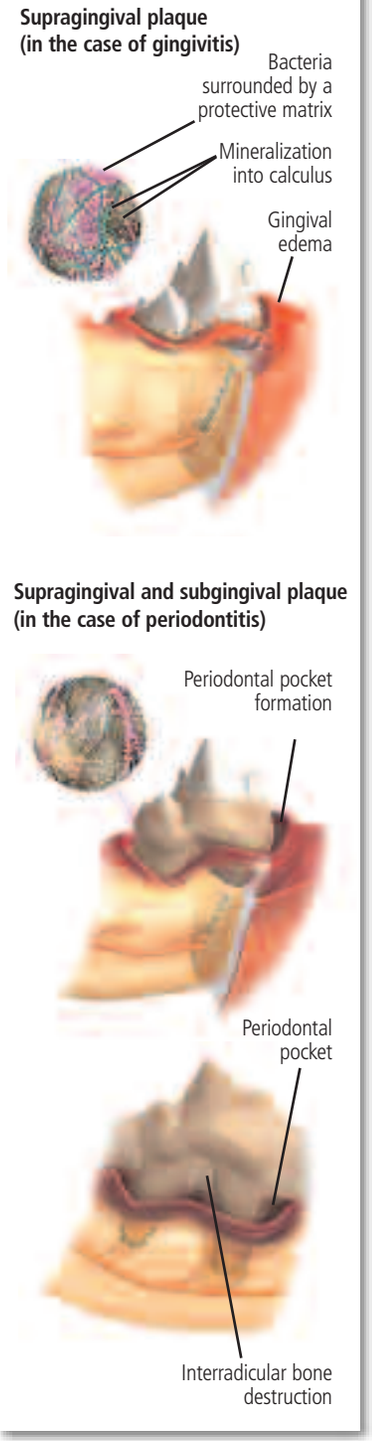
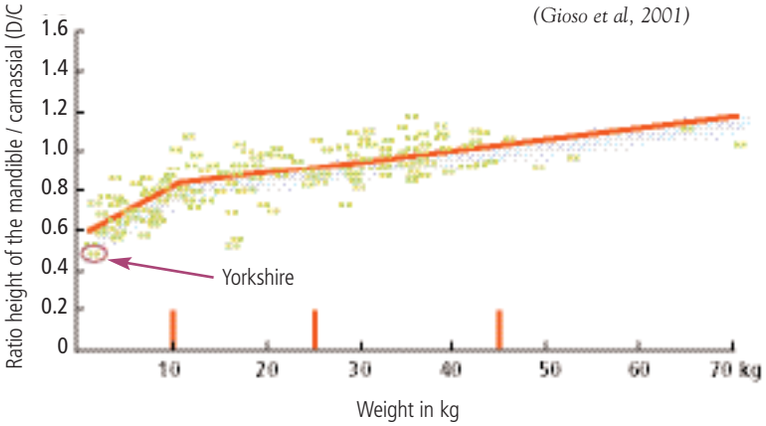


Figure 7 - Relationship between the dog's weight and the ratio "height of the mandible (D)/height of the mandibular carnassial (C)"

(Gioso et al, 2001)

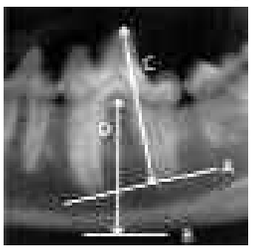


The average D/C ratio of dogs weighing less than 5 kg is 0.64, compared with 1 for dogs weighing more than 30 kg: this means that the height of the mandibular carnassial of a small dog is almost twice that of the height of the jaw itself (Gioso et al, 2001). The record is held by the Yorkshire Terrier, which has a ratio of 0.49.

Dog's weight (kg)	Number of dogs studied	Ratio: height of mandible / height of carnassial (D/C)
< 5.0	33 (14.1%)	0.64 ± 0.019a
5.0-10.0	31 (13.3%)	0.76 ± 0.020b
10.1-20.0	53 (22.7%)	0.87 ± 0.015c
20.1-30.0	45 (19.2%)	0.97 ± 0.016d
> 30.0	72 (30.8%)	1.00 ± 0.013e

Radiograph of the mandibular carnassial of a dog

A = line joining apices of the mandibular carnassial, B = line along mandibular ventral cortex, C = height of the mandibular carnassial, D = height of the mandible

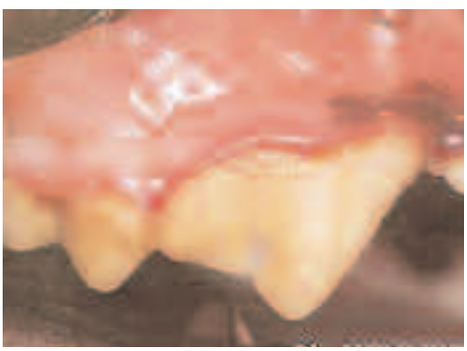


• *Influence of the individual*

The transition from gingivitis to periodontitis is a phenomenon specific to each individual. It depends on limiting the development of infection through oral hygiene and/or the individual's local immune system.

• *Influence of age*

A study has shown that 80% of dogs older than six years of age presented with moderate to severe periodontitis characterized by destruction of bone *(Hamp et al, 1984)*. The supragingival dental plaque is gradually mineralized into calculus by salivary secretions. The calculus may become visible a few weeks after the dental plaque starts to accumulate. In a study of young Beagles, by the age of 26 months, 95% of the dogs presented with a very large accumulation of calculus as well as serious gingival inflammation accompanied by periodontitis *(Rosenberg et al, 1966)*. Periodontal disease is naturally aggravated with age. There is a significant statistical correlation between age and the gingival index (intensity of the inflammation), the calculus index (quantity of calculus), the tooth mobility index and the furcation index (importance of the interradicular bone resorption) *(Harvey et al, 1994)*.



Gingivitis in dogs.
Accumulation of dental plaque with gradual formation of calculus, responsible for inflammation of the gingiva without destruction of deeper-lying tissue.

• *Influence of sex*

No sexual predisposition has been shown in the canine species.

> The causes of the disease

Bacterial dental plaque is a natural bacterial film (biofilm) that develops on the surface of the teeth *(Overman, 2000)* **(Figure 8)**.

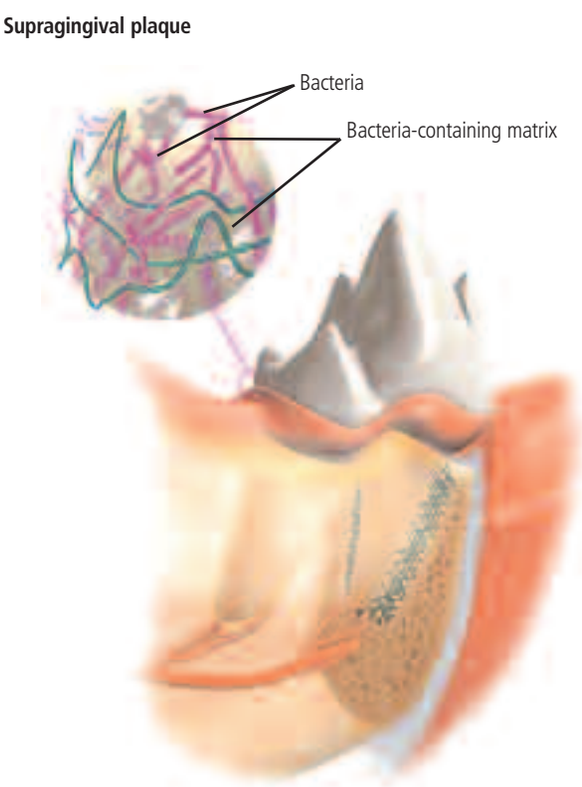
There are more than 350 recorded strains of bacteria in the oral cavity. Periodontal disease is accordingly not caused by a single strain. These bacteria first accumulate in

large numbers on the visible surface of the teeth (supragingival dental plaque), before spreading under the gingiva (subgingival plaque). A milligram of dental plaque contains around 10 million bacteria *(Loesche, 1988)*. In contact with the gingiva, these bacteria naturally provoke an inflammatory reaction, known as gingivitis.

The bacteria that spread under the gingiva may also gradually provoke more deep-lying lesions (destruction of the gingiva, periodontal ligament lesions, lesion of the alveolar bone that supports the tooth). These deep lesions loosen the tooth, which becomes more and more mobile. This characterizes the periodontitis phase. The normal attachment of the periodontium to the tooth is destroyed and migrates to the extremity of the root (= loss of attachment), resulting in the creation of a periodontal pocket. The depth of this pocket depends on the concomitant rate of gingival recession.

Calculus is formed by the gradual mineralization of the dental plaque caused by mineral salts (especially calcium) provided by the saliva for supragingival plaque, or by the gingival fluid in which the gingival crevice is immersed, for subgingival plaque. Calculus is not responsible for periodontal disease, but on a rough surface it is an ideal medium for bacterial dental plaque. In the event of chronic periodontal disease the calculus is indivisible from the bacterial dental plaque. It must be eliminated to enable the eradication of plaque. Limiting the formation of calculus while curbing the formation of bacterial dental plaque is one of the objectives of oral hygiene.

FIGURE 8 - HEALTHY TOOTH AND GUM



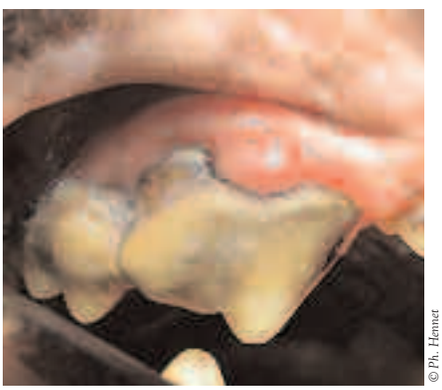
The biofilm constituting the dental plaque is made up of numerous bacteria inserted in a glycoprotein matrix that forms a kind of natural glue. The bacteria communicate with each other by chemical signals that trigger the production of proteins and potentially harmful enzymes.

Certain factors (reduced masticatory activity, dental malocclusion, persistence of deciduous teeth, absence of oral hygiene) can advance the accumulation of dental plaque. Other factors that affect the individual's capacity to develop a normal defense reaction include: systemic diseases (diabetes mellitus, kidney failure, liver failure) and innate or acquired immunodeficiency. The individual's capacity to develop an appropriate defense reaction is an innate factor. In general, the dog presents increased dental plaque and calculus accumulation and more serious gingivitis when it is nourished with soft, sticky food compared with firm, fibrous food *(Egelberg, 1965; Kaplan et al, 1978)*.

This apparent advantage in favor of firm, fibrous food applies only when the food is given in the form of large pieces, which encourages the use of the teeth.

► Oral hygiene

While not every individual that presents gingivitis automatically develops periodontitis, gingivitis is the essential preliminary stage in the development of periodontitis. The very principle of oral hygiene is therefore based on the control of supragingival dental plaque. A study of Beagles suffering from light to moderate periodontitis has shown that professional periodontal treatment (scaling, subgingival debridement and polishing), followed by daily brushing, helps reduce the initial loss of attachment and maintains this gain over a three-year period. Additional periodontal treatment every six months over this period does not improve the periodontal condition: neither does this same treatment every six months



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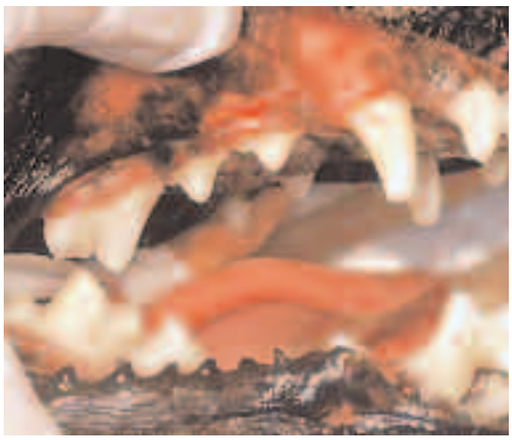
Periodontitis in the dog.
Destruction of the tissue that attaches to the tooth. In the absence of treatment, this will ultimately result in tooth loss.

A



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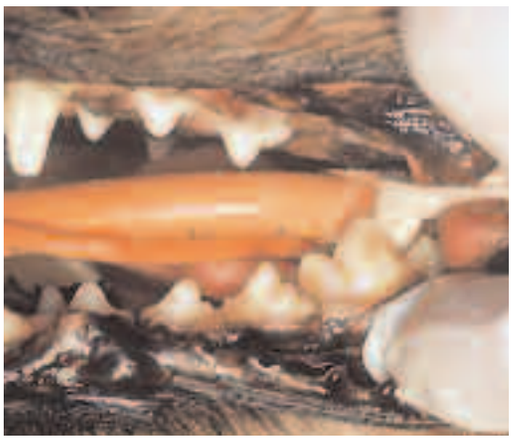
B



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Aspect of the teeth of the same dog from the right (A) and the left (B). *At right all teeth are presented and the deposits of dental plaque and calculus are very low. At right, the maxillary carnassial is absent, which means that there is no mechanical effect with the mandibular carnassial, resulting in major accumulation of dental plaque and calculus.*

in the absence of daily brushing which helps prevent the deepening of the pockets and the loss of attachment *(Morrison et al, 1979)*.

Oral hygiene can be split into primary hygiene (preventive measures on healthy gingivae before periodontal disease develops) and secondary hygiene (prevention of recurrence, after professional periodontal treatment of a pre-existing periodontal disease). In all cases, primary prevention is always desirable, because it occurs earlier and thefore is more effective. The puppy must be educated from a very early age. **While oral hygiene applies to all dogs and all breeds, the main targets are small and miniature dogs**.

> Brushing

Tooth brushing is the gold standard in terms of controlling supragingival dental plaque.

In humans, an efficacy of the order of 70% inhibition of dental plaque can be asserted, at least for the most accessible vestibular surfaces *(Mankodi et al, 1998; Van der Weijden et al, 1998)*. Studies of Beagles have shown that brushing at least three times a week helps maintain healthy gingivae, while brushing once a week does not *(Tromp et al, 1986a)*. In the presence of gingivitis, only daily brushing will re-establish healthy gingivae *(Tromp et al, 1986b)*. The only clinical study published on tooth brushing in dogs shows that, during a 13-month period, 49 of 51 owners (96%) recall having received brushing instructions and 34 of 51 owners (67%) recall having been shown how to brush teeth; 15 of 51 owners (2%) always brush the dog's teeth several times a week and 12 of 51 owners (24%) do so every day or every second day *(Miller & Harvey, 1994)*.

While being a reference in oral hygiene, brushing is not an easy task for owners to accomplish. Brushing can be complemented with the use of active chemical substances, of which chlorhexidine is still the most effective. In a study of Beagles in which the dogs' teeth and gums were massaged every day with a dental gel containing chlorhexidine and other ingredients, dental plaque on the vestibular surfaces was reduced by 42-49% *(Hennet, 2002)*. Whether these products are applied through brushing or massage, they do necessitate the intervention of the owner and the cooperation of the animal. These limitations have naturally led to the development of other oral hygiene means that do not require the owner's direct intervention. These indirect means comprise collagen-based chewing bones that can or cannot be eaten and specific dental foods.

3 - Role of food in oral hygiene

► Influence of the food's composition

When the composition of a food is changed but not its consistency, no significant influence is observed on the development of periodontal disease. Protein deficiency does not appear to have any consequence *(Ruben et al, 1962)*. A protein-lipid (P-L) diet (50-50% in dry weight) or the addition of carbohydrates (C) (60% C, 20% P, 20% L) does not lead to an aggravation of periodontal disease *(Carlsson & Egelberg, 1965; Egelberg, 1965)*. Osteopenia of alveolar bone induced by secondary hyperparathyroidism with a nutritional cause (Ca/P = 0.1) does not appear to influence the initiation and advancement of periodontal disease *(Svanberg et al, 1973)*.

The active agents against dental plaque or calculus can be incorporated into a kibble or a chewing bar. They are then released in the oral environment during mastication. Anti-calculus agents such as polyphosphates were studied first *(Stookey et al, 1993)*. These are phosphate polymers

(pyrophosphate, polyphosphate, hexametaphosphate), some of which present sequestering properties with bivalent cations like calcium **(Figure 9)**.

The chelation of salivary calcium is responsible for inhibiting the formation of calculus. To facilitate the release and the contact with salivary calcium, the polyphosphates must be incorporated in the kibble coating *(Stookey et al, 1993)*.

Other compounds (polyphenols, essential oils, metallic ion salts, etc.) that have exhibited *in vitro* or *in vivo* activity on the formation of dental plaque may also be incorporated. Studies are needed to evaluate their activity in these conditions and to determine the best way of optimizing the release of these substances in the oral cavity (in the external coating or in the kibble proper).

FIGURE 9 - MECHANISM OF SALIVARY CALCIUM CHELATION BY SODIUM POLYPHOSPHATE

The free calcium (Ca^{2+}) in the saliva is trapped by two sodium polyphosphate molecules. It takes the place of two sodium ions (Na^{+}) and is essential to the formation of calculus.

► Influence of the physical presentation of the food

While it appears logical that a soft food or food in very small pieces would not help the function of the teeth and manducation in canids, interest in the role played by the food is a relatively recent phenomenon.

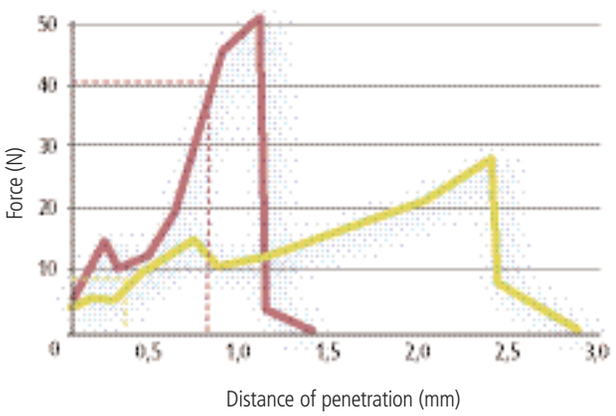
Studies conducted by physiologists have shown that gastrectomized dogs fed with a soft food developed more calculus *(Ivy et al, 1931)*. In a study in which one group of dogs were fed with slices of entire beef, the esophagus, the muscles and a mineral and vitamin supplement, and another group was fed with the same food minced, the dogs in the second group presented with greater accumulation of dental plaque than the dogs in the first group *(Egelberg, 1965)*. Many other studies have confirmed this *(Krasse & Brill, 1960; Kaplan et al, 1978)*. In addition to the absence of mechanical action, a soft food can provoke a reduction in the flow of saliva, a reduction in enzyme secretions and functional atrophy *(Sreebny, 1972)*.

It cannot simply be concluded however that a food in kibble form or a hard food is generally more effective than a soft food. In Egelberg's study (1965) the main factor is the fibrous character of the food rather than its hardness. A multicenter study on 1350 dogs in North America has shown that there is no significant difference between dogs fed exclusively with a dry food and other dogs. On the other hand, dogs that have a number of objects to chew present less calculus, fewer cases of gingivitis and less alveolysis than those that have few or no objects to chew *(Harvey et al, 1996)*.

A dry food is potentially beneficial for dental hygiene if the shape and texture of the kibbles are specially designed for a particular size or breed of dog to contribute to passive tooth brushing mechanism. To scrape the surface of the tooth when the dog eats, the dog must chew so that the tooth penetrates the kibble deeply before the kibble breaks. Size and breed are two parameters that influence the pressure exercised on the kibble at the moment of prehension. Devices have been studied to test the kibble penetration threshold before fragmentation. This enables a comparison between various kibbles **(Figure 10)**.

FIGURE 10 - FORCE NEEDED TO BREAK THE KIBBLE: COMPARISON BETWEEN TWO DIFFRENT TYPES OF KIBBLES FOR SMALL DOGS

(Royal Canin, 2003)



An elastic kibble that resists the pressure on it for longer before breaking enables the tooth to penetrate much deeper and so produces a more pronounced 'cleaning' effect.

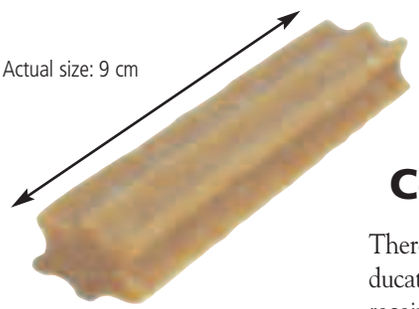
► Control of dental hygiene with food

Royal Canin laboratory texturometer.
The texturometer is used to measure the resistance of the kibble to the force of the dog's jaws and teeth. Interchangeable modules mimic the shape and the dimensions of the teeth of dogs of various ages and sizes.

The possibility of controlling dental plaque and the development of periodontal disease by the mechanical action of a chewing bone or specific foods was picked up on in the pet food industry in the early 1990s. Various studies were conducted on dogs with respect to dental plaque, calculus, coloration and gingivitis. Only dental plaque and gingivitis presented a medical interest. Dental coloration, important in humans for aesthetic reasons, is not of interest in dogs.

A significant 19% reduction in dental plaque compared with the control group was obtained after one week of feeding with a kibble specifically targeting oral hygiene *(Jensen et al, 1995)*. More recently, significant reductions of 39% in dental plaque and 36% in gingival inflammation were obtained after six months with the same food among dogs weighing 9-25 kg *(Logan et al, 2002)*. In another study on the preventive effect of a daily food bone in dogs weighing an average of 23 kg, a significant reduction of dental plaque at 12 and 21 months (but not at 18 months) and gingivitis at 12, 18 and 21 months was observed *(Gorrel & Bierer, 1999)*. Unfortunately, the reduction percentages are not given in this study, but an extrapolation based on the graphs show a maximum reduction of dental plaque and gingivitis of 15-20%.

The improvement of oral hygiene by food or dietary complement is accordingly a blossoming field. Besides the action on calculus, dental plaque and gingival inflammation must also be targeted. While the above results are very interesting, they have been obtained on medium-sized dogs, which is not at all the group most seriously affected by periodontal disease. Dogs weighing less than 8 kg are most seriously affected by periodontal disease. Studies must be conducted on specific breeds (Yorkshire Terrier, Poodle, Dachshund, etc) to verify whether the same results can be obtained. The author has conducted a study on 18 small dogs [average 7 kg] belonging to one of two groups depending on their genetic relationship. The test group that was given a dental chewing bar presented significant statistical reductions of 17% in dental plaque and 45% in calculus at the end of four months of study *(Hennet, 2004)*.



Example of a dental bar for small dogs that helps limit the accumulation of dental plaque and calculus.
It is recommended that this type of complement be first given after scaling. The resistant yet elastic texture of this type of bar requires the dog to use its teeth to chew before swallowing.

The methodology of these studies has been questioned, mainly with respect to the evaluation of the dental plaque *(Hennet, 1999; Harvey 2002)*. An improvement in the methodology could be considered to achieve results that are not only statistically significant but more importantly, biologically significant.

Conclusion

There are various ways of controlling the formation of dental plaque and calculus through manducation, all of which have been studied a great deal. Product shape, texture and appetence have received most attention, as has the possibility of incorporating chemical agents that act on the dental plaque, the calculus or the inflammatory reaction. These innovations have undoubtedly advanced the efforts to prevent periodontal disease.

We're witnessing a new era in veterinary nutrition. After mastering the food at the dietary level, the specific characteristics of the species and the various breeds must be given due consideration. Besides offering a good nutritional balance, the food can also play a role in preventing medical problems. Food with added value in oral hygiene and chewing bars that encourage mastication and have a texture that maximizes the self-cleaning effect contribute to reducing the accumulation of dental deposits and perhaps to preventing gingivitis. While daily brushing remains the best way of preventing periodontal disease, the complementary use of dental foods is recommended.

References

Carlsson J, Egelberg J - Local effect of diet on plaque formation and development of gingivitis in dogs. II. Effect of high carbohydrate versus high protein-fat diets. Odont Revy 1965; 16: 42-49.

Egelberg J - Local effect of diet on plaque formation and development of gingivitis in dogs. I. effect of hard and soft diets. Odont Revy 1965; 16: 31-41.

Gaspard M - Essai d'analyse bio-mécanique comparative de la mastication chez les carnivores, les anthropodes et l'homme. Rev Fr Odont Stom 1967; 14: 85-108.

Gioso MA, Shofer F, Barros PS et al – Mandible and mandibular first molar tooth measurements in dogs; relationship of radiographic height to body weight. J Vet Dent 2001; 18 (2): 65-68.

Gorrel C, Bierer TL - Long term effects of a dental hygiene chew on the periodontal health of dogs. J Vet Dent 1999; 16(3): 109-113.

Hale FA - Dental caries in the dog. J Vet Dent 1998; 15(2): 79-83.

Hamp SV, Olsson, Farso-Madsen K et al - A macroscopic and radiologic investigation of dental diseases of the dog. Vet Rad 1984; 25(2): 86-92.

Harvey CE, Shofer FS, Laster L - Association of age and body weight with periodontal disease in North American dogs. J Vet Dent 1994; 11(3): 94-105.

Harvey CE, Shofer FS, Laster L - Correlation of diet, other chewing activities and periodontal disease in North American client-owned dogs. J Vet Dent 1996; 13(3): 101-105.

Harvey CE - Shape and size of teeth of dogs and cats-relevance to studies of plaque and calculus accumulation. J Vet Dent 2002; 19(4): 186-195.

Hennet P - Review of studies assessing plaque accumulation and gingival inflammation in dogs. J Vet Dent 1999; 16(1): 23-9.

Hennet P - Effectiveness of a dental gel to reduce plaque in beagle dogs. J Vet Dent 2002;19(1): 11- 4.

Hennet P, Servet E, Venet C - Effects of feeding a daily oral hygiene chew on dental deposits in small breed dogs : a 4-month trial. Proceedings of the 13th European Congress of Veterinary Dentistry, Krakow 2004: 47-48.

Isogai H, Isogai E, Okamoto H et al - Epidemiological study on periodontal diseases and some other dental disorders in dogs. Jpn J Vet Sci 1989; 51(6): 1151-1162.

Ivy AC, Morgan JE, Farrell JI - Effects of total gastrectomy. Surg Gynec Obst. 1931; 53: 612.

Jensen L, Logan E et al. Reduction in accumulation of plaque, stain and calculus in dogs by dietary means. J Vet Dent 1995; 12(4): 161-163

Krasse B, Brill N - Effect of consistency of diet on bacteria in gingival pocket in dogs. Odontol Rev 1960; 11: 152-165.

Kaplan ML, Davis MA, Aschaffenburg PH et al - Clinical, radiographic and scintigraphic findings in experimental periodontal disease in dogs. Arch Oral Biol 1978; 23: 273-278.

Lafond M - Essai de physiologie mandibulaire chez les carnivores. Rev Stomat 1929; t XXXI, 1: 1- 17.

Lavergne J, Vanneuville G, Santoni S - Précis d'anatomie comparée crânio-faciale des vertébrés. Nantes, Heures de France, 1996.

Loesche WJ - Ecology of the oral flora. In Newman and Nisengard (eds). Chp 25: Oral microbiology and immunology; Philadelphia, WB. Saunders, 1988.

Logan EI, Finney O, Hefferren JJ - Effects of a dental food on plaque accumulation and gingival health in dogs. J Vet Dent 2002; 19(1): 15-18.

Mankodi S, Berkowitz H, Durbin K et al - Evaluation of the effects of brushing on the removal of dental plaque. J Clin Dent 1998; 9(3): 57-60.

Miller BR, Harvey CE - Compliance with oral hygiene recommendations following periodontal treatment in client-owned dogs. J Vet Dent 1994; 11(1): 18-19.

Morrison EC, Lang NP, Löe H et al - Effects of repeated scaling and root planing and/or controlled oral hygiene on the periodontal attachment level and pocket depth in beagle dogs. I. Clinical findings. J Periodontal Res 1979; 14: 428-437.

Overman PR – Biofilm: a new view of plaque. J Contemp Dent Pract 2000; 1(3): 18-29.

Rosenberg HM, Rehfeld CE, Emmering TE - A method for the epidemiologic assessment of periodontal health-disease state in Beagle hound colony. J Periodontol 1966; 37: 208.

Ruben MP, McCoy J, Person P et al - Effects of dietary consistency and protein deprivation on the periodontium of the dog. Oral Surg 1962; 15(9): 1061-1070.

Sreebny LM - Effect of physical consistency of food on the crevicular complex and salivary glands. Int Dent J 1972; 22(3): 394-400.

Stookey GK, Warrick JM, Miller LL - Effect of sodium hexametaphosphate on dental calculus formation in dogs. Am J Vet Res 1993; 56(7): 913-918.

Svanberg G, Lindhe J, Hugoson A et al - Effect of nutritional hyperparathyroidism on experimental periodontitis in the dog. Scand J Dent Res 1973; 81: 155-162.

Tromp JAH, Van Rijn LJ, Janssen J - Gingival health and frequency of tooth brushing in the beagle dog model. J Clin Periodontol 1986a; 13: 164-168.

Tromp JAH, Van Rijn LJ, Janssen J - Experimental gingivitis and frequency of tooth brushing in the beagle dog model. J Clin Periodontol 1986b; 13: 190-194.

Van der Weijden GA, Timmerman MF, Danser MM et al - Relationship between the plaque removal efficacy of a manual toothbrush and brushing force. J Clin Periodontol 1998; 25(5): 413-416.

Verchère L, Budin P, Santoro JP et al - Dictionnaire des termes odonto-stomatologiques. Paris, Masson, 1992.

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Food is a useful tool for the prevention of periodontal disease, as it helps to slow down the development of dental plaque and calculus. The most efficient approach combines a mechanical effect coupled with active ingredients.

Key Points
in the analysis of:

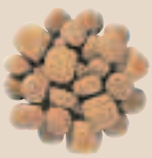
Ingredients that play a role in the prevention of periodontal disease

Kibbles with a dental function have a special form and texture that obliges the dog to chew to obtain a light abrasion of the teeth. However, kibbles are less effective than brushing.

When it comes to oral hygiene, the kibble can support the active agents which are released in the oral cavity during mastication. Upon release, the active agents are incorporated with saliva. Until now, the objective of various solutions has been to limit bacterial proliferation through substances that have a bacteriostatic or even bactericidal effect. The inconvenience of these products is that they disrupt the natural floral equilibrium, because the bacterial action targets all bacteria, even beneficial strains.

New lines of research are focusing on molecules that limit the adhesion of bacteria to the surface of the teeth.

Kibbles with a dental function.



Frequently asked questions about kibbles with a dental function

Q	A
Should kibbles with a dental function be prescribed to a dog that already has calculus?	Prior dental care is essential because a dog that suffers from periodontitis may feel discomfort or pain when eating and refuse to eat the kibbles. The prescription of a specific food with a dental function delays calculus accumulation but it does not remove it.
Which is preferable, a chewing bar or kibbles with a dental function?	Selection is based on the age (kibbles with a dental function are for adult dogs) and the size of the dog, as well as the motivation and the budget of the owner. The ideal solution for dogs is a combination of the two.
Do kibbles with a dental function contain any ingredients against plaque?	**No**, but they can contain nutrients that significantly curb the development of dental plaque.

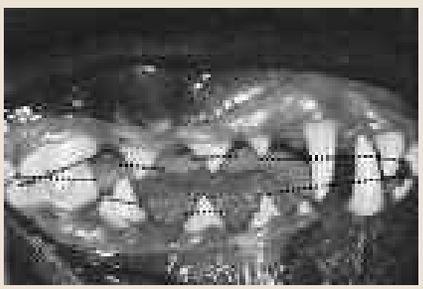
1 • Evaluation of the Logan & Boyce plaque index for a study on the accumulation of dental plaque in the dog

Many index systems have been developed to evaluate the accumulation of plaque on the dental surfaces. The Silness & Loë index *(1964)* focuses on the thickness of the plaque that accumulates on the tooth along the gingival line, while most methods evaluate the spread of the plaque on the dental surface after the action of a colorant; e.g. Quigley & Hein *(1962)*, Turesky et al *(1970)*.

• A modification of the Turesky index was introduced into veterinary dentistry by Logan & Boyce *(1994)*. This index has since been used in several studies evaluating the influence of chewing toys, bones or specific foods on the formation of dental plaque *(Gorrel, 1999; Logan et al, 2002)*. Since this new evaluation method differs significantly from the original Turesky index, the name Logan & Boyce index has been proposed *(Hennet, 1999)*. In the original description of this index, a horizontal division of the surface of the crown in two parts (coronary and gingival) was proposed, without this being precisely described *(Logan & Boyce, 1994)*. Other systems used in human dentistry, like the Navy plaque index, use a horizontal division of the surface of the crown, based on anatomical criteria *(Fischman, 1986, 1988)*. In contrast to the Turesky method, the Logan & Boyce index evaluates the surface and the thickness of the plaque on every half of the dental crown. The intensity of coloration (light, medium or intense) is used to evaluate the thickness of the plaque. The Logan & Boyce index has been validated for use in veterinary dentistry *(Gorrel, 1999)*. But to our knowledge, no study has been published to document the reliability of this index in dogs (intra-observer repeatability and inter-observer reproducibility).

• The aim of this study was to follow the repeatability of the scores provided by an experienced observer (intra-observer repeatability) and to compare the scores provided by an experienced or inexperienced observer (inter-observer reproducibility), utilizing the Logan & Boyce index. The authors were also interested in the influence of a modified Logan & Boyce index, in which the anatomical points are used for a horizontal division of the tooth, and an intensity gradient was used to evaluate the intensity of coloration, so as to improve the repeatability of the measures.

ANATOMICAL POINTS FOR THE HORIZONTAL DIVISION OF THE TEETH



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***Third incisor**: horizontal line to the gingival line at the distal tubercle of the second incisor.*
***Canine**: horizontal line to the gingival line at the level of the cusp of the first premolar.*
***Second and third premolars**: horizontal line to the gingival line at the distal tubercle of the first incisor.*
***Fourth premolar**: horizontal line to the gingival line at the distal talon.*
***First molar**: horizontal line to the gingival line at the oral tubercle of the tooth.*

References

Fischman SL - Current status of plaque. J Clin Periodontol 1986; 13: 371-380.

Fischman, SL - Current index systems used to assess the efficacy of mouth-rinses on plaque and gingivitis. J Clin Periodontol 1988; 15: 506-510.

Gorrel C, Bierer TL - Long-term effects of a dental hygiene chew on the periodontal health of dogs. J Vet Dent 1999; 16: 109-113.

Hennet P - Review of studies assessing plaque accumulation and gingival inflammation in dogs. J Vet Dent 1999; 16: 23-9.

Hennet P, Servet E, Salesse H et al - Evaluation of the "Logan & Boyce" plaque index for the study of dental plaque accumulation in dogs. Res Vet Sci 2006; 80: 175-180.

Logan EI., Boyce EN - Oral health assessment in dogs: parameters and methods. J Vet Dent 1994; 11: 58-63.

Logan, EI, Finney O, Hefferren JJ - Effects of a dental food on plaque accumulation and gingival health in dogs. J Vet Dent 2002; 19:15-18.

Quigley GA, Hein JW - Comparative cleansing efficiency of manual and power brushing. J Am Dent Assoc 1962; 65: 26-29.

Turesky S, Gilmore ND, Glickman I - Reduced Plaque Formation by the Chloromethyl analogue of vitamin C. J Periodontol 1970; 41: 41-43.

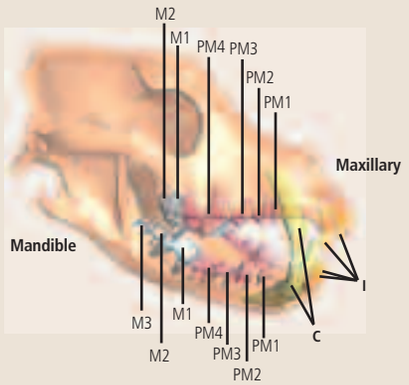
2 • Prevention of periodontal disease: complementing the mechanical action with active principles

A survey conducted in the United States on more than 30,000 dogs presented to their veterinarian shows that calculus and gingivitis are the most common presenting complaints (respective prevalence 20.5% and 19.5%), ahead of otitis externa, dermatoses and infestation by fleas *(Lund, 1999)*. A spectacular advance in the field of veterinary dentistry means we can offer companion animals effective and preservative care. Prevention continues to be the best approach in the fight against the development of this disease, however this is often neglected in comparison with other disease conditions.

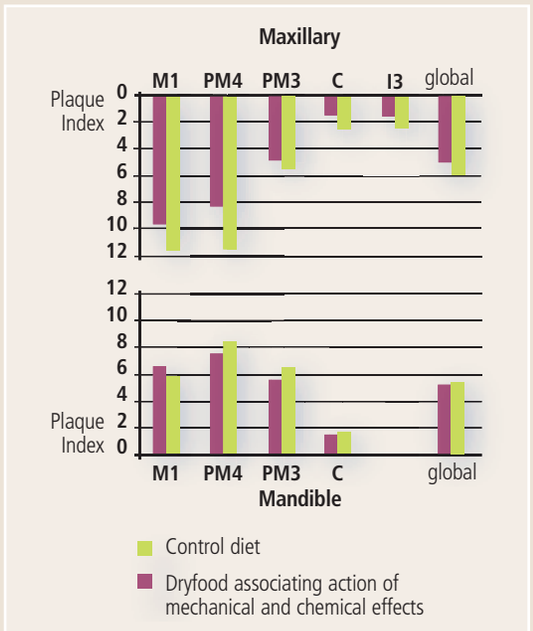
COMPARISON OF PLAQUE AND CALCULUS DEPOSITS 28 DAYS AFTER SCALING

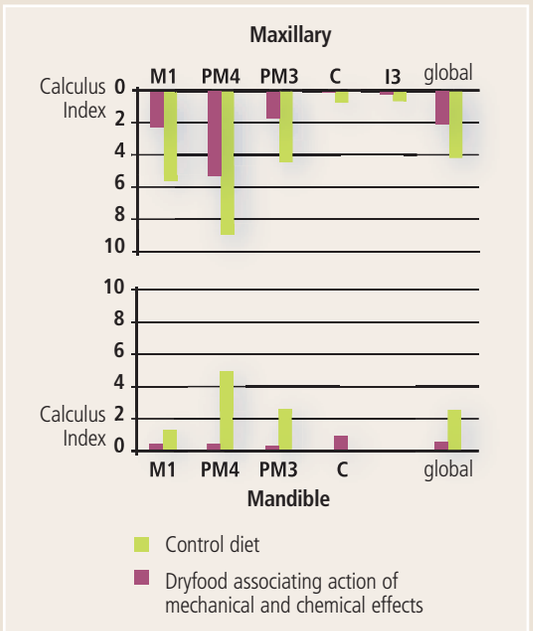
(Sources Royal Canin, 2004)

I3 : incisor 3
C : canine
PM3 : premolar 3
PM4 : premolar 4
M1 : molar 1



After tooth brushing, which is acknowledged as the most effective way of preventing periodontal disease, nutritional supplements and/or specific foods can be very useful.





Reference

Lund EM, Armstrong J, Kirk CA et al - Health status and population characteristics of dogs and cats examined at private veterinary practices in the United States. J Am Vet Med Assoc 1999; 214: 1336-41.

3 • Significance of specific phosphates for oral health

The use of polyphosphate salts is significant because they chelate salivary calcium. Chelation varies depending on the type of polyphosphate. To facilitate the release and the contact with salivary calcium, the polyphosphates must be incorporated into the external coating of the kibble.

The various types of phosphate

Phosphates constitute a very large family of more than 150 different molecules (including orthophosphate, pyrophosphate, polyphosphate and metaphosphate). Some phosphates present sequestering properties with bivalent cations such as calcium (e.g. Ca^{2+}). These properties depend on the length of the phosphate chain (the longer the chain, the greater their capacity to chelate bivalent cations) and on the local pH. These types of compounds are used in many human toothpastes *(Sowinski et al, 1998)*.

Phosphates: type of action

The Ca^{2+} cations in saliva have a direct role in the calcification of dental plaque (calculus deposition). The phosphates which are able to chelate polyvalent cations will be able to capture the Ca^{++} cations in the saliva. If polyphosphates are released in the oral cavity they will naturally chelate the salivary calcium in ionic form, thus limiting its integration in the dental calculus matrix. Calcium is then released as normal in the digestive tract and absorbed by the organism in accordance with its needs.

Scientific studies

The anti-calcification effect of hexametaphosphate (HMP) on the dental biofilm has been verified *in vitro* where the formation of calcium hydroxyapatite crystals was shown to be significantly reduced *(White et al, 2002)*.

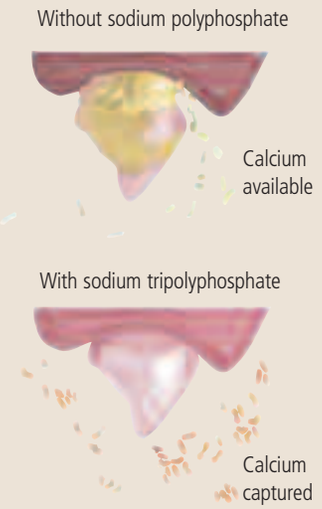
Beagles fed for one month with kibbles coated with HMP present a significantly reduced calculus deposit (-58%) compared with dogs fed with the same diet when polyphosphates were incorporated into the interior of the kibble *(Cox et al, 2002)*.

The chelating effect varies depending on the type of polyphosphate used, even when the dose is identical. Compared with a control group, the reduction in the calculus deposit after a month among Beagles given kibbles coated with polyphosphates was as follows:

- 36% with hexametaphosphate
- 55% with sodium tripolyphosphate

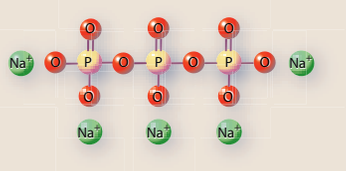
(Royal Canin Research Centre, 2001-2002)

ACTION OF THE SODIUM TRIPOLYPHOSPHATE

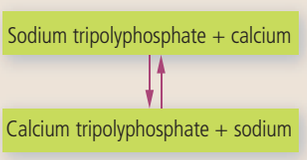


The chelated calcium ions are unavailable for the formation of calculus

MOLECULE OF SODIUM TRIPOLYPHOSPHATE



REACTION BETWEEN SODIUM TRIPOLYPHOSPHATE AND Ca^{2+} CATIONS



References

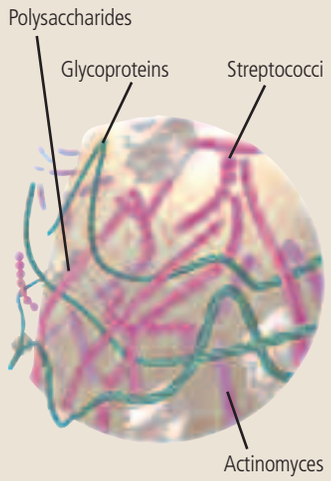
Cox ER, Lepine AJ - Use of polyphosphates in canine diets to control tartar. IADR Meeting, San Diego, CA (USA) 2002; Poster n°2793.

Royal Canin Research Centre - Hennet P, Servet E, Soulard et al - Effect of two kibble sizes and two different phosphate salts in preventing calculus accumulation in dogs. 14th European Congress of Veterinary Dentistry 22- 24 Sept 2005; Ljubljana, Slovenia.

Sowinski J, Petrone DM, Battista et al – Clinical comparison of two tartar control dentifrices: a twelve-week study. J Clin Dent 1998; 9(4): 101- 104.

White DJ, Cox ER, Suszcynskymeister EM et al - In vitro studies of the anticalculus efficacy of a sodium hexa-metaphosphate whitening dentifrice. J Clin Dent 2002; 13(1): 33-7.

4 • Significance of zinc salts for oral health



More than 300 strains of bacteria are present in the oral cavity. Streptococci and Actinomyces, which have adherence properties, are the first to colonize the dental biofilm. The primary supragingival plaque will reach the sub-gingival area, where the development of an anaerobic flora is favored. This transition from a commensal flora to a pathogenic bacterial population is responsible for the development of periodontal disease.

Zinc salts have potential beneficial effects in the area of oral health. They can act as oral antiseptics that tend to limit bacterial proliferation in the oral cavity, and can reduce the formation of dental plaque and calculus.

The various zinc salts

There is organic zinc (e.g. zinc citrate) and inorganic zinc (e.g. zinc sulfate, $ZnSO_4^{2-}$).

Scientific studies

Inhibition of calculus formation

In vitro the zinc salts can help limit the deposit of dental calculus by inhibiting the formation of calcium hydroxyapatite complex, and by promoting the formation of more soluble calcareous complexes like tricalcium phosphate.

A study conducted on rats has shown that animals whose teeth are brushed with a toothpaste formulated with zinc salts present significantly less calculus deposit than the control group *(Putt et al, 2002)*. This finding has been confirmed in humans *(Sowinski et al, 2001; Barrea et al, 2001)*.

Inhibition of the production of sulfonated volatile fatty acids

In vitro the zinc salts help control the production of foul-smelling molecules responsible for halitosis *(Weesner, 2003)*.

A study of humans has also shown that zinc salts inhibit the production of foul-smelling volatile fatty acids from 14C-glucose *(Harrap et al, 1984)*.

Inhibition of bacterial growth

The zinc salts present bacteriostatic properties that have been demonstrated *in vitro*, especially a high anti-microbial activity against *Streptococcus mutans* *(Belcastro et al, 1994)*.

This anti-microbial activity has been confirmed in cats. A significant reduction in plaque deposition and the burden of anaerobic pathogenic bacteria involved in periodontal disease have been observed in a group of cats treated with a gel containing zinc salts *(Clarke, 2001)*.

References

Barrea RA, Perez CA, Ramos AY - Zinc incorporation in human dental calculus. J Synchrotron Radiat 2001; 8(Pt 2): 990-2.

Belcastro S, Staffolani N, Pugliese M et al - An in vitro study of the antimicrobial activity of copper and zinc salts on pure and mixed microbial cultures. Minerva Stomatol 1994; 43 (9): 393-6.

Clarke DE - Clinical and microbiological effects of oral zinc ascorbate gel in cats. J Vet Dent 2001; 18(4): 177-83.

Harrap GJ, Best JS, Saxton CA - Human oral retention of zinc from mouthwashes containing zinc salts and its relevance to dental plaque control. Archs oral Biol 1984; 29(2): 87-91.

Putt MS, Yu D, Kohut BE - Inhibition of calculus formation by dentifrice formulations containing essential oils and zinc. Am J Dent 2002; 15(5): 335-8.

Sowinski J, Petrone DM, Battista G et al - Clinical efficacy of a dentifrice containing zinc citrate: a 12-week calculus clinical study in adults. Compend Contin Educ Dent 1998; 19(2 Suppl): 16-9.

Weesner BW Jr - Curing halitosis: the sweet smell of success. J Tenn Dent Assoc 2003; 83(4): 20.

5 • Significance of specific polyphenols for oral health

Some polyphenol sources can be incorporated into the food to limit the formation of dental biofilm. Green tea, which is rich in active polyphenols (e.g. epigallocatechin gallate or EGCg), is considered to be beneficial in the prevention of periodontal disease.

The various types of polyphenols

More than 8000 types of polyphenol have been identified. Some have a highly complex chemical structure. This decidedly varied group comprises molecules containing a simple phenolic nucleus and highly polymerized compounds (tannins). Naturally present in all living beings, polyphenols play an essential antioxidant role.

Polyphenols: type of action

The bacteriostatic action of certain polyphenols is allied to their antioxidant properties, especially to the presence of the hydroxyl group (OH^-) in ortho configuration, as well as the presence of the gallate function on the phenolic ring.

Scientific studies

Inhibition of the growth of bacteria in dental plaque

In dogs, the flora of the periodontal pockets is marked by the presence of specific bacteria, such as *Porphyromonas endodontalis*, *gingivalis* and *circumdentaria* *(Isogai et al, 1999)*.

• In vitro

Certain phenolic compounds (particularly those of the catechin family) present an anti-bacterial effect against the bacteria in the dental plaque, such as *Porphyromonas gingivalis* and *Prevotella spp.* *(Hirasawa et al, 2002)*, *Escherichia coli*, *Streptococcus salivarius* and *Streptococcus mutans* *(Rasheed et al, 1998)*.

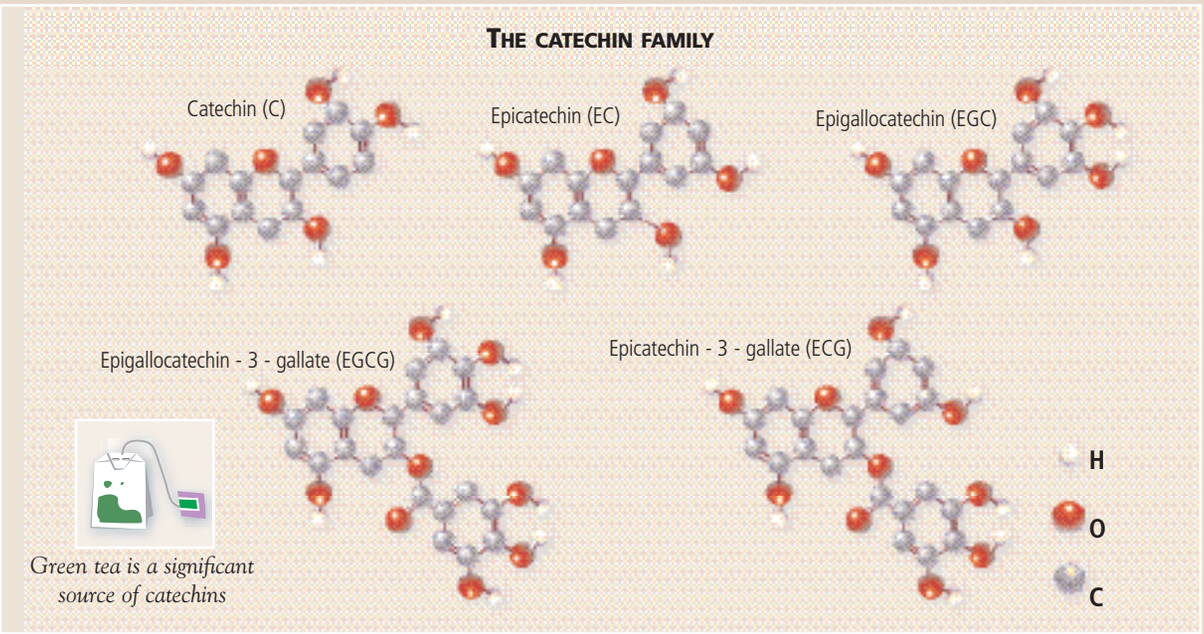
Among the polyphenols present in green tea, epigallocatechin gallate (EGCg) has the strongest bactericidal activity. Its minimal inhibition concentration is between 250 and 500 µg/mL depending on the various strains of *Porphyromonas gingivalis* *(Sakanaka et al, 1996)*.

• In vivo

In dogs, a diet formulated with green tea, which is naturally rich in catechins, has helped inhibit the growth of bacteria and after two months, to significantly reduce the *Porphyromonas* percentage in the microbial population of dental plaque *(Isogai et al; 1995, 1992)*.

Inhibition of the capacity of bacteria to adhere to the epithelial cells in the mouth

In vitro, the polyphenols contain a gallate function (epigallocatechin gallate or EGCg; gallocatechin gallate or GCg; catechin gallate or Cg), which reduces the capacity of *Porphyromonas gingivalis* to adhere to the surface of epithelial cells *(Sakanaka et al, 1996)*.



Green tea is a significant source of catechins

On average, every epithelial cell can capture 300 *P. gingivalis*. At 250 µg/mL of pure polyphenols (which possess a gallate function), the inhibition of the adherence is almost complete, but at 7.8 µg/mL the number of *P. gingivalis* adhering is reduced by 30% *(Sakanaka et al, 1996)*. According to these authors the anti-adhesion capacities of polyphenols will be targeted on the bacteria rather than the epithelial cells.

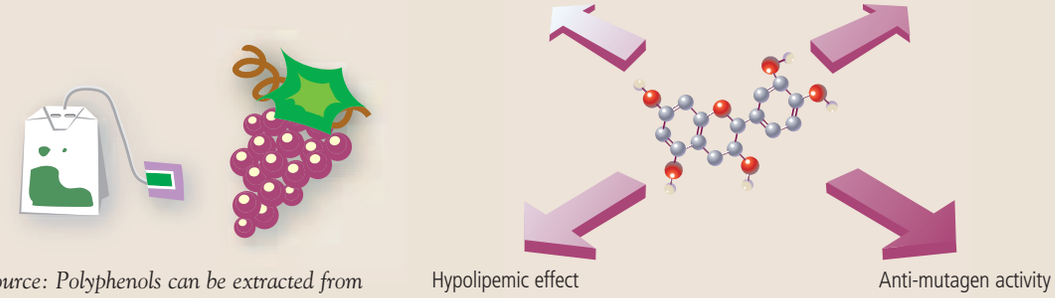
The adhesion of other bacteria is also limited by polyphenols which possess a gallate function.

At concentrations between 125 and 250 µg/mL the adhesion of *Porphyromonas melaninogenicus* and *Streptococcus sanguis* is reduced by 50%. *Streptococcus sanguis* is one of the first bacteria that leads to the formation of plaque *(Sakanaka et al, 1996)*.

Inhibition of the production of acid metabolites by the bacteria of dental plaque

The bacteria of the plaque (such as *Porphyromonas gingivalis*) generate acids: n-butyric acid, phenylacetic acid or propionic acid. *In vitro*, some polyphenols are capable of inhibiting the production of these acid metabolites generated by the bacteria of the plaque (e.g. *Porphyromonas gingivalis*). This inhibitor effect is due to the presence of the gallate function of certain phenolic compounds, especially EGCg, GCg, and Cg, which are present in green tea *(Sakanaka et al, 2004)*.

ROLES OF POLYPHENOLS



Source: Polyphenols can be extracted from green tea and grapes.

Polyphenols are known among humans for their protective qualities against cardiovascular diseases (hypolipemic effect). In dogs, they are valued for their major antioxidant activity and for their antiseptic role against certain bacteria of dental plaque.

References

Hirasawa M, Takada K, Makimura M et al - Improvement of periodontal status by green tea catechin using a local delivery system: a clinical pilot study. J Periodontal Res 2002; 37(6): 433-8.

Isogai E, Isogai H, Kimura K et al - Effect of Japanese green tea extract on canine periodontal diseases. Microbial Ecology in Health and disease 1995; 8: 57-61.

Isogai E, Isogai H, Fujii N et al - Inhibitory Effect of Japanese green tea extracts on growth of canine oral bacteria. bifidobacteria Microflora 1992; 11 (2): 53-59.

Isogai H, Kosako Y, Benno Y et al - Ecology of genus Porphyromonas in canine periodontal disease. Zentralbl Veterinarmed B 1999; 46 (7):467-73.

Rasheed A, Haider M - Antibacterial activity of Camellia sinensis extracts against dental caries. Arch Pharm Res 1998; 21(3): 348-52.

Sakanaka S, Aizawa M, Kim M et al - Inhibitory effects of green tea polyphenols on growth and cellular adherence of an oral bacterium, Porphyromonas gingivalis Biosci Biotechnol Biochem 1996; 60(5): 745-9.

Sakanaka S, Okada Y - Inhibitory effects of green tea polyphenols on the production of a virulence factor of the periodontal-disease-causing anaerobic bacterium Porphyromonas gingivalis. J Agric Food Che. 2004; 52(6): 1688-92.

6 • Significance of specific essential oils for oral health

Some essential oils (e.g. eucalyptus oil) act to reduce bad breath and gingiva inflammation, while curbing bacterial proliferation.

Which essential oils?

Manuka oil, tea oil, eucalyptus oil, lavender oil and rosemary oil.

Oils rich in antioxidant molecules have a bacteriostatic or bacteriocidal action.

Scientific studies

Inhibition of bad breath

Some oils, notably eucalyptus or rosemary oil, help to limit bad breath (halitosis). The significance of eucalyptus oil is due to the fact that it not only masks bad smells, but actively participates in reducing the production of sulfonated volatile fatty acids.

In a study evaluating volative sulfonated compounds (VSCs), cookies containing 0.1 % eucalyptus role significantly reduced bad breath in dogs, compared to a control group *(Waltham Research Centre, 2001)*.

Inhibition of inflammatory activity

In vitro, 1.8-cineol (or eucalyptol), the main eucalyptus monoterpene, inhibits the metabolism of arachidonic acid which produces molecules that cause inflammation (prostaglandins E2 and B4), and cytokines in human monocytes. This mechanism is promissing for limiting the development of nascent gingivitis *(Juergens et al, 2003)*.

Inhibition of bacterial activity

Eucalyptus oil inhibits the growth of certain bacteria involved in periodontal disease such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, Streptococcus *mutans* and *Streptococcus sobrinus*. These periodontogenic bacteria are destroyed by 30-minutes of exposure to a solution containing 0.2% of eucalyptus or rosemary oil. The eucalyptus oil inhibits the adhesion of *Streptococcus mutans* *(Takarada et al, 2004)*.

Conclusion

Periodontal disease always develops from the bacterial biofilm that makes up the dental plaque. Any factors that can limit the formation of this plaque are potentially significant. Brushing the teeth with toothpaste adapted for dogs remains the best means of preventing the formation of dental plaque. The kibbles can be complementary to brushing due to their mechanical (crunching-friction) and chemical (anti-plaque/calculus actives) actions. Further studies are required to determine how to optimize the liberation of these active substances in the oral cavity (in the coating or in the interior of the kibble).

References

Juergens UR, Dethlefsen U, Steinkamp G et al - Anti-inflammatory activity of 1.8-cineol (eucalyptol) in bronchial asthma: a double-blind placebo- controlled trial. Respir Med 2003; 97(3): 250-6.

Takarada K, Kimizuka R, Takahashi N et al - A comparison of the antibacterial efficacies of essential oils against oral pathogens. Oral Microbiol Immunol 2004; 19(1): 61-4.

Waltham Centre for Pet Nutrition - Efficacy of the active ingredients of the Breath Freshening Biscuit in Reducing VSC levels in Canine Oral Malodour. Unpublished internal results, 2001.

7 • Short- to medium-term effect of a chewing bar on dental deposits in dogs

Over a short period (28 days)

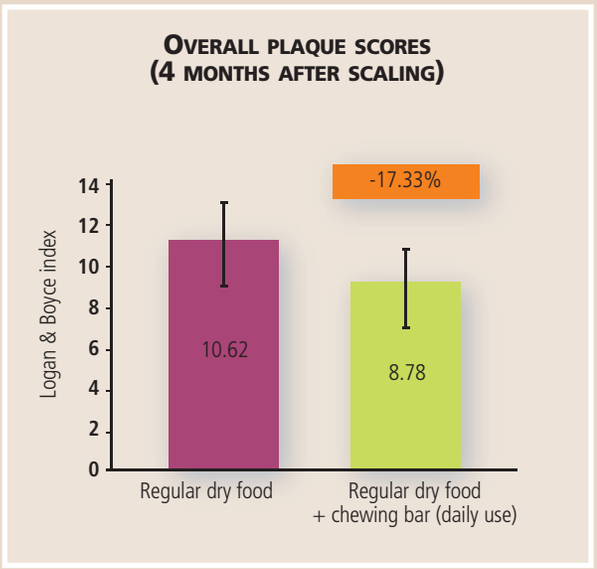
The combination of traditional kibbles and a chewing bar for daily use was associated with a significant reduction in plaque deposition [-27%; p-value < 0.05] and the formation of calculus [-53%; p-value < 0.05], compared with a diet constituted solely of traditional kibbles.

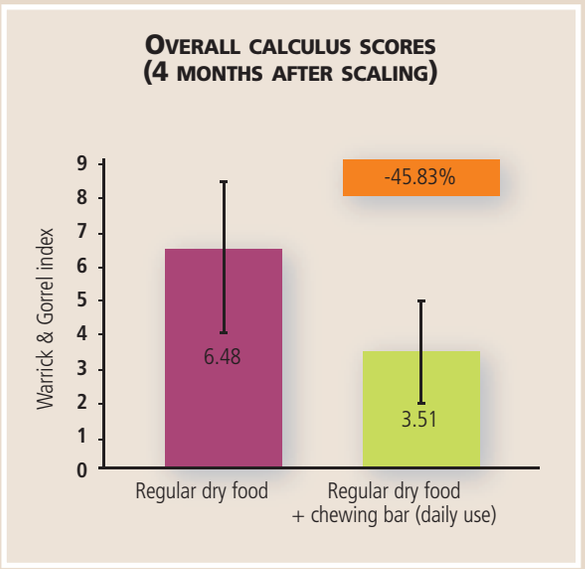
Over a short period (28 days)

The combination of traditional kibbles and a chewing bar for daily use is more effective than commercially available kibbles that are specially designed for oral hygiene, in terms of both plaque [-12%; p-value < 0.084] and calculus deposit reduction [-37%; p-value < 0.077].

Over a longer period (4 months)

The combination of traditional kibbles and a chewing bar for daily use is associated with a significant reduction in plaque deposit [-17%; p-value < 0.05] and the accumulation of calculus [-45%; p-value < 0.05], compared with a food constituted solely of kibbles.





Cavalier King Charles
A specially conceived chewing bar (formula, texture, shape and size) is an effective means of preventing periodontal disease as it limits dental deposits. This product is recommended as soon as the dog's final dentition has erupted.

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Nutritional status of dogs with cancer: dietetics evaluation and recommendations

1 - Nutritional assessment of the cancer patient 435
2 - The role of nutrition in cancer and cachexia 436
3 - Nutritional considerations for cancer and cachexia 439
4 - Nutritional intervention during cancer treatment 444

Frequently asked questions: Nutrition of dogs with cancer 445
References 446
Examples of home-prepared diets adapted to the treatment of cancer cachexia 448
Royal Canin Nutritional Information 450

Nutritional status of dogs with cancer: dietetic evaluation and recommendations

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Joseph Wakshlag graduated with a BS and MS from Montclair State University, and a DVM from the Cornell College in Veterinary Medicine. He is currently pursuing a Ph.D in pharmacology and is involved in residency training in Veterinary Nutrition. Research interests include the mechanisms of lean body wasting in dogs and cats, as well as amino acid and fatty acid metabolism in neoplasia. Extracurricular interests include metabolism of the athletic animal, which he directly examines 365 days a year in his kennel of Euro-hound sprint racing sled dogs.

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Francis Kallfelz graduated from the Cornell College of Veterinarian Medicine in 1962 and continued on to receive his Ph.D in physiology in 1966 studying calcium metabolism. Soon after graduating he became a faculty member in the department of Clinical Sciences at the Cornell College of Veterinary Medicine. He served as hospital Director from 1986-1997 and was also intimately involved with the Chartering of the American College of Veterinary Nutrition, which was established in 1988. Francis Kallfelz is presently the James Law Professor of Nutrition in the Department of Clinical Sciences. Though much of his career has been spent researching calcium, phosphorus, magnesium and vitamin D metabolism and absorption, his more recent research interests have been examining protein requirements and the molecular mechanisms of lean body wasting.

Nutrition is not often thought of as a critical issue in cancer management, but can be an important variable that effects quality of life and survival times. In patients with cancer, particularly metastatic disease, it is not a question of curing the patient, but a question of how can the quality of life for the patient be increased. Over the past 20 years there has been a growing literature base concerning the role of certain macronutrients (fats, protein, and carbohydrate) and micronutrients, (vitamins, minerals, fatty acids and amino acids) on neoplastic diseases. Though this area of investigation is still in its infancy, there is increasing evidence that nutritional management of neoplasia can have profound effects on the lives of the animals and owners that are involved in this disease process.

1 - Nutritional assessment of the cancer patient

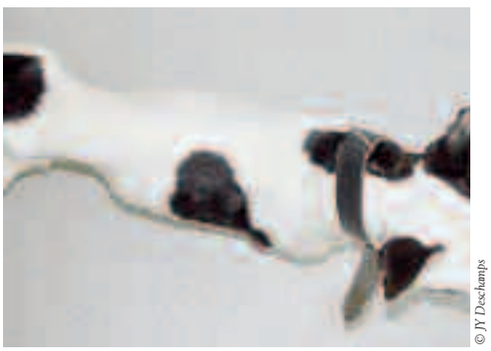
Though not the focus of this chapter, a patient that presents with anorexia requires immediate attention including administration of enteral, or possibly partial or total parental nutrition **(see chapter 14)**. It is often difficult to determine whether weight loss is due to anorexia, or cancer cachexia. Often in advanced neoplastic diseases there is an element of intermittent anorexia associated with chemotherapeutic treatment of the disease itself.

WHEN CANCER IS DIAGNOSED IN A DOG, THE VETERINARIAN GENERALLY ENCOUNTERS ONE OF THREE SITUATIONS:

1) Neoplasia without nutritional complications
2) Neoplasia with anorexia
3) Neoplasia with cachexia

Clinically, cachexia can be defined as progressive weight loss in the face of apparent adequate caloric intake. This situation may be caused by a variety of mechanisms, but is most commonly thought of as an alteration in the basal metabolic rate resulting in an increased resting energy requirement. However, other factors which are not due to an increase in the metabolic rate may also result in lean body wasting.

Obtaining a good history, a thorough physical examination, personal assessment and patient follow-up is critical in determining the metabolic status of the animal. To differentiate whether a cancer patient is hypermetabolic or if there are other mechanisms causing lean body wasting requires not only assessment of body weight, but also determining body condition score and attempting to subjectively determine whether there has been abnormal lean body wasting in the patient.



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In general, anorexia will result in weight loss primarily of adipose tissue, while patients with cachexia will lose nearly equal amounts of skeletal muscle and fat mass.

A veterinary study suggested that a significant sub-population (27%) of feline cancer patients will develop cachexia *(Baez et al, 2002)*. The percentage of canine cancer patients with cachexia has not yet been determined, but as treatment modalities extend the survival times of canine cancer patients, cachexia may become more prevalent.

Sophisticated tools including Dual Energy X-ray Absorptiometry (DEXA) and bioelectrical impedence can be used to assess lean body mass, however, these modalities are not available to most clinicians. Therefore regular measurement of body weight and body scoring are essential when monitoring neoplasia.

When assessing the cancer patient for excessive weight loss and lean body wasting, other diseases that must be ruled out include diabetes mellitus, cardiac disease, renal disease, and hyperthyroidism, since biochemical and hormonal stimulation of weight loss and cachexia may also occur in these diseases as well.

Guidelines that have been reported in studies of human cancer patients help to define abnormal weight loss and aid the definition of the cachectic response *(Inui, 2002)* **(Tables 1 & 2)**.

TABLE 1 - FEATURES OF STARVATION/ ANOREXIA VERSUS CACHEXIA

	Anorexia	Cachexia
Energy intake	⇩	⇧/⇨
Energy expenditure	⇩	⇧/⇨
Body fat	⇩	⇩
Skeletal muscle mass	⇨	⇩

TABLE 2 - GUIDELINES TO DETERMINE WHETHER CACHEXIA IS A COMPONENT OF WEIGHT LOSS

Nutritional Status	Change in body weight	Time interval
Healthy Adult	2%	1 month
Healthy Adult	3.5%	3 months
Suspect Cachexia	**5%**	**6 months**
Definite Cachexia	**> 10%**	**< 6 months**

Close scrutiny of scapular, hindlimb, and masticatory musculature is routinely necessary is cachexia is suspected *(Baez et al, 2002)*. Bony prominences such as the glenoid tuberosity, the spine of the scapula, the tuber ischii, greater trochanter of the femur and the sagittal crest of the skull become more evident in a short period of time.

Examination of the gluteal musculature and paralumbar muscles which lead to prominence of the ileal crest and vertebral spines are also easily useful for assessing lean body wasting **(Figure 1)**. Similar to body condition scoring (BCS) for obesity, there is a muscle condition scoring (MCS) system in development. This tool should be available for clinicians in the near future to help define cachexia and abnormal lean body wasting in dogs.

FIGURE 1 - CLINICAL CANCER CACHEXIA

Emaciated appearance due to inappropriate lean body wasting. Note the prominent ribs, hips, vertebrae and sagittal crest as well as the loss of hindlimb and pectoral musculature

THE TWO MAJOR NUTRITIONAL GOALS THAT NEED TO BE EQUALLY ADDRESSED IN A CANCER PATIENT ARE:

1) Inhibiting tumor growth

2) Preventing or managing cachexia

2 - The role of nutrition in cancer and cachexia

In some cases the demise of the patient with neoplasia is not due to the neoplasia itself, but to the overwhelming loss of body condition. Understanding these processes is important for appropriate nutritional intervention.

► Nutritional epidemiology of cancer in veterinary medicine

The role of nutrition in cancer prevention has become the subject of tremendous research in human medicine because of the variability in the human diet, and the awareness that certain dietary regimens may decrease the relative risk of neoplasia. This may also be true for companion animals, although most veterinary patients are receiving a more balanced diet than most humans. There have been three epidemiologic studies in dogs examining dietary and body conformation risk factors for mammary neoplasia. The results of these studies reported that the fat content of the diet had no significant relationship to the incidence of neoplasia, yet obesity did increase the relative risk of mammary carcinoma *(Sonnenshein et al, 1991)*.

Interestingly, one study showed that as the protein concentration of the diet increased, the relative risk of mammary neoplasia decreased, while a second study reported an increased relative risk of neoplasia in bitches fed raw meat as the primary source of caloric intake *(Shofer et al, 1989; Perez-Alenza et al, 1998)*. When interpreting the results from these studies, it can be deduced that

as the protein concentration in the dog food increases, the quality of the food is often better. Conversely, raw meat based diets are usually nutritionally unbalanced. Therefore, as the overall nutrient balance of the feed decreases, the incidence of neoplasia may increase. Hence, in veterinary patients it may be ideal to feed well balanced diets that comply with nutritional (National Research Council, NRC) guidelines for feeding dogs, when attempting to decrease the prevalence of certain neoplasias.

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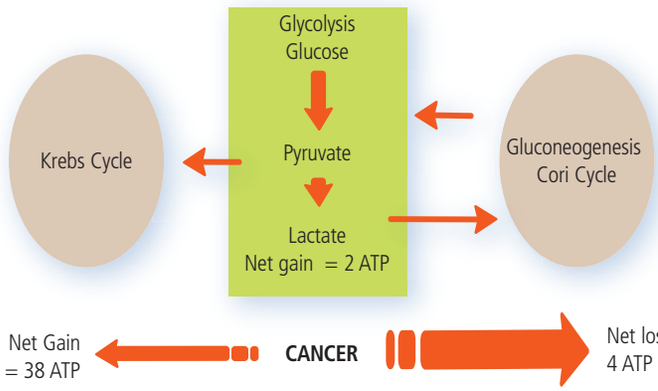
Many approaches have been taken over the past 40 years to influence neoplastic growth through nutritional modification.

► Energy requirements and neoplasia metabolism

Understanding the metabolism of neoplastic cell growth is essential to understanding nutritional intervention in cancer.

In general, neoplastic cells have higher rate of anaerobic energy metabolism than normal cells, therefore they rely more heavily on glucose, i.e. an up-regulation of the glycolytic pathway. This up-regulation of glycolysis leads to an accumulation of pyruvate which is rapidly converted to lactate, thereby resulting in a mild lactic acidosis, which has been documented in canine cancer patients *(Vail et al, 1990; Olgivie et al, 1997)*. Once lactate has been liberated from the neoplastic cell into the bloodstream it will be taken up by the liver, converted back into glucose, and may return to the neoplastic cell to undergo glycolysis, similar to the Cori Cycle *(Olgivie & Vail, 1990; Howard & Senior, 1999)* **(Figure 2)**. During this process of converting glucose into lactate there has been a gain of 2 ATP from glycolysis in the cancer cell, yet the conversion of lactate back into glucose in the hepatic cell requires 4 ATP and 2 GTP yielding a net loss of 2 ATP.

FIGURE 2 - GLUCOSE METABOLISM (CORI CYCLE)



Glucose metabolism during neoplasia indicating futile cycling and energy loss due to resynthesis of glucose from lactate in the Cori cycle.

Additionally, it has been shown that the humoral release of certain cytokines from inflammatory tissue around the neoplasia or from the neoplasia itself leads to uncoupling of oxidative phosphorylation in mitochondria, which may result in reduced ATP production *(Giordano et al, 2003)*.

Certain cytokines may also down-regulate endothelial lipoprotein lipase activity causing fatty acid and triglyceride accumulation in the bloodstream and prevent the storage of fatty acids within adipocytes. Together these changes may result in alterations in serum lipid profiles and hypertriglyderidemia which have been observed in dogs with lymphoma *(Olgivie et al, 1994)*.

To supply adequate energy for the futile cycling of various systems, and in an attempt to alter the dependency of neoplastic processes on anaerobic glycolysis, alterations in dietary levels of the energy providing substrates (protein, fat and carbohydrate) are often made in an attempt to slow progression of disease and thus increase survival time *(Argiules et al, 2003)*.

A major risk factor for cancer cachexia is the increase in energy requirements due to activation of proteolytic systems.

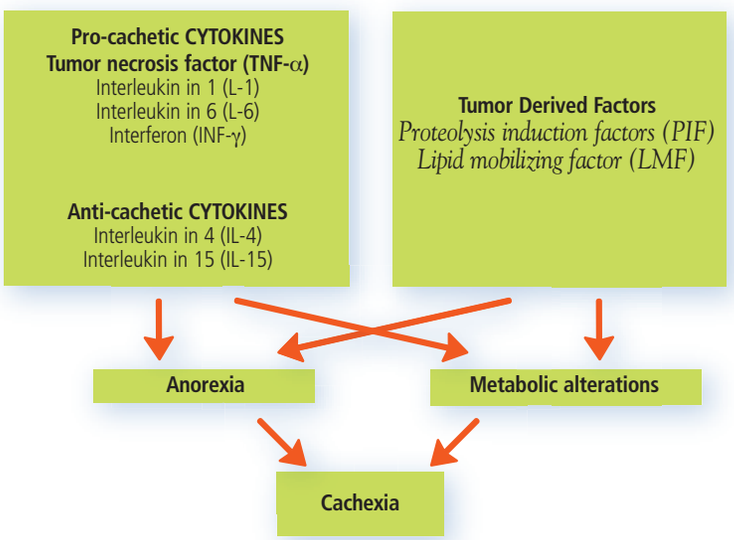
► Cancer cachexia

For many years it was thought that all patients with cancer cachexia had elevated resting metabolic rates due to the increased metabolism in cancerous tissue. However, many studies in human, and now veterinary medicine have shown that the resting metabolic rate after removal of tumors does not change. Furthermore, the resting metabolic rate can be extremely variable, and is often not correlated with the cachectic syndrome *(Vail et al, 1990; Olgivie et al, 1997; Argiules et al, 2003)*. Until recently it was thought that excessive lean body wasting was due to increased degradation of amino acids to support cancer growth, and without adequate intake the body would catabolize skeletal muscle to meet these demands.

Over the past ten years the role of various proteolytic systems (capthesins, calpains and ubiquitin/proteasome) involved in skeletal muscle atrophy associated with cancer cachexia have been studied. The ubiquitin/proteasome system has recently received a lot of attention as this system is up-regulated in cancer cachexia and other diseases associated with lean body wasting *(Baracos, 2000; Inui, 2002; Argiules et al, 2003)*. This is a complex system that marks a protein for degradation and then shuffles the tagged protein through a large multi-subunit protease called the proteasome. The process requires ATP, and may play a role in increasing the ATP consumption observed in neoplasia.

Though speculative, it is thought that the amino acids liberated from this process may be either used for energy production or lost in the urine. Many factors (i.e cytokines) have been implicated in the up-regulation of this system in cancer cachexia. Many of these factors are secreted into the blood stream by the primary or metastatic neoplastic tissue. Some of the more important factors include Tumor Necrosis Factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and a newly identified factor called Proteolysis Inducing Factor (PIF). PIF may be the most important factor involved in cancer cachexia *(Argiules et al, 2003; Baracos, 2000)* **(Figure 3)**.

FIGURE 3 - HUMORAL AND TUMOR DERIVED FACTORS ASSOCIATED WITH ANOREXIA AND CACHEXIA IN CANCER



A lipid mobilizing factor may be secreted by the tumor cells which induces an increase in the cytoplasmatic activity of the lipoprotein lipase in the adipocytes, exacerbating the loss of fat (Hirai et al, 1998; Tisdale, 2001).

3 - Nutritional considerations for cancer and cachexia

► Energy sources

Carbohydrate is often the most abundant energy source found in companion animal diets, particularly dry type canine diets. Since neoplastic tissue thrives on glucose as its primary energy substrate, the strategy is to force the neoplasia to use other substrates which may help in decreasing cell proliferation. During cachexia it may be important to provide extra dietary protein to help attenuate the cachectic process. Therefore, choosing a diet high in fat and protein with low carbohydrate may be helpful. Many premium dry and canned products, in particular specialty foods for active or stressed canines, may be used. Most of these products contain higher quality and quantities of protein and fat as compared to adult maintenance diets.

When changing commercial food, the guaranteed analysis for protein and fat content must be examined. Good guidelines are at least 35% protein and at least 25% fat on a dry matter basis for dogs. The guaranteed analysis can be used to estimate what percentage of protein, fat and carbohydrate are in the chosen food but it should be converted to a dry matter basis **(Table 3)**. Canned foods are often around 70-75% water, therefore the "as fed" percentages of protein and fat listed in the guaranteed analysis are much lower than in dry foods, but when examined for protein, fat and caloric content based on dry matter, they can actually be better than extruded products.

Contraindications for feeding such a diet include dogs and cats with congenital or acquired hypertriglyceridemia, a history of pancreatitis, or chronic renal disease.

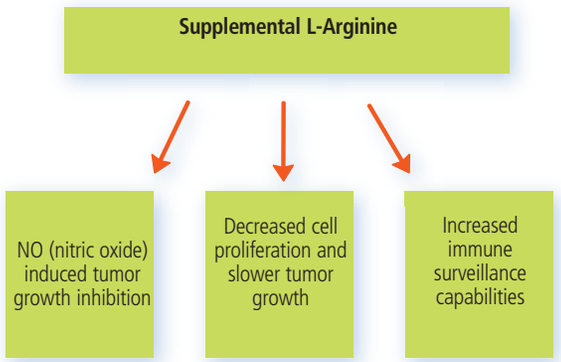
TABLE 3 - COMPARATIVE NUTRITIONAL ANALYSES OF DRY MATTER FROM GUARANTEED ANALYSIS OF DRY OR WET FOOD

dry food	canned food
1) Guaranteed Analysis: Not Less than 32% protein Not Less than 24% fat Not More than 10% moisture Not More than 3% fiber Not More than 7% ash	**1) Guaranteed Analysis:** Not Less than 12% protein Not Less than 10 % fat Not More than 72% moisture Not More than 2% ash Not More than 1% fiber
2) Add all percentages together 32 + 24 + 10 + 3 + 7 = 76%	**2.) Add all percentages together** 12 + 10 + 72 + 2 + 1 = 97%
3) 100 – 76 = 24 % **carbohydrate**	3) 100 – 97 = 3% **carbohydrate**
4) 100 – 10 (% moisture)/100 = 0.90 **DM**	4) 100 – 72 (% moisture)/100 = 0.28 **DM**
Protein: 32/0.9 = 35.5 %/MS **Fat:** 24/0.9 = 27.0%/MS **Fiber:** 3/0.9 = 3.3 %/MS **Ash:** 7/0.9 = 7.7 %/MS **Carbohydrate:** 24/0.9 = 26.5 %/MS	**Protein:** 12/0.28 = 42.0%/MS **Fat:** 10/0.28 = 36.0%/MS **Fiber:** 1/0.28 = 3.5%/MS **Ash:** 2/0.28 = 7.5%/MS **Carbohydrate:** 3/0.28 = 11.0%/MS

► Amino acids and fatty acids

It has been well documented that dietary amino acid alterations may be beneficial as an intervention to retard tumor growth in animal models *(Mills et al, 1998; Epner et al, 2002)*. Further developments in this area will likely lead to a better understanding of how manipulating amino acid metabolism can retard tumor progression and aid in quality of life and survival time of the patient with neoplasia.

FIGURE 4 - THE POTENTIAL ROLE OF ARGININE IN CANCER



Supplementing the arginine concentration in the diet to at least 2% of the amino acids may prove beneficial in dogs with cancer (Olgivie et al, 2000).

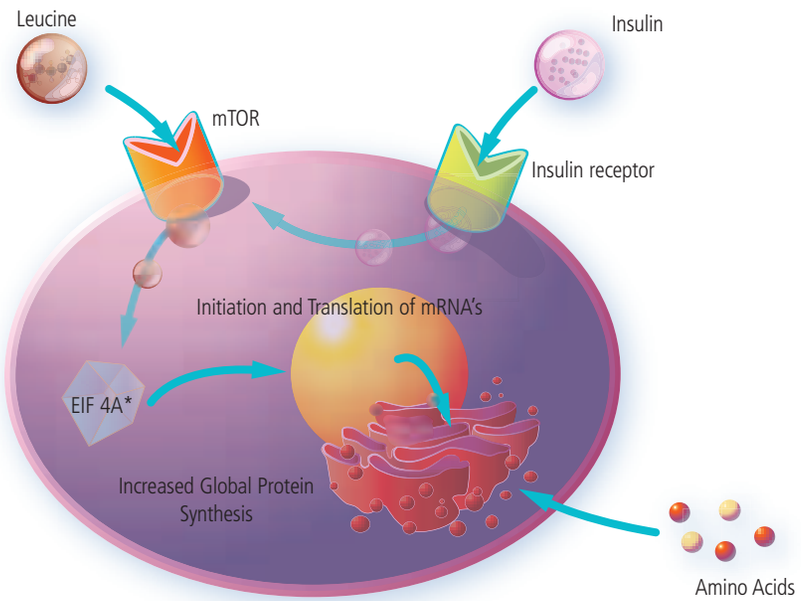
Increased dietary **arginine** has been shown to slow tumor progression in a number of animal models *(Burns et al, 1984; Milner et al, 1979; Robinson et al, 1999)*. This effect may be either due to the ability of arginine to form nitric oxide through NO synthase activity in neoplastic cells leading to retarded cell division, and/or its ability to increase cellular immune surveillance properties *(Reynolds et al, 1990; Robinson et al, 1999)*. The exact mechanism has yet to be elucidated, but providing up to 2% of dietary proteins as arginine may be beneficial to the canine cancer patient *(Olgivie et al, 2000)* **(Figure 4).**

Glutamine may also have suppressive effects on tumorigenesis. Glutamine appears to have a profound immuno-stimulatory role, which leads to greater whole body immunomodulation, and this immunomodulatory function may reduce tumor or metastasis growth rates *(Souba, 1993; Kaufmann et al, 2003)*. Glutamine has also been shown to improve gastrointestinal function and may be considered as a potential GI nutrient to optimize enterocyte function *(Souba, 1993)*. However, glutamine in foods appears to be very labile, particularly if they are exposed to excessive temperatures or in liquid format. After absorption, glutamine is rapidly transaminated by the liver, therefore its efficacy in pet foods for long term clinical cases of neoplasia is uncertain *(Bergana et al, 2000)*.

Branched Chain Amino Acids (BCAA - isoleucine, leucine, valine) are increasingly used as a supplement in critically ill patients due to the potential benefits cited in human literature. The use of BCAA's as anti-tumorigenic amino acids has been debated *(Danner & Priest, 1983; Blomgren et al, 1986; Saito et al, 2001)*, but it is likely that dietary supplementation with certain BCAA's (leucine) may be beneficial in conjunction with other amino acids like arginine in retarding tumor growth *(Wakshlag et al, 2004)*.

FIGURE 5 - PROPOSED ACTIONS OF LEUCINE ON SKELETAL MUSCLE PROTEIN SYNTHESIS

(Anthony et al, 2001 ; Kadawaki & Kanazawa, 2003)



**eukaryotic initiation factor 4A*
Compared with other amino acids, leucine may alter the balance towards anabolism and away from catabolism.

Interestingly, recent literature has demonstrated the beneficial effects of BCAAs for their anti-proteolytic effects during cachexia by increasing lean body mass and preventing excessive lean body wasting in cancer patients. Leucine, as a single amino acid supplement, has been shown to have profound effects of increasing protein synthesis in skeletal muscle when compared to dietary increases of other amino acids, shifting the balance towards anabolism rather than catabolism *(Kadawaki & Kanazawa, 2003; Anthony et al, 2001)* **(Figure 5)**.

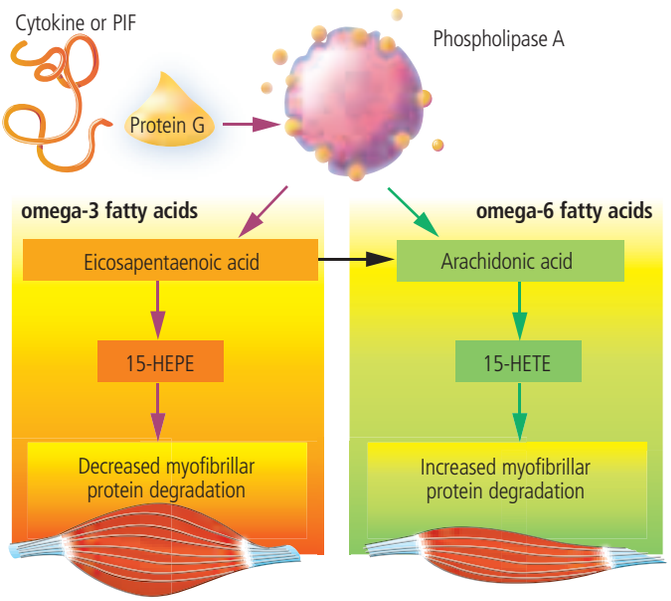
Recent clinical studies in humans have revealed increased survival times, improved nitrogen balance, and increased quality of life when diets supplemented with up to 12 grams of BCAAs were fed daily *(Ventrucci et al, 2001; Hiroshige et al, 2001; Inui, 2002; Gomes-Marcondes et al, 2003)*. Though there is no literature in veterinary medicine to support the use of BCAA's, experimental diets with up to 5% of dry matter as BCAAs or the addition of 3% leucine have been used without adverse effects in rodent models. Therefore a safe non-toxic dose for veterinary patients may be approxi-

mately 100-200 mg/kg.

► Fatty acids

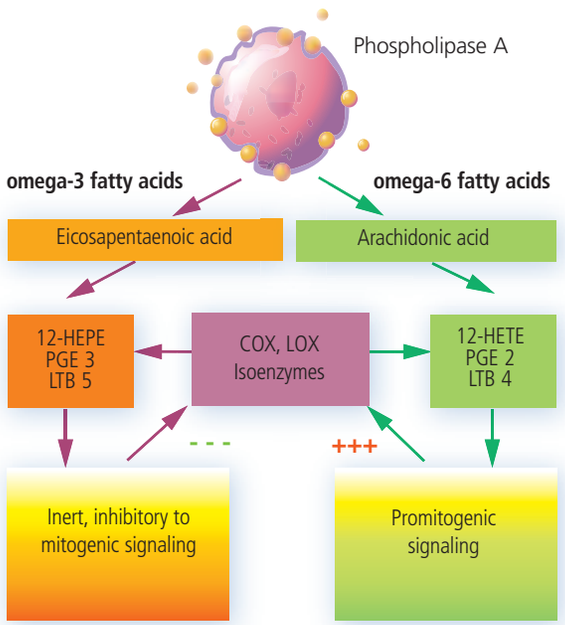
Increased intake of omega-3 fatty acids has shown strong correlation with remission and survival times, and decreased growth rate of carcinomas in animal models *(Thomson et al, 1996; Olgivie et al, 2000; Togni et al, 2003)*. In addition, human clinical studies have shown positive effects of omega-3 fatty acids supplementation on body weight, quality of life, disease free intervals and survival times in cancer cachexia patients. These changes may also be true for canine cancer patients

FIGURE 6 - PROPOSED ACTIONS OF OMEGA 3 VERSUS 6 FATTY ACIDS ON SKELETAL MUSCLE DEGRADATION



Omega-3 fatty acid supplementation, in particular eicosapentaenoic acid (EPA), has been shown to decrease 15-hydroxytetraenoic acid (15-HETES) concentration thereby suppressing proteolytic activity (i.e. proteasome activity) in skeletal muscle in a model of cancer cachexia (Belezario et al, 1991; Smith et al, 1999).

FIGURE 7 - PROPOSED ACTIONS OF OMEGA 3 VERSUS 6 FATTY ACIDS ON TUMOR CELL PROLIFERATION



EPA slows tumor growth by decreasing the production of promitogenic agents from arachidonic acid.

(Olgivie et al, 2000; Wigmore et al, 2000; Barber et al, 2001; Fearon et al, 2003) **(Figure 6)**. EPA and DHA can have a profound negative effect on cachexia. Furthermore, they may also attenuate tumor growth through their ability to decrease arachidonic acid metabolism by preventing the promitogenic production of PGE2 in neoplastic cells *(Yuri et al, 2003)* **(Figure 7)**. Fish oils (eg. Menhaden oil) are the richest source of the omega-3 fatty acids EPA and DHA **(Table 4)** and have been shown to be useful in ameliorating cachexia in human clinical trials *(Wigmore et al, 2000; Fearon et al, 2003)*. Some "premium" dog foods are supplemented with omega 3 fatty acids to achieve a 10:1-5:1 ratio of omega 6 to omega 3 fatty acids. The addition of fish oil can significantly alter the omega 6 to 3 ratio beyond what is already found in most pet foods *(Olgivie et al, 2000)*. Though not detrimental to most patients, ratios lower than 1:1 have been associated with increased clotting times and decreased vitamin E concentrations within cellular membranes *(Valk et al, 2000; Hendriks et al, 2002)*.

Only one canine clinical study has been performed with the use of fish oil at a ratio of 0.3:1 and the results showed increased survival times and disease free intervals in dogs with lymphoma, with no discernable side effects *(Olgivie et al, 2000)*. The clinical evaluation of fish oil supplementation in multiple other neoplastic conditions is presently underway and unpublished data suggest that fish oil may be promising for the management of several neoplastic conditions.

TABLE 4 - AVERAGE QUALITATIVE AND QUANTITATIVE COMPOSITION OF DIFFERENT SOURCES OF UNSATURATED FATTY ACIDS

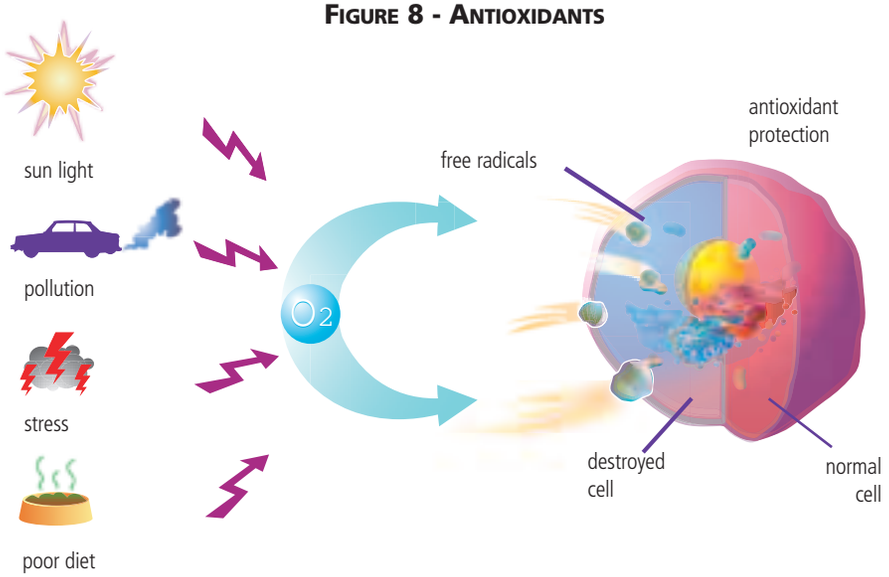
Fatty acids (% dry matter)	Soya oil	Flax seed oil	Rapeseed oil	Poultry fat	Fish oil
Linoleic acid (ω 6 precursor)	54	18	17	17	0,5
α-Linolenic (ω 3 precursor)	8	**51**	9	2,5	1,5
EPA + DHA	< 1	< 1	< 1	< 1	**20**
ratio ω6/ω3	6	0,35	1,8	9	0,15

► Vitamins and minerals

Supplemental feeding of common dietary antioxidants such as β-carotene, retinoids and vitamins C and E have all been associated with decreased risk of carcinogenesis in animal models and in epidemiological cohort studies. Selenium is the only mineral with similar anti-carcinogenic effects. The standing hypothesis is that many of these compounds, except for retinoids, act primarily as antioxidants to decrease cell damage **(Figure 8)**, in particular DNA damage, thus lowering the incidences of functional mutations in DNA resulting in lower incidences of cancer.

Many of these vitamins and minerals are present in adequate concentrations in most dog feeds, and their usefulness in neoplasia once already diagnosed, are largely undetermined. There are multiple human epidemiologic longevity and relative risk studies in progress, using many of these potential anti-carcinogenic agents. However, to date the indiscriminate use of these antioxidants as supplements cannot be supported in veterinary medicine because of the very different dietary patterns and metabolism of these substances in veterinary as compared to human patients.

FIGURE 8 - ANTIOXIDANTS



Antioxidants help the organism combat the destructive effects of free radicals, which are unstable elements continuously produced by the organism. The role of antioxidants constitutes one of the dominant themes in current medical research, particularly in the prevention or treatment of certain cancers.

β-Carotene, and other natural carotenoids and polyphenol compounds have been linked to cancer prevention through their ability to scavenge free radicals within cells in vitro *(Duthie et al, 2003; Cooper, 2004)*. β-carotene has been one of the most widely studied antioxidants in cancer prevention due to its potent antioxidant capabilities. Studies in humans predisposed to neoplasia (lung cancer) have shown that β-carotene supplementation may actually increase the relative risk of neoplasia *(Bendich, 2004; Russell, 2004)*. Considering these recent findings supplemental β-carotene in human medicine has evolved into a cautionary tale of micro-nutrient supplementation.

Sources of carotenoids, (β-carotene, lutein, lycopene, xanthene), generally found in red, green, yellow

and orange colored fruits and vegetables, are receiving significant attention because of their beneficial effects in specific cancers *(Wu et al, 2004; Murtaugh et al, 2004)*. However, their benefit in companion animals is confounded by the fact that carotenoids are absorbed differently in dogs than in humans. Dogs have a far better capacity to cleave β-carotene into retinal than humans, and absorb very little intact β-carotene *(Baskin et al, 2000)*. In light of these findings safety and efficacy data is needed in veterinary medicine before recommendations can be made for supplementing cancer patients with these potentially beneficial antioxidants.

Vitamins C and E are both potent antioxidants which have been shown in human clinical trials to reduce the risk of carcinogenesis *(Henson et al, 1991; Slung et al, 2003; Virtamo et al, 2003)*. Much like β-carotene, these antioxidants have been proven to be preventative rather than therapeutic. Vitamin C (ascorbic acid) has been associated with augmenting the effects of certain chemotherapeutic agents such as vincristine *(Osmak et al, 1997)*. While ascorbic acid supplements may help in some cases of drug resistant chemotherapy, it has also been argued that their use may have tumor promoting effects for some neoplasias, and anti-neoplastic activities for others *(Seifried et al, 2003; Lee et al, 2003)*. No controlled studies have been performed to assess its efficacy in the veterinary patient. Ascorbic acid is synthesized in the dog therefore the relative risk of neoplasia due to deficiency over the lifetime of the animal is not an known. Vitamin E, on the other hand, is required in the diet and further investigation into its efficacy as an anti-neoplastic agent is warranted.

Retinoids (Retinoic acid and retinoic acid derivatives) have been extensively used in the treatment of acute promyelocytic leukemias, and have been associated with increased remission rates in human mammary cancer *(Paik et al, 2003; Altucci et al, 2004)*. They attach to nuclear receptors initiating transcription of genes, promoting cellular differentiation or apoptosis of neoplastic cells. These findings have lead to the use of natural and synthetic retinoid derivatives in the treatment of human cancer. In time such approaches may cross over to veterinary medicine as experimental clinical data is collected regarding efficacy of these retinoids in various neoplastic conditions in animals. Considering the highly potent effects of retinoids, such as retinoic acid which is a known teratogen, and due to toxic effects, e.g cervical spondylosis in cats, as well as anorexia and clotting disorders, recommendations cannot be made at this time for their use in the small animal cancer therapy *(Hayes, 1982)*.

Selenium is the only mineral known to have anti-tumorigenic and preventative properties. There is conclusive evidence that higher serum selenium concentrations are associated with lower incidences of skin, lung and prostate carcinomas in humans *(Duffield-Lillico et al, 2003; Reid et al, 2002; Nelson* et *al, 1999; Clark et al, 1996)*. These actions are thought to be separate from the antioxidant properties of selenium via its role in glutathione peroxidase.

The AAFCO dog food nutrient profile recommended concentration of selenium is met in most commercial pet foods, but the NRC recommendation has recently tripled, therefore the selenium intake of many companion animals may be low normal or deficient. In light of this, and the human clinical studies showing that selenium supplementation has the greatest effects in reducing the relative risk of cancer in those people with low normal serum selenium concentrations *(Clark et al, 1996; Nelson et al, 1999; Reid et al, 2002; Duffield-Lillico et al, 2003)*, it may be wise to supplement (2-4 µg/kg BW/day) animals with a history of neoplasia or a predisposition to develop cancer. At this conservative recommended dose the risks for toxicity are minimal and such supplementation will likely ensure adequate selenium intake.

Overall, when using specific nutrients pharmacologically one may be able to retard tumor growth, enhance quality of life and ameliorate body condition to a certain extent. Yet, it can be difficult to address the specific needs for each neoplastic condition due to the complex nature of cancer, and the various nutrient compositions of the variety of feeds that are available. To properly

Table 5 - Recommended dosages for nutritional intervention in cancer

Supplement	Condition	Canine Dose
Arginine	Cancer & Cachexia	2% of Dry Matter
Fish oil (EPA-DHA)	Cancer & Cachexia	1:1- 0.5:1 ratio of 6 to 3*
Branch chain amino acids	Cachexia	100-150 mg/kg
Selenium	Cancer	2-4 µg/kg

** It is essential to know either or both the omega-3 fatty acid, omega-6 fatty acid content in dry matter to properly formulate the diet at the desired ratio.*

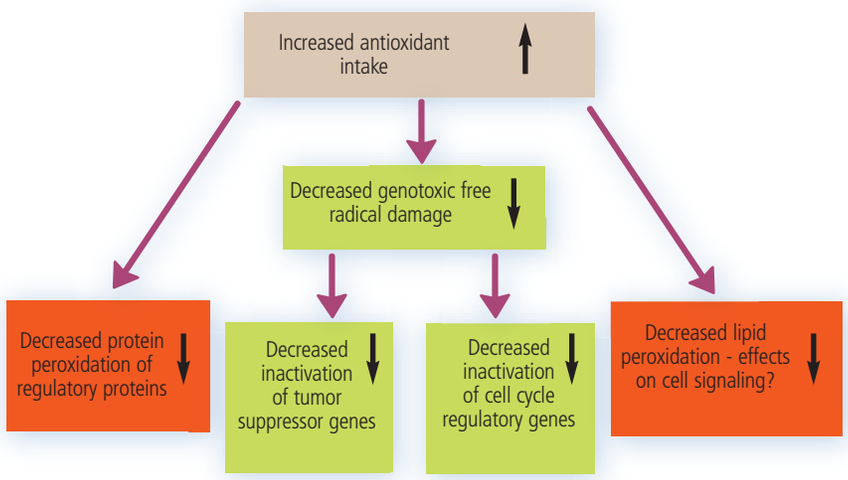
address these nutritional issues, the practitioner needs to know the food consumption and the dry matter content of various nutrients in the given feed, before an effort to alter ratios or total intake of many of the aforementioned nutrients can be made. **Table 5** provides some guidelines for nutritional intervention that should be beneficial in most aggressive neoplastic conditions and can be used once the practitioner has calculated contents of various nutrients in the given food.

4 - Nutritional intervention during cancer treatment

In recent years there has been a significant increase in the use of antioxidants in pet foods, which has hypothetically been associated with less free radical damage in cells throughout the body. This antioxidant supplementation has been associated with amelioration of a variety of different disease processes **(Figure 9)**.

Though these approaches to cancer prevention may be beneficial in theory, once the veterinary patient has been diagnosed with cancer and is undergoing chemotherapy or radiation therapy, use of various antioxidants may actually be contraindicated. If antioxidants are used to prevent free radical damage, and a chemical or radiation treatment has been initiated, the higher levels of cytosolic or membrane bound antioxidant may actually provide a survival advantage to cancer cells. Therefore, it has been recommended by many veterinary oncologists that pets not be given these antioxidant supplements during such treatment. This hypothesis is very controversial, and has yet to be proven. Since the veterinary patient is usually already ingesting sufficient amounts of the essential antioxidants, supplementation may not be necessary *(Virtamo et al, 2003; Prasad, 2004)*.

Figure 9 - Antioxidants and cancer prevention



Massive antioxidant supplementation may be contra-indicated during chemotherapy or radiation therapy, as antioxidant supplementation may facilitate the survival of cancer cells.

On the other hand, many other ingredients and nutrients such as fish oil and arginine, are unlikely to be detrimental. Indeed, supplementation with fish oil has been associated with better radiation therapy recovery and less inflammation to surrounding tissue. Studies in animal models have also suggested that the increase in long chain polyunsaturated fatty acids in cell membranes resulting from fish oil supplementation may actually provide more highly reactive fatty acids for lipid peroxidation during radiation therapy, thus promoting cell death in the neoplastic tissue *(Colas et al, 2004)*.

Conclusion

Clinical veterinary studies have shown that a number of metabolic anomalies produced in human and rodent cancer models are also found in dogs. The nutritional approach to cancer used in human medicine could therefore be adapted to veterinary medicine to influence the progression of the cancer.

Frequently asked questions: Nutrition of dogs with cancer

Q	A
If my dog refuses to eat a new food can I give fish oil on top of the present feed?	Fish oil can be added to regular grocery store brand dog food, but it is ideal to know how much omega-3 fatty acids is already present in the food. A typical beagle, eating a typical grocery store brand food will eat about 6 grams of omega 6 fatty acids a day and only 100 mg of omega-3 fatty acids, so to get to a 1:1 ratio, you would need about 6 grams of omega-3 fatty acids from fish oil. Remember that only 30% of fish oil are omega-3 fatty acids, so you have to triple the fish oil given, thus 18 grams or just over a tablespoon is needed each day.
My dog doesn't like the fish oil. Can I give another source of omega-3 fatty acids?	Flax-seed oil is rich in linolenic acid, a EPA-DHA precursor. It may prove interesting but its clinical efficiency has not been demonstrated with respect to cancer. Another alternative is to feed descented fish oil or lemon flavored fish oil.
If an owner wants to use various antioxidants, which are recommended, and when should they be given if radiation or chemotherapy treatment has been initiated?	The antioxidants that are likely to be safest are those that have the most clinical and cell biological research behind them. Often vitamin E and vitamin C come to mind. Recent research on thiol antioxidants like lipoic acid and the glutathione precursor s-adenosyl-methionine, both of which have few to no known side effects, maybe of interest. If owners feel strongly about using these antioxidants, it is ideal to use them as directed by the manufacturers, and using veterinary formulated products is often safer than using human formulations. If dogs are receiving chemotherapy/radiation treatments then removing all supplemental antioxidants one week before treatment and continuing them again one week after the treatment protocol has been terminated is likely to be the safest approach at this time.
Some owners feel that changing their animal to a "holistic" or "homemade" diet would provide some benefit during cancer, is this a wise approach?	Often owners find diets on the internet that have been designed for canine cancer patients and will implement them, hoping they will prolong survival or cure the neoplasia. More often than not, there are gross imbalances in vitamins and minerals in these diets. It is ideal to have a veterinary nutritionist intervene in these cases and analyze the proposed diet to ensure that there are no gross imbalances.
Often in the anorexia/cachexia syndrome it becomes difficult to implement the diet changes needed, and a diet with lower caloric density may be the diet of choice by the patient? What should the owner do?	In those cases it easier to let the patient choose their feed and attempt to supplement fat and protein sources to increase the caloric density and protein content of the meal. Remember during anorexia/cachexia some caloric intake though not optimal for the disease is better than no caloric intake at all.

References

Altucci L, Wilhelm E, Gronemeyer H - Leukemia: beneficial actions of retinoids and rexinoids. Int J Biochem Cell Biol 2004; 36: 178-82.

Anthony JC, Anthony TG, Kimball SR, et al - Signaling pathways involved in translational control of protein synthesis in skeletal muscle by leucine. J Nutrition 2001; 131: 856S-860S.

Argiules JN, Rodrigo MC, Busquets S et al - Catabolic mediators as targets for cancer cachexia. Drug Disc Today 2003; 838-844.

Baez JL, Michel KE, Sorenmo KU - The characterization of cancer cachexia in cats, of the Am Coll Vet Intern Med Proceedings of the Am Coll Vet Intern Med 2002: 4.

Baracos VE - Regulation of skeletal muscle-protein turnover in cancer associated cachexia. Nutrition 2000; 16: 1015-1018.

Barber MD, Fearon KC, Tisdale MJ et al - Effect of a fish oil-enriched nutritional supplement on metabolic mediators in patients with pancreatic cancer cachexia. Nutr Cancer 2001; 40: 118-24.

Baskin CR, Hinchcliff KW, DiSilvestro RA et al - Effects of dietary antioxidant supplementation on oxidative damage and resistance to oxidative damage during prolonged exercise in sled dogs. Am J Vet Res 2000; 61: 886-91.

Belezario JE, Katz M, Chenker E et al - Bioactivity of skeletal muscle proteolysis-inducing factors in the plasma proteins from cancer patients with weight loss. Br J Cancer 1991; 63: 705-10.

Bendich A - From 1989 to 2001: what have we learned about the "biological actions of beta-carotene"? J Nutr 2004; 134: 225S-230S.

Bergana MM, Holton JD, Reyzer IL et al - NMR and MS analysis of decomposition compounds produced from N-acetyl-L-glutamine. J Agric Food Chem 2000; 48: 6003-6010.

Blomgren H, Naslund I, Esposti PL et al - L-isoleucine and L-leucine: tumor promoters of bladder cancer in rats. Science 1986; 231: 843-5.

Burns RA, Milner JA - Effects of arginine on the carcinogenicity of 7,12-dimethylbenz(a)-anthracene and N-methyl-N-nitrosurea. Carcinogenesis 1984; 5: 1539-1542.

Colas S, Paon L, Denis F et al - Enhanced radiosensitivity of rat autochthonous mammary tumors by dietary docosahexaenoic acid. Int J Cancer 2004; 109: 449-54.

Clark LC, Comb GF Jr, Turnbull BW et al - Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. JAMA 1996; 276: 1957-63.

Cooper DA - Carotenoids in health and disease: recent scientific evaluations, research recommendations and the consumer. J Nutr 2004; 134: 221S-224S.

Danner DJ, Priest JH - Branched-chain ketoacid dehydrogenase activity and growth of normal and mutant human fibroblasts: the effect of branched-chain amino acid concentration in culture medium. Biochem Genet 1983; 21: 895-905.

Duffield-Lillico AJ, Dalkin BL, Reid ME et al - Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. BJU Int 2003; 91: 608-12.

Duthie GG, Gardner PT, Kyle JA - Plant polyphenols: are they the new magic bullet? Proc Nutr Soc 2003; 62: 599-603.

Epner DE, Morrow S, Wilcox M et al - Nutrient intake and nutritional indexes in adults with metastatic cancer on a phase I clinical trial of dietary methionine restriction. Nutr Cancer 2002; 42: 158-66.

Fearon KC, Von Meyenfeldt MF, Moses AG et al - Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial. Gut 2003; 52: 1479-86.

Giordano A, Calvani M, Petillo A et al - Skeletal muscle metabolism in physiology and in cancer disease. J Cell Biochem 2003; 90: 170-186.

Gomes-Marcondes MC, Ventrucci G, Toledo MT, et al - A leucine-supplemented diet improved protein content of skeletal muscle in young tumor-bearing rats. Braz J Med Biol Res 2003; 36: 1589-94.

Hayes KC - Nutritional problems in cats: taurine deficiency and vitamin A excess. Can Vet J 1982; 23: 2-5.

Hendriks WH, Wu YB, Shields RG et al - Vitamin E requirement of adult cats increases slightly with high dietary intake of polyunsaturated fatty acids. J Nutr 2002; 132: 1613S-5S.

Henson DE, Block G, Levine M - Ascorbic Acid: biologic functions and relation to cancer. J Natl Cancer Inst 1991; 83: 1483-1492.

Hirai K, Hussey HJ, Barber MD et al - Biological evaluation of a lipid mobilizing factor isolated from the urine of cancer patients. Cancer Res 1998; 58: 2359-2365.

Hiroshige K, Sonata T, Suda T et al - Oral supplementation of branched chain amino acid improves nutritional status in elderly patients on chronic hemodialysis. Nephrol Dial Transplant 2001; 16: 1856-1862.

Howard J, Senior DF - Cachexia and nutritional issues in animals with cancer. J Am Vet Med Assoc 1999 ; 214: 632-636.

Inui A - Cancer Anorexia-Cachexia Syndrome: Current issues in research and management. A Cancer Journal for Clinicians 2002; 52: 72-91.

Kadawaki M, Kanazawa T - Amino acids as regulators of proteolysis. J Nutr 2003; 133: 2052S-2056S.

Kaufmann Y, Kornbluth J, Feng Z et al - Effect of glutamine on the initiation and promotion phases of DMBA-induced mammary tumor development. J Parenter Enteral Nutr 2003; 27: 411-8.

Lee KW, Hyong JL, Surh YJ et al - Vitamin C and cancer chemoprevention: reappraisal. Am J Clin Nutr 2003; 78: 1074-1078.

Mills RM, Diya CA, Reynolds ME et al - Growth inhibition of subcutaneously transplanted hepatomas without cachexia by alteration of the dietary arginine-methionine balance. Nutr. Cancer 1998; 31: 49-55.

Milner JA, Stepanovich MA - Inhibitory effect of dietary arginine on growth of Ehrlich ascites tumor cells in mice. J Nutr 1979; 109: 489-94.

Murtaugh MA, Ma KN, Benson J et al - Antioxidants, carotenoids, and risk of rectal cancer. Am J Epidemiol 2004; 159: 32-41.

National Research Council of the National Academies - Nutrient requirements of dogs and cats.The National Academies Press, 2006; Washington D.C

Nelson MA, Porterfield BW, Jacobs ET et al - Selenium and prostate cancer prevention. Semin Urol Oncol 1999; 17: 91-6.

Olgivie GK, Fettman MJ, Mallinckrodt CH et al - Effect of fish oil, arginine, and doxorubicin chemo-

therapy on remission and survival time for dogs with lymphoma: a double-blind, randomized placebo-controlled study. Cancer 2000; 88: 1916-28.

Ogilvie GK, Ford RB, Vail DM et al - Alterations in lipoprotein profiles in dogs with lymphoma. J Vet Intern Med 1994; 8: 62-66.

Ogilvie GK, Vail DM - Nutrition and cancer. Recent developments. Vet Clin North Am Small Anim Pract 1990; 20: 969-85.

Ogilvie GK, Walters L, Salman MD et al - Alterations in carbohydrate metabolism in dogs with nonhematopoietic malignancies. Am J Vet Res 1997; 58: 277-81.

Osmak M, Kovacek I, Ljubenkov et al - Ascorbic acid and 6-deoxy-6-chloro-ascorbic acid: potential anticancer drugs. Neoplasma 1997; 44: 101-7.

Paik J, Blaner WS, Sommer KM et al - Retinoids, retinoic acid receptors, and breast cancer. Cancer Invest 2003; 21: 304-12.

Perez-Alenza D, Rutteman GR, Pena L et al - Relation between habitual diet and canine mammary tumors in a case-control study. J Vet Intern Med 1998; 12: 132-139.

Prasad KN - Antioxidants in cancer care: when and how to use them as an adjunct to standard and experimental therapies. Expert Rev Anticancer Ther 2004; 3: 903-15.

Reid ME, Duffield-Lillico AJ, Garland L et al - Selenium supplementation and lung cancer incidence: an update of the nutritional prevention of cancer trial. Cancer Epidemiol Biomarkers Prev 2002; 11: 1285-91.

Reynolds JV, Daly JM, Shou J et al - Immunologic effects of arginine supplementation in tumor-bearing and non-tumor-bearing hosts. Ann. Surg 1990; 211: 202-210.

Robinson LE, Bussiere FI, LeBoucher J et al - Amino acid nutrition and immune function in tumor bearing rats: a comparison of glutamine-, arginine- and ornithine 2-oxoglutarate-supplemented diets. Clin. Sci 1999; 97: 657-669.

Russell RM - The enigma of beta-carotene in carcinogenesis: what can be learned from animal studies. J Nutr 2004; 134: 262S-268S.

Saito Y, Saito H, Nakamura M et al - Effect of the molar ratio of branched chain to aromatic amino acids on growth and albumin mRNA expression of human liver cancer cell lines in a serum-free environment. Nut Canc 2001; 39: 126-131.

Seifried HE, McDonald SS, Anderson DE et al - The antioxidant conundrum in cancer. Cancer Res 2003; 63: 4295-8.

Shofer FS, Sonnenschein EG, Goldschmidt MH et al. Histopathologic and dietary prognostic factors for canine mammary carcinoma. Breast Cancer Res Treat 1989; 13: 49-60.

Smith HJ, Lorite MJ, Tisdale MJ - Effect of a cancer cachectic factor on protein synthesis/degradation in murine C2C12 myoblasts: modulation by eicosopentaenoic acid. Canc Res 1999; 59: 5507-5513.

Sonnenshein EG, Glickman LT, Goldschmidt MH et al - Body conformation, diet, and risk of breast cancer in pet dogs: a case-control study. Am J of Epidem1991; 133: 694-703.

Souba WW - Glutamine and cancer. Ann Surg 1993; 218: 715-728.

Sung L, Greenberg ML, Koren G et al - Vitamin E: the evidence for multiple roles in cancer. Nutr Cancer 2003. 46: 1-14.

Thompson LU, Rickard SE, Orcheson LJ et al - Flaxseed meal and its lignin and oil components reduce mammary tumor growth at a late stage of carcinogenesis. Carcinogenesis 1996; 17: 1373-1376.

Tisdale MJ - Cancer anorexia and cachexia. Nutrition 2001; 17: 438-442.

Togni V, Ota CC, Folador A et al - Cancer cachexia and tumor growth reduction in Walker 256 tumor-bearing rats supplemented with N-3 polyunsaturated fatty acids for one generation. Nutr Cancer 2003; 46: 52-8.

Vail DM, Ogilvie GK, Wheeler SL et al - Alterations in carbohydrate metabolism in canine lymphoma. J Vet Intern Med 1990; 4: 8-11.

Valk EE, Hornstra G - Relationship between vitamin E requirement and polyunsaturated fatty acid intake in man: a review. Int J Vitam Nutr Res 2000; 70(2): 31-42.

Ventrucci G, Mello MA, Gomes-Marcondes MC - Effects of a leucine-supplemented diet on body composition changes in pregnant rats bearing Walker 256 tumor. Braz J Med Biol Res 2001; 4: 333-8.

Virtamo J, Pietinen P, Huttunen JK et al - Incidence of cancer and mortality following alpha-tocopherol and beta-carotene supplementation: a postintervention follow-up. JAMA 2003; 290: 476-85.

Wakshlag JJ, Kallfelz FA, Wakshlag RR - Effects of branched chain amino acids on canine neoplastic cell lines. J of Animal Phys and Animal Nutr. 2004; submitted for publication.

Wigmore SJ, Barber MD, Ross JA et al - Effect of oral eicosapentaenoic acid on weight loss in patients with pancreatic cancer. Nutr Cancer 2000; 36(2): 177-84.

Wu K, Erdman JW Jr, Schwartz SJ - Plasma and dietary carotenoids, and the risk of prostate cancer: a nested case-control study. Cancer Epidemiol Biomarkers Prev 2004; 13: 260-9.

Yuri T, Danbara N, Tsujita-Kyutoku M - Dietary docosahexaenoic acid suppresses N-methyl-N-nitrosourea-induced mammary carcinogenesis in rats more effectively than eicosapentaenoic acid. Nutr Cancer 2003; 45: 211-7.

EXAMPLES OF HOME-PREPARED THE TREATMENT OF

Example 1

COMPOSITION
(1000 g diet)

Quark, fresh cheese, 40% fat . . . . . 415 g
Acid curd cheese * . . . . . 150 g
Whole egg . . . . . .120 g
Cow's milk, UHT . . . . . 120 g
Potato, cooked, with skin . . . . . .150 g
Honey . . . . . .20 g
Wheat bran . . . . . .5 g
Rapeseed oil . . . . . 20 g

**40% fat grasses on dry matter*

Add a well-balanced mineral and vitamin supplement.

ANALYSIS

The diet prepared in this way contains 28% dry matter and 72% water

	% dry matter	g/1000 kcal
Protein	40	78
Fat	31	59
Available carbohydrate	21	41
Fiber	2	3

INDICATIVE RATIONING

Energy value (metabolizable energy): 1465 kcal/1000 g of diet prepared 5150 kcal/1000 g DM

Dog's weight (kg)	Daily amount (g)*	Dog's weight (kg)	Daily amount (g)*
2	150	45	1540
4	250	50	1670
6	340	55	1790
10	500	60	1910
15	680	65	2030
20	840	70	2150
25	990	75	2260
30	1140	80	2370
35	1280	85	2480
40	1410	90	2590

Key Points

- **High energy density to** favor the amelioration of the body condition and of palatability
- **Maintaining a high protein-calorie ratio despite the high fat content** to combat muscle atrophy
- **Highly digestible ingredients** to maximize the nutritional benefit for the dog

**The fractioning of the daily amount over two or three meals is recommended to favor good digestion.*

DIETS ADAPTED TO CANCER CACHEXIA

Example 2

COMPOSITION
(1000 g diet)

Beef, minced meat, 10% fat . . . . . 500 g
Cow's milk, UHT . . . . . 130 g
Whole egg . . . . . 75 g
Potato, cooked, with skin . . . . . 255 g
Wheat bran . . . . . 20 g
Rapeseed oil . . . . . 20 g

Add a well-balanced mineral and vitamin supplement.

INDICATIVE RATIONING

Energy value (metabolizable energy): 1445 kcal/1000 g of diet prepared 4870 kcal/1000 g DM

Dog's weight (kg)	Daily amount (g)*	Dog's weight (kg)	Daily amount (g)*
2	150	45	1560
4	250	50	1690
6	340	55	1820
10	510	60	1940
15	690	65	2060
20	850	70	2180
25	1010	75	2290
30	1150	80	2410
35	1290	85	2520
40	1430	90	2630

ANALYSIS

The diet prepared in this way contains 30% dry matter and 70% water

	% dry matter	g/1000 kcal
Protein	40	83
Fat	29	60
Available carbohydrate	17	35
Fiber	4	9

Examples of home-made diets are proposed by Pr Patrick Nguyen
(Nutrition and Endocrinology Unit; Biology and Pathology Department, National veterinary School of Nantes)

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Cancerous conditions are relatively common in giant breeds, especially osteosarcoma.

Key Points
to remember in:

Nutritional management of dogs with cancer

- The preferred energy sources are fat and protein, at the expense of carbohydrate, which is highly valued by cancer cells. The main principles of formulation are the same as diets that meet the requirements of sporting and working dogs.
- **Fat** helps to increase the energy concentration of the food, which is necessary in anorectic or cachexic patients.
- Enriching the **long-chain omega 3 fatty acid** (EPA-DHA) content in the food helps the dog benefit from the anti-neoplastic properties of EPA-DHA.
- **A high-protein diet** helps combat muscle wasting during cancer cachexia. The amino acids that play an important role in slowing the progression of the tumor, include:
  - **arginine**, which favors nitric oxide production
  - **glutamine**, which has immune-modulating actions
  - **branched chain amino acids** (e.g. leucine, isoleucine and valine), which help combat cachexia.
- **Antioxidant supplementation** (e.g. vitamins E and C, β-carotene, polyphenols, selenium) is of major interest in preventing cancer. However, based on our knowledge at this time, antioxidant supplementation should be avoided during chemotherapy or radiation therapy so that the efficacies of these therapies are not compromised.
- **The palatability of the food** is key in anorexic and cachectic dogs.

Focus on:

BRANCHED CHAIN AMINO ACIDS

Among the essential amino acids, leucine, isoleucine and valine constitute a category of their own called the branched chain amino acids (BCAA's). The dog is incapable of synthesizing adequate amounts of these three amino acids, so dietary intake is needed to meet daily requirements. The concentration of these three amino acids in the blood is very dependent on dietary intake.

Valine, leucine and isoleucine represent at least one third of the essential amino acids constituting muscle proteins and are the only amino acids that are initially degraded by muscles. These three amino acids are unique among the essential amino acids because they are able to undergo reversible transamination to enrich the organism's nitrogen pool.

Valine, leucine and isoleucine are able to stimulate the synthesis of proteins and slow protein degradation in muscles. This property has been specifically attributed to leucine, as it proves as effective as a mixture of the three BCAA's.

In rats, stimulation of protein synthesis by leucine follows a dose-response type curve. This stimulation is produced at very low leucine concentrations, identical to those observed in the blood just before a meal. In older rats, much higher leucine concentrations are needed to obtain maximum stimulation *(INRA, 2002)*. The sensitivity to leucine intake is therefore reduced. This loss of sensitivity may explain the absence of increased muscle protein synthesis after meals in aging subjects.

Leucine
Isoleucine
Valine + α-ketoglutarate → glutamate + α-ketoisocaproate
α-keto β methylvalerate
α-ketoisovalerate

EXAMPLES OF BRANCHED CHAIN AMINO ACID LEVELS IN SELECTED RAW INGREDIENTS USED IN DOG FOODS

(Source: Royal Canin internal data)

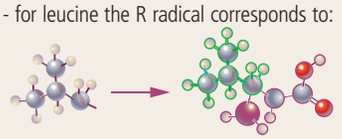
% of the protein of the food	leucine	isoleucine	valine	total BCAA's
Poultry protein	6.5	3.5	4.3	14.3
Corn gluten	14.7	3.6	4.2	22.5
Corn	13.0	3.9	5.1	22.0
Barley	7.0	3.8	5.3	16.1
Rice	7.7	4.1	5.6	17.4

Corn proteins are particularly high in leucine.

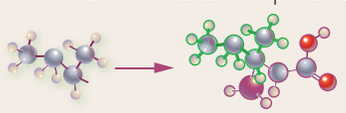
CHEMICAL FORMULA OF BRANCHED CHAIN AMINO ACIDS

The general structure of amino acids is:

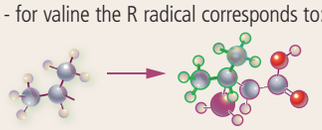
- for leucine the R radical corresponds to:



- for isoleucine the R radical corresponds to:



- for valine the R radical corresponds to:



Reference

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Critical care nutrition of dogs

1 - Pathophysiology 455
2 - Indications for nutritional support 455
3 - Supplementary tests 456
4 - Determination of the best approach regarding nutritional support: decision trees 459
5 - Enteral nutrition 459
6 - Parenteral feeding 466
7 - Complications linked to enteral or parenteral feeding 472

References 475
Royal Canin Nutritional Information 476

Critical care nutrition of dogs

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The beneficial effects derived from the nutritional support of diseased human patients and experimental animal models include enhanced immune function, wound repair, response to therapy, recovery time, and survival. Despite these benefits, the nutritional needs of hospitalized patients are often ignored due to the intense focus on life-threatening medical and surgical problems. The goal of nutritional support is to provide energy and nutrients in proportions that can be utilized by the patient with maximal efficiency.

Malnutrition is probably more common in veterinary patients than is recognized. Malnutrition is an unbalanced intake of protein and/or calories to support tissue metabolism and has the potential to undermine proper medical or surgical therapeutic management of a hospital case *(Remillard et al, 2001)*. Some dogs are likely to be deficient in either protein and/or calories due to a reduction in food intake.

A recent publication estimated the proportion of hospitalized canine patients in a negative energy balance *(Remillard et al, 2001)*. The study was conducted at four veterinary referral hospitals across the USA. Overall, daily feeding data and outcomes for 276 dogs over 821 days in the hospital were evaluated. In 73% of those days a negative energy balance was obtained (< 95% RER [resting energy requirement]).

This was attributed to three main factors:
- 22% due to poorly written orders
- 34% due to orders to withhold food
- 44% of the dogs refused to eat.

Overall, the study found that caloric intake had a significant, positive effect on patient outcome.

1 - Pathophysiology

Simple starvation implies that the patient is healthy, but is somehow deprived of food, while complicated starvation is reserved for patients where disease has induced a state of anorexia. The ability of the body to respond to starvation is often altered in disease. Therefore, the healthy dog's ability to cope with starvation should not be relied upon exclusively as a model for the sick and anorexic patient. Many disease states may result in an increased need for both energy and additional nutrients beyond what is required during simple starvation **(Table 1)**.

TABLE 1 - INFLUENCE OF STARVATION AND STRESS ON METABOLISM

	Starvation	Physiological stress
Activation of mediators	⇧	⇧⇧⇧
Protein synthesis	⇩	⇩⇩
Catabolism	⇩	⇧⇧⇧
Gluconeogenesis	⇧	⇧⇧⇧
Energy expenditure	⇩	⇧⇧
Malnutrition level	⇧	⇧⇧⇧

There are marked elevations in catecholamines, glucocorticoids and glucagon in patients that are physiologically stressed. Although the exact increase in nutrient requirements in differing states of complicated starvation is not known, it is significant justification for nutritional support.

No evidence suggests that there are specific and consistent risk factors for needing nutritional support. Disease severity has been the only common factor among patients in need of nutritional support.

Independent of breed predisposition for diseases that require nutritional support for patient management, no breed is more likely to need nutritional support than another.

2 - Indications for nutritional support

Some clinicians find it helpful to have metrics to use to determine when to intervene with nutritional support. Ideally, a specific and sensitive biomarker that is easily measured would exist as such an indicator. Unfortunately, despite attempts at identification, no one reliable indicator exists *(De Bruijne, 1979; Fascetti et al, 1997)*. However, there are recommendations in the literature

regarding patient criteria that can serve as indicators to when nutritional support should be instituted *(Remillard et al, 2001)*.

► First criterion: the length of anorexia prior to presentation or anticipated duration of anorexia

Canine patients that have been anorexic for three to five days are already in a state of starvation and, based on human respiratory quotients (RQs), are relying mainly on muscle and adipose tissue as energy substrates *(Owen et al, 1979)*. There are no protein stores in the body, and, therefore, any catabolism results in the loss of functional proteins. A state of protein catabolism is contraindicated in any state of disease and minimizing or eliminating this catabolism is vital to the successful management of critically ill patients.

If anorexia lasts or is expected to last at least three to five days, it should elicit a nutritional response (enteral or parenteral feeding).

Not all patients have a clear starting point regarding anorexia. The client may not have recognized diminished food intake depending on the patient's home environment and the feeding strategy employed.

- Food intake for patients residing in a multi-dog household fed ad libitum is notoriously difficult to assess.
- Clients may, in hindsight, be reluctant to admit the length of anorexia or may exaggerate food intake.

In order to address this difficulty, the authors recommend that the practitioner make an effort to quantify the volume of food that the animal is consuming. Using this information, the approximate caloric intake of the patient can be calculated and compared to the animal's energy requirement **(see section 5B for energy requirement calculations)**.

It is even more difficult to anticipate the length of expected anorexia. Disease progression is inherently unpredictable; however, many diseases do behave relatively predictably. In cases where there is a high likelihood that the patient will not eat voluntarily, plans should be made to provide nutritional support. Anticipating the potential need for nutritional intervention when patients undergo anesthesia for further diagnostics or treatment is strongly recommended. In this case, concurrently placing a feeding tube during the procedure is a critical management strategy. This approach drastically increases the odds that patients in need of nutritional support will receive it.

► Other criteria: body condition score, body weight change and albumin status

There are three parameters that need to be monitored in order to ensure that nutritional support is adequate.

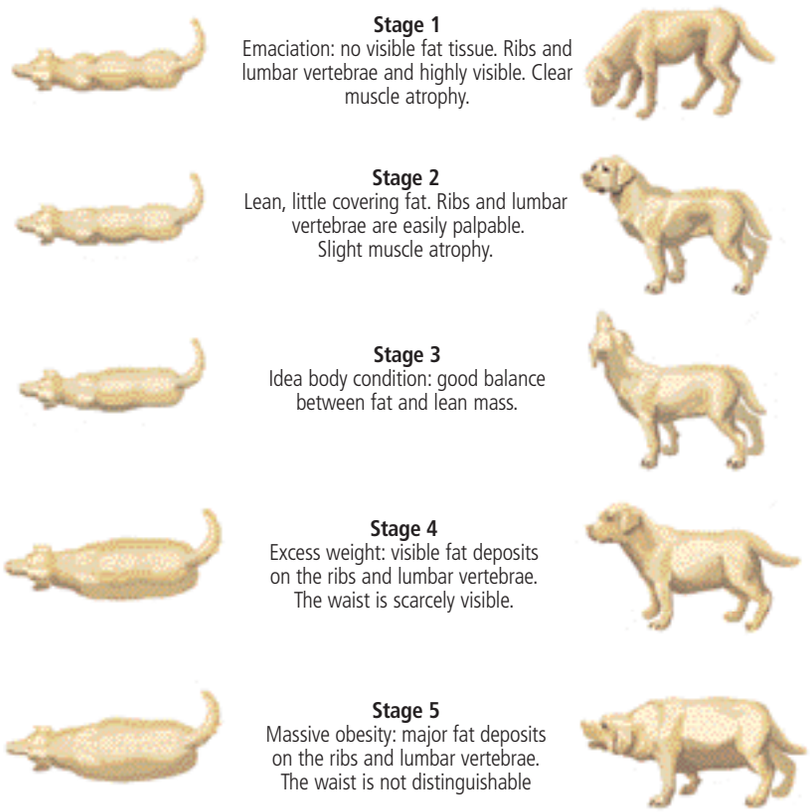
- Patients with a body condition score of less than 3 on a 9-point scale *(Laflamme et al, 1994)* or 2 on a 5-point scale *(Edney & Smith, 1986)* should be considered to be in poor nutritional status, and nutritional support should be considered immediately **(Figure 1)**.
- A body weight reduction of greater than five or ten percent that is not due to dehydration also signals the need for immediate nutritional support.
- Hypoalbuminemia due to decreased production is a clear indicator that intervention should occur.

3 - Supplementary tests

► Diet history

Collecting an accurate and complete diet history should be done for every patient and can prove to be very helpful in determining the length and degree of anorexia. Clients should be carefully

Figure 1 - 5 point body condition scoring system



A body condition score lower than 2 justifies the introduction of nutritional support.
A weight loss in excess of 10%, starvation lasting more than 3 days and hypoalbuminemia are other criteria for evaluating the dog's nutritional condition.

questioned not only about the brand and type of food offered, but also about the amount and the feeding frequency. The diet history should include enough detail to allow for the total daily caloric intake to be determined and compared to the calculated caloric requirement. The determination of food intake is often complicated by the fact that many clients have moved away from the patients' typical diets to novel foods in an attempt to entice their pets to eat. The new foods are frequently higher in moisture and/or fat content. The loss of an easy comparison makes interpreting unintentional weight loss difficult. There is a natural tendency to assume that the patient's food consumption has been adequate, since that would imply a better prognosis to the client and that the veterinarian would not need to intercede with nutritional support. However, this assumption must be proven quantitatively.

Fortunately, the advent of the internet has made previously difficult to find energy density data more accessible to anyone with computer access. Many pet food manufacturers' websites provide kilocalories per volume or kilogram often not found on their product labels. In addition, product guides are readily available from many manufacturers. Energy density data for human foods can be easily obtained from the USDA Nutrient Database for Standard Reference, which is available at *www.nal.usda.gov*. The lead author's (SJD) website (*www.balanceit.com*) is also designed to provide information for petfood as well as for human food. With these tools, accurate and complete diet histories can be evaluated in all patients and used to determine the degree and length of patient anorexia.

► Body weight

Determination of a patient's body weight, adjusted for hydration status, is an important clinical measurement. However, for the critically ill patient in need of nutritional support, its value is diminished unless recent body weight data is available. Comparisons should only be made based on readings from the same scale, since scale-to-scale variation can be misleading.

Every animal should be weighed, and weight readings should be recorded daily during hospitalization. Intervention that only occurs when the patient has lost weight while hospitalized is a poor management strategy. Ideally, all hospitalized patients will remain relatively weight stable or, if indicated, gain weight during their stay. Weight gain should be interpreted cautiously as most patients will gain weight upon rehydration. Thus, every patient should be weighed daily to ensure that nutritional intervention is appropriate. The routine occurrence of weight loss in hospitalized patients should be a clear sign to the clinician that nutritional intervention is not adequate or has not been instituted soon enough.

Beauceron on the scale - *A body weight that was recorded years or even months earlier cannot be used to determine the rate of unintentional weight loss.*

► Body composition

Clinical assessment of body composition is limited to a validated system of using visual and tactile cues for assessing adiposity *(Laflamme et al, 1994)*. Although the body condition scoring system has limitations, such as in its inability to quantify lean body mass, it requires minimal training and no special patient preparation or equipment.

More precise experimental methods of determining body composition such as dual energy X-ray absorptiometry (DEXA), bioelectrical impedance, and stable isotope dilution, are technically and economically demanding, limiting their clinical use.

Thus, the use of a body condition score (BCS) is the most practical method of quantifying a patient's body composition **(Figure 1 and see Chapter 1)**. It is also an excellent tool to convey a "picture" of the animal to colleagues in the same practice or to referring veterinarians. Although subtle changes over several days cannot be detected by even the most experienced clinician, the use of a BCS does provide an insight into the patient's overall nutritional status that cannot be achieved by measuring body weight alone. Therefore, a BCS should be used as a measure of the "chronic" condition, and daily body weight changes should be used as indicators of the more "acute" condition.

Body weight and BCS are usually not dynamic enough for daily evaluations and adjustments, but rather they are a better indicator of an animal's long-term response to nutritional support.

► Albumin status

Approximately 50% of all daily protein synthesis is committed to the production of albumin. Inadequate intake of dietary protein can impair that production. However, given that albumin's half-life in the dog is approximately eight days, reflective changes in albumin status can take days to occur *(Kaneko et al, 1997)*. An example of the discrepancy between albumin status and caloric intake is provided in a paper by De Bruijne *(1979)*. In this study, no changes in blood albumin concentrations were detected in healthy dogs undergoing simple starvation for 21 days. In another study, admission serum albumin concentration of 105 hospitalized dogs was shown to have a statistically significant predictive value regarding clinical outcome *(Michel, 1993)*. Thus, reductions in albumin should be seen as evidence that production is severely decreased, or may not be keeping up with demand, or that losses are excessive. Consequently, normoalbuminemia should not be used as justification for foregoing nutritional intervention.

► Other Biomarkers

Currently, no single clinical pathology or biochemical marker exists that helps to determine the nutritional status of dogs. Leukopenia, creatine kinase in cats and proteins such as C-reactive protein, prealbumin, transferrin and retinol binding protein in humans have all been investigated as measures of nutritional status. However, all of these biomarkers are affected by multiple other factors that render their interpretation difficult *(Phang & Aeberhardt, 1996; Fascetti et al, 1997)*. At this time, the clinician's best tools for nutritionally assessing their patients are:

- complete medical and dietary histories
- physical examinations
- body weights
- current and historical BCSs
- and routine blood work.

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Weighing a West Highland White Terrier puppy
Early enteral nutrition helps combat weight loss and minimizes the effects of catabolism in diseases such as parvoviral gastroenteritis.

4 - Determination of the best approach regarding nutritional support: decision trees

Nutrients can be administered two ways: enterally or parenterally. It is the clinician's responsibility to determine the best approach regarding nutritional support for each patient **(Figure 2)**.

Parenteral nutrition should be used only when enteral feeding is not possible. Parenteral nutrition is complicated, more expensive and concerns regarding infection exist.

5 - Enteral nutrition

Enteral nutrition should be the first choice for nutritional management unless the patient's condition can not support enteral feedings. The mantra "If the gut works, use it" was derived because enteral feeding is considered more physiologically sound than intravenous feeding. Enteral feeding maintains the health of the gastrointestinal tract, and prevents bacterial translocation. A recent randomized controlled clinical trial investigated the effect of early enteral nutrition in dogs with parvo-viral enteritis, compared to nil per os *(Mohr et al, 2003)*.

Enteral nutrition was associated with a shorter time to recovery, increased body weight gain, and improved gut barrier function. This study suggests that early enteral feeding is associated with more rapid clinical improvement. Enteral feeding can be achieved via nasoesophageal, esophagostomy, gastrostomy or jejunostomy devices.

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Most critically ill patients will tolerate nasoesophageal tube placement, but some individuals may require sedation.

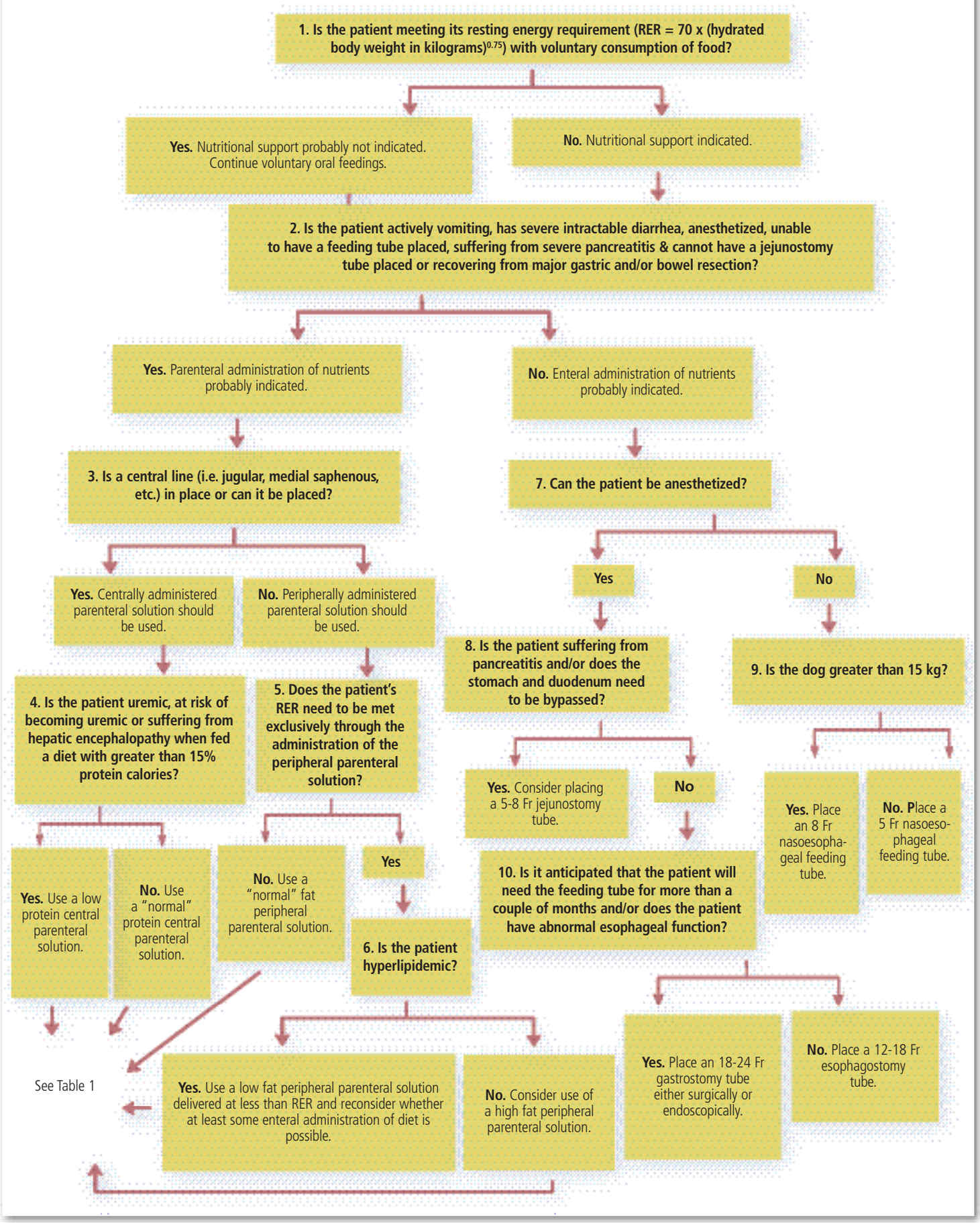
► Different types of tubes for enteral nutrition

The appetite of the hospitalized patient typically waxes and wanes. Hence the meal is offered orally, and if not consumed, is blended and administered via a tube.

> Nasoesophageal tubes

This type of tube is an excellent option for short-term feeding (<7 days) of hospitalized patients. Nasoesophageal tubes do not require specialized equipment and are not expensive. Generally tubes between 3-8F are selected. For a dog, the optimal length of the nasoesophageal tube is equal to the distance from the tip of the nose to the seventh rib.

Figure 2 - Algorithm to assist the selection of the type of nutritional support to implement



Contraindications include patients that have had severe facial trauma involving the nares, protracted vomiting and/or regurgitation, semiconsciousness, or those patients that have laryngeal, pharyngeal, or esophageal physical or functional abnormalities.

However, the small diameter of the tube can be inconvenient and mandates only liquid feedings. Nasoesophageal tubes may also increase the risk of aspiration pneumonia if the tube is either inadvertently placed in the trachea, or the pet regurgitates the tube and it is inhaled into the trachea. To minimize this complication, the placement of the nasoesophageal tube should always be ascertained prior to feeding.

There are three ways of placing an esophagostomy tube:

- via a percutaneous needle technique
- via surgical cut-down
- by utilizing the Eld percutaneous feeding tube applicator.

> Esophagostomy tubes

Esophagostomy tubes are indicated for patients requiring medium term nutritional support. Esophagostomy tubes are generally well tolerated and can easily be placed under a light anesthetic with minimal equipment. The only major associated complication is the potential for infection at the entry site and meticulous care of the surgical wound is essential to maintain the tube. Indications include patients with mandibular, maxillary, nasal and nasopharyngeal disease or an inability to prehend or masticate.

The patient is lightly anesthetized, placed in right lateral recumbency, and an aseptic preparation of the left cervical region is performed. A 5-12 Fr red rubber, plastic or silicone feeding tube can be placed.

The tip of the esophagostomy tube should be placed in the mid-esophagus. The exterior portion of the tube is secured to the neck via butterfly or Chinese finger trap suture.

Feeding through the tube can commence once the patient has recovered from anesthesia. The food must be presented in the form of liquid slurry: it may be a dry or canned food mixed with water or a ready to use solution. The wound will heal via granulation tissue within two weeks of tube removal.

FIGURE 3 - DIFFERENT TYPES OF GASTROSTOMY TUBES

Gastrostomy tubes are available in several sizes and designs and are constructed of latex or silicone. The most common initial placement design is a latex Pezzar-type mushroom catheter. Silicone tubes typically survive 6-12 months and are less irritating at the stoma site.

> Gastrostomy tubes

Gastrostomy tubes are available in several sizes; 18-20 Fr are appropriate for small dogs, and 24 Fr are adequate for larger dogs. Tubes are constructed of latex or silicone. Various designs are available **(Figure 3)**. An array of feeding adapters can be attached to the feeding tube; a Y-port device is preferred as it has two ports:

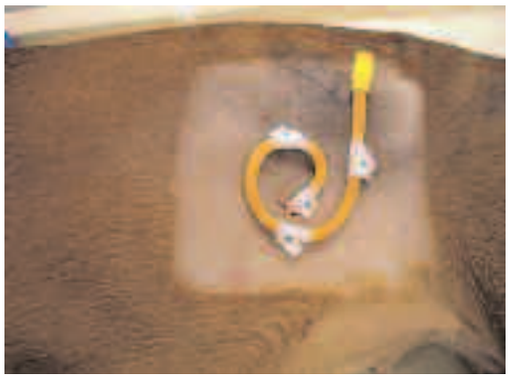
- a catheter port for administration of food when the tube has been in place for at least 24 hours
- a Luer tip syringe port used for oral medication.

More recently low-profile gastrostomy devices (LPGD's) have been developed and are available in North America for both initial and replacement procedures. These devices are positioned flush with the body wall **(Figure 4)**. LPGD's are constructed of silicone and appear to cause less stoma site inflammation. A feeding adapter is attached to the end of the device during the feeding procedure.

FIGURE 4 - ILLUSTRATION OF A LOW PROFILE GASTROSTOMY TUBE AFTER PLACEMENT

Client and patient acceptance is much higher than with traditional tubes as the patient appears "normal" without a long tube attached to the body or the need for a stockinette cover. In addition, the mushroom tip has an anti-flux valve design to prevent reflux of gastric contents.
LPGD's are expensive but have been documented to last at least 12 months.

FIGURE 5 - ILLUSTRATION OF A DOG WITH A TRADITIONAL GASTROSTOMY TUBE AFTER PLACEMENT



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Latex tubes are less expensive but generally require replacement within 8-12 weeks due to tube wear and tear.

Silicone tubes typically survive 6-12 months and are less irritating at the stoma site **(Figure 5)**.

> Jejunostomy tubes

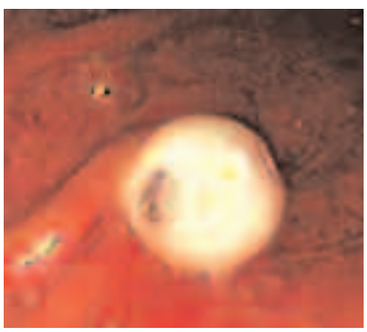
Jejunostomy tube feeding is justified only when the stomach or the duodenum must be by-passed. The tube is typically placed via laparotomy and enteropexy. The food used must be liquid and elemental as tubes are typically 5-8 Fr in diameter and inserted directly into the jejunum.

► Enteral tube feeding: practical aspects

Water is introduced through the feeding tube 12-18 hours following initial placement (except for feeding via the esophagus when no delay is necessary), and feeding is scheduled to begin within 24-36 hrs. Generally 1/2 to 1/3 of the daily caloric intake (typically RER) is administered on the first day.

***RER = 70 x (body weight in kg)$^{0.75}$ = kilocalories/day**

If no complications occur, the amount fed is gradually increased to reach total caloric requirements by the third or fourth day, or the seventh day in case of prolonged starvation.



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An endoscope should be used to verify that the gastrostomy tube is in the correct position.

The total volume of food is divided into 4-6 equal sized meals which should not exceed the gastric capacity of the patient (initially 5 mL/kg to up to 15 mL/kg per feeding). The food should be warmed to room temperature and administered slowly, over 5-15 mins **(Figure 6)**. Upon completion, the tube should be flushed with 5-10 mL of tepid water.

Research shows no beneficial effect from continuous intragastric feeding over intermittent enteral feeding with regard to weight gain and nitrogen balance in healthy dogs *(Chandler et al, 1996)*. However, in animals that are volume intolerant, continuous administration of nutrients is better tolerated.

FIGURE 6 - ENTERAL FEEDING

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The diet is blended with the least amount of water required to achieve syringability. If the food is administered as a slurry, the tip of the syringe must be sufficiently wide to prevent obstruction.

Frequent small meals are generally better tolerated than larger less frequent meals. If the owner feels able to continue frequent feedings when the dog is discharged from the hospital then such a regimen should be continued. However, if frequency will need to be reduced, it is important that the dog is adapted to the larger less frequent meals that the owner will employ at home prior to discharge. With time and adaptation to the feeding procedure, the meal frequency may be reduced to a convenient BID to TID daily schedule.

Prior to every meal, the gastric residuals should be aspirated with a syringe. If more than 50% of the prior feeding is present, the contents should be returned to the stomach and the feeding skipped until the next scheduled time. Frequent aspiration of the previous meal may suggest delayed gastric emptying and warrant medical management (e.g. metoclopramide 20-30 minutes prior to feeding).

Most oral medications should be administered prior to feeding, with the exception of phosphate binders that must be mixed directly with the food.

The position of the tube on the body wall should be examined daily for migration and the stoma site inspected for pain, redness, odor and discharge **(Figure 7)**. The site should be cleaned daily with an antiseptic solution and antimicrobial ointment applied. Food residue should not be left near the stoma.

► Nutritional support

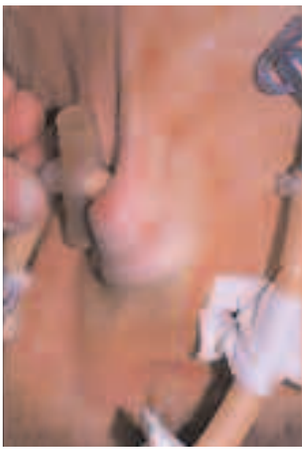
> Water

Water is one of the four basic macronutrients, and, in a state of deficiency, will cause the most immediate detrimental effects. Therefore, nutritional support in its most minimal form is provided to most hospitalized patients in the form of ad libitum water and/or parenterally administered fluids. Unfortunately, there is a tendency to only administer the minimum and provide no further support. Fluid therapy should be viewed as a component of nutritional support and not as complete nutritional support.

> Energy density of the diet

Most veterinary clinical nutritionists believe that the energy requirement of most hospitalized patients is close to a patient's resting energy requirement (RER), calculated using the above equation *(Remillard et al, 2001)*.

FIGURE 7 - MIGRATION OF THE GASTROSTOMY TUBE IN THE SUBCUTANEOUS TISSUE



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This situation is a surgical emergency as it may result in septic peritonitis.

Although this equation does not always meet the patient's precise needs, it serves as a starting point that should minimize the likelihood of overfeeding or underfeeding the patient. It is the authors' experience that, for most dogs, using RER results in weight stability and maintenance of the patient's BCS during several weeks of hospitalization.

To keep the volume of any single bolus at a minimum, the energy density of the diet must be maximized. To achieve this, the volume and type of liquid used to lower the viscosity of a canned food must be carefully selected. The importance of finding a balance between slurry energy density and viscosity cannot be overemphasized. Even small increases in the kilocalories per unit volume can often have a large impact on the frequency and the volume of enteral feedings. This, in turn, can significantly affect the success of the feeding program and the ability to meet the animal's energy requirements.

Oil provides the maximum amount of energy, but also the greatest dilutional effect on nutrients. Thus, essential nutrients can be significantly decreased inadvertently. Using water does not change the ratio of nutrients to kilocalories, but does decrease the amount of kilocalories per unit volume. Alternatively corn or maple syrup can be used in dogs to increase the energy density of a slurry while still decreasing the diet's viscosity. In most cases, water can effectively be used to create slurries that can then be fed through a 12 Fr or larger feeding tube. As a general guide, increasing the canned diet to a moisture level of 80% typically creates a slurry once blenderized that is both relatively energy dense (diet dependent) and easily administered **(Figure 8)**.

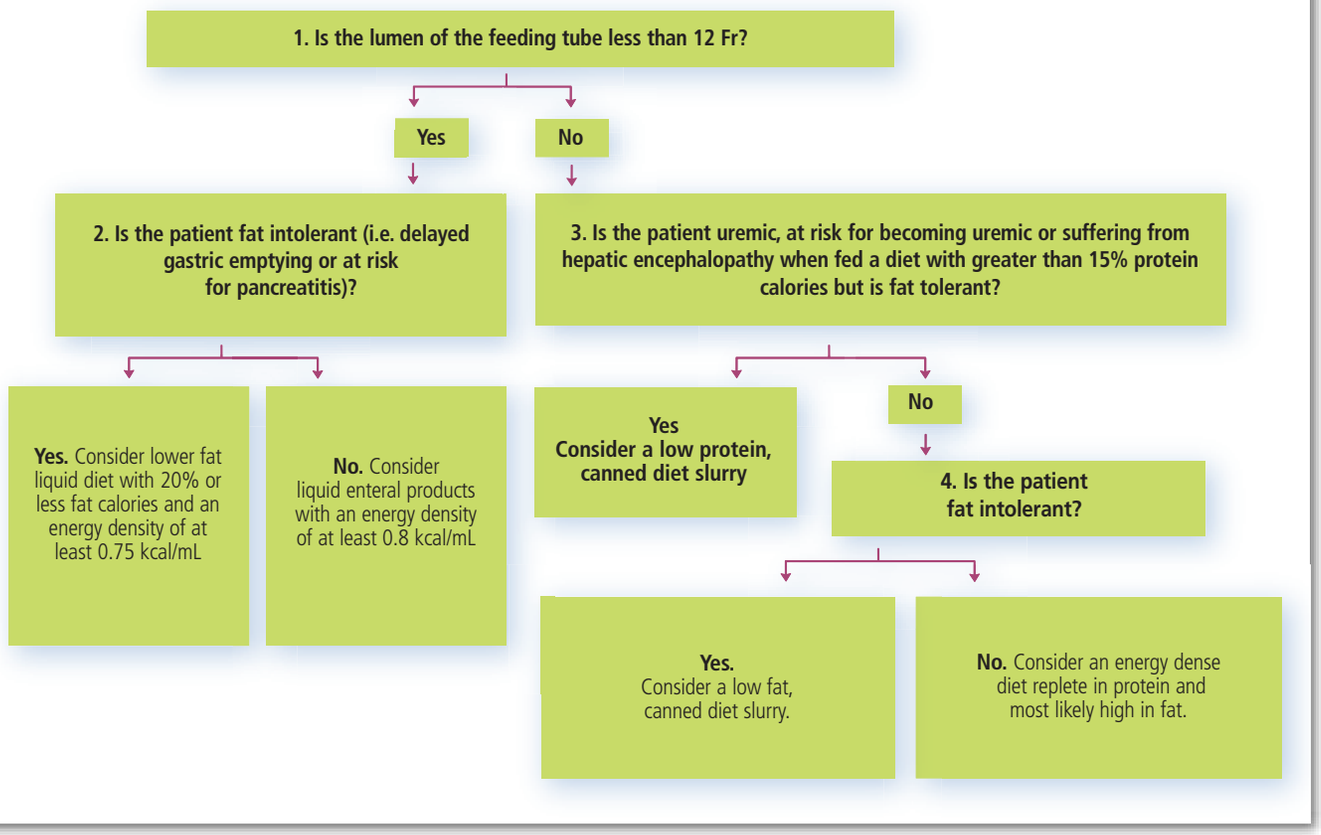
> Balance of energy sources

The basic macronutrients that provide energy are protein, fat and carbohydrate. When the patient's resting energy requirement is not met with the administration of a single energy-providing macronutrient, there is debate as to how the macronutrient is utilized. Some believe that all macronutrients are used solely for energy until the patient's energy requirements are met. Others advocate that some substrates may have a limited, protein-sparing effect even when the patient's caloric requirements are not being achieved.

- ***Fats***

High fat diets, as a rule, are usually well accepted and tolerated. Fat provides at least twice as many calories per unit of volume, thereby enabling an increased caloric consumption in patients with

Figure 8 - Algorithm to assist the selection of the enteral tube feeding diet



limited food intake. Although fat can increase the palatability and the initial acceptance of a diet, it is the authors' experience that sudden increases in dietary fat appear to be one of the most consistent and least recognized causes of gastrointestinal distress, especially pancreatitis.

Many highly digestible commercial foods are not fat-restricted and often provide up to 30% of the calories from fat. The use of these diets should be limited to patients in which there is no concern of fat intolerance.

When initially refeeding a hospitalized patient, such foods as cottage cheese or skinless chicken combined with rice are often recommended. These foods are palatable, highly digestible and are excellent alternatives to high-fat commercial foods.

- ***Amino acids***

Enterally administered amino acids such as glutamine have been suggested to have a protein-sparing effect. There is one study that supports the potential benefit of enterally administered glutamine based on whole-body leucine kinetics *(Humbert et al, 2002)*.

Unfortunately, there is no clinical evidence that a patient will tolerate an enterally administered amino acid solution in amounts to meet their energy needs, when they will not tolerate a complete diet. However, a constant rate infusion of an enteral product below the patient's RER, with the concurrent administration of the remaining caloric requirement parenterally may be of value in reducing the occurrence of villous atrophy and bacterial translocation *(Qin et al, 2002; Kotani et al, 1999)*.

► Complications linked to enteral feeding

For critically ill dogs, the majority of the monitoring is focused on avoiding complications associated with nutritional support.

> Surgical complications

Splenic laceration, gastric hemorrhage, pneumoperitoneum, displacement into the peritoneal cavity and peritonitis have been reported as infrequent placement complications.

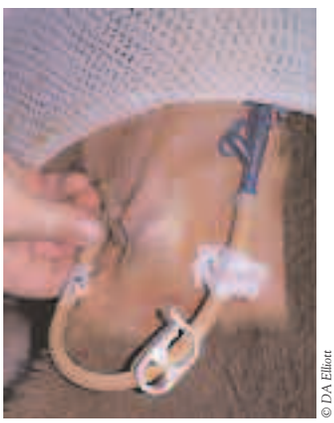
Patient tolerance of the feeding tube should be closely observed. This can manifest as sneezing, cellulitus at the stoma, gagging, and/or vomiting, depending upon the type of tube. The major associated complication is the potential for infection at the entry site.

Meticulous care of the surgical wound is essential to maintain the tube. Abnormalities at the stoma site including discharge, pain, swelling, erythema, abscess formation and ulceration which can be minimized by strict attention to cleaning and prohibiting the patient from licking the site. Warm packs containing antiseptic solution placed on the stoma site will minimize problems or hasten recovery.

Inappropriate patient removal of the tube is undoubtedly the most problematic complication. In one review approximately 20% of dogs removed their gastrostomy tubes which emphasizes the importance of restraining the gastrostomy tube in a stockinette and utilizing e-collars **(Figure 9)** *(Elliott et al, 2000)*.

Patient removal of the gastrostomy tube is an emergency. In most situations a new tube can be placed through the existing stoma site using a guide catheter. Appropriate replacement should be verified radiographically following injection of an iodinated contrast agent. If the tube has been in place for less than seven days, or there is evidence of peritonitis or radiographic contrast agent leakage, an exploratory laparotomy is required to correct the situation. The use of LPGD's may reduce the incidence of inadvertent gastrostomy tube removal.

FIGURE 9 - FIXATION OF THE TUBE



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A traditional gastrostomy tube must be protected from the risk of displacement by the dog. This can be achieved by securing the gastrostomy tube to the body wall, placing a stockinette over the abdomen, and using an Elizabethan collar.

> Obstruction of the tube

Periodically tubes will become blocked with food. Techniques to facilitate removal of the obstruction include massaging the outside of the tube while simultaneously flushing and aspirating with water; instilling carbonated drinks (e.g. cola soda), meat tenderizers or pancreatic enzyme solutions for 15 to 20 minutes; or gently using a polyurethane catheter to dislodge the obstruction. The final resort is tube removal and replacement.

> Aspiration Pneumonia

The perception of enteral feeding increasing the risk of aspiration pneumonia in the critically ill patient is most likely justified if the enteral feeding increases the risk of the patient vomiting, or aspirating or if the patient is laterally recumbent, sedated or anesthetized. Incorrectly positioned nasoesophageal tubes will cause aspiration pneumonia when the food is inadvertently placed into the trachea, and not the esophagus.

Gastric contents following enteral feedings serve as an excellent reservoir of pneumonia-genic compounds given their acidity and high microbial load. However, it should be noted that a human produces up to 63 mL per hour of bacteria-laden saliva *(McClave & Snider, 2002)*. Thus, it is most likely inappropriate to assume that all aspirated material comes from the stomach. The role of enteral feeding in the development of aspiration pneumonia is controversial in the human arena *(McClave & Snider, 2002)*. However due to the more horizontal, rather than vertical posture of dogs, it appears likely to play a significant role in the canine patient.

Intolerance to enteral feeding is usually related to an excessive meal volume which exceeds gastric capacity. The frequency with which clients can administer feedings is generally limited. Patient discomfort, the risk of diarrhea and vomiting can be minimized by:
- reducing the total volume (increase the meal frequency and/or the meal energy density)
- slowing down the rate of administration
- serving the food at ambient temperature
- reducing the food's osmolarity
- simultaneously managing fluid, electrolyte and acid base disturbances.

> Overfeeding

Volume intolerance is a frequent complication of enteral feeding in humans *(Davies et al, 2002)* It can lead to simple nausea or to vomiting.

The total number of daily kilocalories to be delivered has a large impact on individual bolus volume. Overestimating the energy requirement of a patient increases the risk of volume intolerance. In human medicine, initial energy requirement recommendations for enteral feeding that are too aggressive often result in the patient receiving fewer kilocalories per day due to skipped feedings based on residuals and/or volume intolerance *(McClave & Snider, 2002)*.

There is debate regarding the predictive ability of gastric residuals (leftover stomach contents measured by aspiration before the next feeding) in avoiding aspiration pneumonia in humans *(McClave & Snider, 2002)*. The volume of each feeding may not be solely responsible for residual volume as gastric emptying rate also plays a role. However, intuitively, it seems like a good indicator of feeding volume tolerance.

Finally, diarrhea can occur with any form of enteral feeding, especially when undigested nutrients or non-elemental diets are fed too rapidly into the jejunum (due to osmotic effects), or when the food is too cold.

> Refeeding syndrome

This syndrome may occur after enteral feeding, as studies on cats and humans have shown *(Solomon & Kirby, 1990; Justin & Hohenhaus, 1995)*.

In order to prevent Refeeding Syndrome, the following three steps should be taken:

(1) Slow re-introduction of food to animals that have been unfed for extended periods (greater than 5 days);
(2) Provide adequate supplementation of potassium, phosphorus and potentially magnesium; and
(3) Closely monitor electrolytes during the first 24 hours of refeeding.

In a state of starvation, the body maintains extracellular concentrations of many electrolytes at the expense of intracellular concentrations. This shift can result in inward rectification when glucose and, subsequently, insulin are reintroduced to the patient with refeeding. This inward rush results in acute decreases in vital serum electrolyte concentrations that can potentially be life threatening. For example, serum potassium concentration is maintained as intracellular potassium is depleted. When blood glucose rises in response to feeding, the body releases insulin that pumps glucose and potassium intracellularly. The result is a rapid and profound hypokalemia **(Figure 10)**. Hypomagnesemia and hypophosphatemia have also been reported *(Justin & Hohenhaus, 1995; Macintire, 1997)*. Hypophosphatemia has been associated with hemolysis and could lead to additional cardiac and neurological complications *(Justin & Hohenhaus, 1995)*.

6 - Parenteral feeding

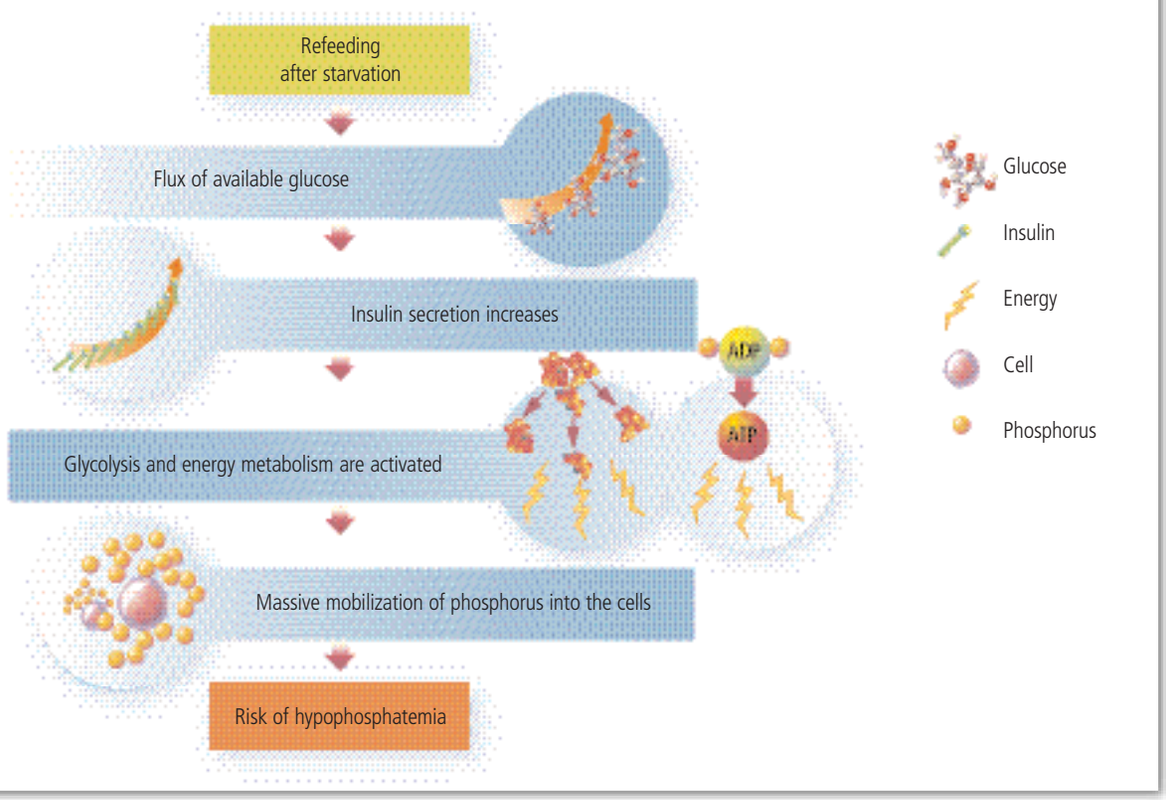
Parenteral feeding is expensive and technically demanding. It is reserved for cases in which the digestive tract must be rested for medical or surgical reasons or in recumbent patients.

► Practical aspects

> Preparation

All the elements are mixed carefully in a sterile bag, in the following order: glucose then amino acids then lipids. The introduction of lipids at the end avoids the risk of emulsion destabilization. The bag is refrigerated and the contents used in less than 48 hours by connection to the intravenous infusion system.

Figure 10 - Physiological mechanisms that may result in hypophosphatemia associated with the refeeding syndrome



> Catheter placement sites

The dog is anesthetized or simply tranquilized if it is already weak. The injection site is surgically prepared **(Figure 11)**.

Due to their high glucose and amino acid content the solutions for parenteral feeding are often very hypertonic. Their administration must therefore be accomplished with a central catheter placed in the cranial (jugular approach – **Figure 12**) or caudal vena cava (saphenous approach). The major blood flow of these veins permits rapid dilution of the mixture.

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Figure 11 *- Placement of a central jugular catheter.*

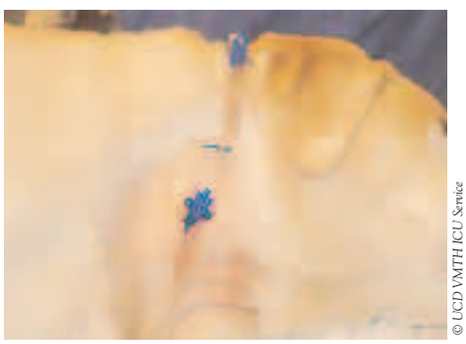

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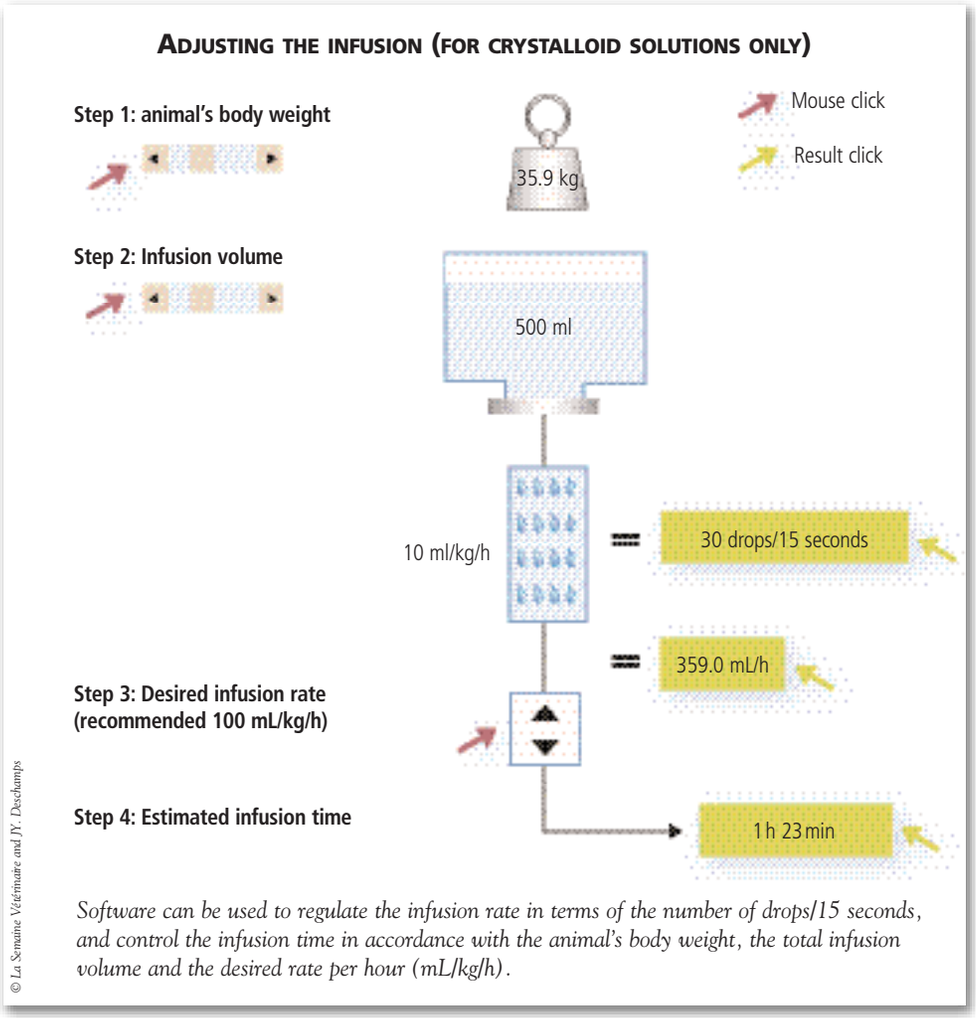
Figure 12 *- The high flow of the cranial vena cava permits rapid dilution of the parenteral solution.*

> Rate of administration

The rate of administration of parenteral solutions is limited by three main factors - fluid volume, osmolarity and the creation of metabolic disturbances. Software is available that can adjust the infusion flow based on the characteristics of the animal.

> Fluid volume

Fluid volume is rarely a major concern except in patients that are fluid overloaded or oliguric/anuric, for example, patients with congestive heart failure, acute renal disease or terminal chronic renal disease. When fluid volume is a concern, an effort should be made to increase the energy density of the solution by increasing the lipid emulsion content when possible.



Software can be used to regulate the infusion rate in terms of the number of drops/15 seconds, and control the infusion time in accordance with the animal's body weight, the total infusion volume and the desired rate per hour (mL/kg/h).

> Electrolyte composition

The electrolyte composition of the parenteral solution can also be adjusted along with the amount of free water to allow for its use as a maintenance fluid and decrease overall administered fluid volume. Use of a solution with a high osmolarity can increase the risk of thrombophlebitis *(Roongpisuthipong et al, 1994)*. For example, a solution with an osmolarity of 650 mOsmol/L delivered through a peripheral catheter at maintenance fluid rates is well-tolerated *(Chan et al, 2002; Chandler et al, 2000a)*. However, the same solution delivered at twice the maintenance rate will not be as well-tolerated based on human studies *(Kuwahara et al, 1998)*. On the other hand, a solution with an osmolarity of 1300 mOsmol/L may theoretically be tolerated if delivered at one half of the normal maintenance rate.

> Metabolic complications

Common metabolic complications associated with parenteral nutrition include:

- hyperglycemia
- hyperlipidemia
- Refeeding Syndrome.

Hyperglycemia can be associated with the rapid administration of dextrose containing solutions that exceed the ability of the pancreas to respond to the hyperglycemia and to secrete appropriate concentrations of insulin. Avoidance of hyperglycemia is frequently achieved by reducing the rate of infusion and/or the administration of exogenous insulin .

TABLE 2 - PROTOCOL TO REGULATE BLOOD GLUCOSE (BG) CONCENTRATIONS

Protocol Blood Glucose
Initially start the infusion at 1/4 to 1/3 of goal rate and wean on per guidelines below increasing the rate in 1/3 to 1/4 of goal rate increments. The same recommendations in reverse apply to discontinuing the infusion. Recommend checking the administration rate every 4hr until 100% of goal rate is achieved.

Blood Glucose (mg/dL)	Action
< 70 mg/dL or 4 mmol/L	Possible problem with the measurement, administration, formula and/or patient. Check to ensure that the correct solution is being administered and that the patient does not have an underlying reason to become hypoglycemic. Consider increasing the administration rate and/or concentration of dextrose in the formula.
< 250 mg/dL or 14 mmol/L	Increase the infusion rate towards 100% of the goal rate if weaning on. Continue at the present rate if already at 100% of goal rate.
250-300 mg/dL or 14-17 mmol/L	Hold the present infusion rate during the weaning on period. Continue the infusion at the present rate if already at 100% of goal rate. Decrease the administration rate if the glucose level continues to be elevated over three to four measurements obtained at 4hr intervals or if the urine glucose is over 1+ on a urine dipstick test.
> 300 mg/dL or 17 mmol/L	Decrease the infusion rate. If the goal rate cannot be reached without >300 mg/dL glucose levels consider: 1. Accepting the highest infusion rate that the animal will tolerate; 2. Adding regular insulin to the nutrient solution (1 unit/10 g dextrose) 3. Decreasing the dextrose content of the solution.

Similarly a state of **hyperlipidemia** may develop when the patient's ability to metabolize the delivered fat is exceeded.

The Refeeding Syndrome refers mainly to electrolyte shifts associated with glucose transport into cells following the reintroduction of food after prolonged anorexia. To minimize most of these complications careful monitoring and a weaning protocol should be utilized. Should electrolyte abnormalities occur with refeeding, the authors recommend reducing and/or gradually discontinuing the rate of solution administration, while simultaneously correcting any electrolyte abnormalities. Once the electrolyte abnormalities have resolved, then administration can be resumed or increased to meet energy requirements.

► Covering nutritional requirements

(Table 3)

Table 3 - Canine Parenteral Nutrition Worksheet

1 - Determine if the solution is to be administered peripherally or centrally
If peripheral, use a 5% dextrose solution. If central (i.e. for a dog with a jugular catheter), use a 50% dextrose solution.

2 - Select the desired caloric distribution on a percent of metabolizable energy (%ME)*			
	Protein (%ME)	**Fat (%ME)**	**Carbohydrate (%ME)**
Low	8-10	20	0-18
Normal	16-18	30-58	20-50
High	20-22	60-80	Contraindicated

** Only one macronutrient can be low or high at one time. Thus, the other two macronutrients must be in the normal range if the third is low or high. The exception to this rule is when creating a high fat solution.*

Selected % ME protein	…%
Selected % ME fat	…%
Selected % ME carbohydrate (CHO)	…%
TOTAL **(MUST = 100%)**	…%

3 - Calculate daily caloric requirement of the hospitalized patient	
If to be delivered peripherally (not using a high fat solution)	1/2 RER = 35 x (… body weight in kg)$^{0.75}$ = … kcal/day
If to be delivered peripherally (using a high fat solution) or centrally	RER = 70 x (… body weight in kg)$^{0.75}$ = … kcal/day

4 - Calculate the daily volume of each macronutrient			
… % of ME protein	x … kcal/day = … ÷ … kcal/mL for amino acid solution		= … mL
… % of ME fat	x … kcal/day = … ÷ … kcal/mL for lipid emulsion solution		= … mL
… % of ME CHO	x … kcal/day = … ÷ … kcal/mL for dextrose solution		= … mL
		TOTAL ml	= … mL

5 - Check the osmolarity

… mL of amino acid solution	x … mOsmol/mL of amino acid solution	= … mOsmol
… mL of lipid emulsion solution	x … mOsmol/mL of lipid emulsion solution	= … mOsmol
… mL of dextrose solution	x … mOsmol/mL of dextrose solution	= … mOsmol
	TOTAL mOsmol	= … mOsmol

(… Total mOsmol ÷ … Total mL) x 1000 = … mOsmol/L)
if mOsmol/L > 750 mOsmol/L & the solution is to be delivered peripherally, increase the %ME fat
if mOsmol/L > 1400 mOsmol/L & the solution is to be delivered centrally, increase the %ME fat

6 - Calculate energy density of the solution

… mL of amino acid solution	x … kcal/mL of amino acid solution	= … kcal
… mL of lipid emulsion solution	x … kcal/mL of lipid emulsion solution	= … kcal
… mL of dextrose solution	x … kcal/mL of dextrose solution	= … kcal
	TOTAL kcal	= … kcal

(… Total kcal ÷ … Total mL) x 1000 = … kcal/L)

if the kcal/mL < 0.4 kcal/mL and the solution is to be delivered peripherally (not using a high fat solution), increase the %ME fat and/or check the calculations
if the kcal/mL < 0.7 kcal/mL and the solution is to be delivered peripherally (using a high fat solution), increase the % ME fat and/or the % ME protein and/or check the calculations
if the kcal/mL < 0.9 kcal/mL & the solution is to be delivered centrally, increase the %ME fat and/or check calculations.

7 - Calculate the amount of potassium and phosphorus to add to the solution

Desired potassium concentration … mEq/L
x (… Total mL ÷ 1000)
= … mEq K to add

Desired phosphorus concentration … mEq/L
x (… Total mL ÷ 1000)
= … mEq P to add

Phosphorous supplementation should be considered cautiously in patients with renal insufficiency.
Potassium supplementation should be reflective of the patient's potassium status.

8 - Calculate the amount of Vitamin B Complex to add to the solution

a. There is a wide variation in the concentrations of B vitamins in commercially available products. Provide enough B Vitamins to meet the following requirements:

Thiamine	0.29 mg/1000 kcal solution
Riboflavin	0.63 mg/1000 kcal solution
Pantothenic acid	2.9 mg/1000 kcal solution
Niacin	3.3 mg/1000 kcal solution
Pyridoxine	0.29 mg/1000 kcal solution
Vitamin B12	0.006 mg/1000 kcal solution

Supplementation with fat soluble vitamins or trace minerals does not appear to be essential. Unless a specific deficiency is evident, the likelihood of developing a clinically significant deficiency in two to three weeks is highly unlikely.

c. Standard canine recommendations on a g protein/100 kcal basis

Low	< 4.0 g/100 kcal
Normal	4.0-8.0 g/100 kcal
High	> 8.0 g/100 kcal

b. Recommended concentrations and characteristics of macronutrients

	mOsmol/mL	kcal/mL	g protein/mL
8.5% amino acid solution without electrolytes	0.78-0,88	0.34	0.085
20% lipid emulsion solution	0.27	2.0	
5% dextrose solution	0.25	0.17	
50% dextrose solution	2.52	1.7	

NOTE: There is debate regarding the amount of amino acids available for protein synthesis if the patient's resting energy requirement (RER) is not met. Therefore, some clinicians will provide the patient with their RER exclusively from fat and carbohydrate and calculate the protein requirement separately. The authors have included the energy contribution of protein in their parenteral solution calculations to provide consistency with accepted methods of evaluating oral/enteral diets. To determine the grams of protein per 100 kcal calories the following calculation can be performed:

…mL of amino acid solution
x … g of protein per mL amino acid solution
= … g protein

(… g protein x … Total kcal)
x 100
= … g protein/100 kcal

Case study: A 20-kg dog whose resting energy requirement equals 70 x $(20)^{0.75}$ = 660 kcal/day.

A liter of 5% dextrose solution provides 200 kcal. 3.3 L will therefore be necessary to cover the dogs daily RER, which is much greater than the volume needed to guarantee the dog's hydration status and would most likely result in thrombophlebitis.

> Dextrose

It is common for clinicians to "spike" crystalloids used for fluid therapy with dextrose in an attempt to provide some nutritional support. Since chronic infusion of greater than 5% is not performed due to the concern of thrombophlebitis from a hyperosmolar solution, patients only receive approximately a third of their RER when this solution is administered at maintenance fluid rates. There is debate regarding the protein-sparing effect that 5% dextrose provides, but limited research has shown that it is not enough to prevent a negative nitrogen balance *(Chandler et al, 2000b)*.

> Amino acids

A study did find that infusion of a 5% amino acid solution resulted in a mean positive nitrogen balance in three, healthy dogs *(Chandler et al, 2000b)*. However, the success of this therapeutic approach in a larger population of dogs in a catabolic state needs to be determined before this form of nutritional support can be endorsed.

> Fats

The ideal solution for parenteral administration would be an energy dense solution with a low osmolarity. Some view lipid emulsions as such an ideal solution. For example, a 20% lipid emulsion can provide 2 kcal/mL with an osmolarity of 268 mOsmol/L. Although the kcal to osmolarity ratio of this solution is ideal, concern exists regarding excessive fat administration. Intravascular fat accumulation has been reported in premature infants with liver dysfunction receiving lipid emulsions *(Levene et al, 1980; Puntis & Rushton, 1991; Toce & Keenan, 1995)*.

In the limited number of cases where this approach has been used, patients have tolerated solutions providing up to 80% of RER from fat. The safety and efficacy of administering 100% of a patient's RER from fat requires further investigation and cannot be recommended at this time.

MONITORING PROTOCOLS FOR PARENTERAL FEEDING MUST INCLUDE THE FOLLOWING DAILY EVALUATIONS:

- body weight
- temperature
- pulse
- breathing and heart rate
- thoracic auscultation
- catheter position and integrity
- blood glucose concentration and/or urine glucose every 4 hours during the weaning on period
- hematocrit and evaluation of serum for lipemia or jaundice.
- potassium and phosphate in the 12-24 hours following initial administration
- BUN and albumin concentration in the 24 hours following initial administration, and thereafter every 2-3 days

It is also recommended to measure ionized magnesium concentrations (where possible) in the 24 hours following initial administration, and perform a complete blood count and biochemical panel every 2-3 days. Depending on the case, thoracic radiographs and serum triglyceride analyses may be of value.

7 - Complications linked to enteral or parenteral feeding

► Thrombophlebitis

Hyperosmolar solutions increase the risk of thrombophlebitis. For peripheral vessels, it is recommended that solutions not exceed 600 to 750 mOsmol/L *(Chan et al, 2002; Chandler et al, 2000a)*. The rate at which milliosmoles (mOsmol) are administered clinically appears to be as crucial as the osmolarity of the solution. Therefore, a 650 mOsmol solution should not be administered at twice the maintenance rate for the purpose of increasing the amount of calories delivered to the patient per unit of time. This limitation results in the need to use parenteral solutions containing high lipid emulsion concentrations with a high energy to milliosmole ratio, or to provide only a portion of the patient's energy requirement. One author reports that using polyurethane catheters in previously unused vessels for the administration of peripheral parenteral solutions when administrating peripheral parenteral nutrition (PPN) is well tolerated *(Chan et al, 2002)*.

► Septicemia

Parenteral nutrition solutions represent an ideal culture environment for bacteria. To minimize the infection risk these solutions should be prepared and administered in completely aseptic conditions.

Once it is in place the catheter and the tube must be protected from any risk of contamination by using a dedicated catheter. Medication must not be administered through the dedicated catheter nor should blood be drawn from the dedicated catheter.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Once it is in position, the catheter and the intravenous tubing must be protected from any risk of contamination.

► Hyperglycemia

There is a growing body of evidence in the human literature that blood glucose clamping with exogenous insulin of ICU patients may decrease mortality rates. This is due to a reduction in multiple-organ failure secondary to sepsis *(van den Berghe, 2002)*.

The effect appears to be due to the maintenance of euglycemia rather than the beneficial effect of insulin itself, since in humans increased insulin administration is positively associated with death *(Finney et al, 2003)*. Hyperglycemia has long been known to decrease immune function due to adverse effects on polymorphonuclear leukocyte phagocytosis as well as impaired chemotaxis, phagocytosis and intracellular killing as seen in diabetic subjects *(Watters, 2001)*. This may, in part explain the lower incidence of sepsis in patients receiving 50% of their RER from PPN in a review by Chan *(2002)* compared to the frequency reported in two retrospective TPN studies by Reuter et al *(1998)* and Lippert et al *(1993)*. Although patient selection probably plays a key role in the likelihood of developing septicemia, it is possible that the lower incidence of hyperglycemia associated with the use of PPN was also important.

► Villous atrophy and bacterial translocation

The enterocytes rely heavily on nutrients derived from the gut lumen as energy sources *(Ziegler & Young, 1997)*. Thus, available energy for enterocytes is diminished with the use of parenteral nutrition. This reduction results in decreased enterocyte health and villous atrophy, and in turn increased intestinal permeability.

The loss of intestinal integrity can increase the risk of gut flora entering the bloodstream; referred to as bacterial translocation *(Steinberg, 2003)*. There is debate as to when and if this breakdown occurs, but in humans it usually occurs after a prolonged period of parenteral nutritional support and may not be as significant as rodent models would indicate *(Alpers, 2002)*.

There is also controversy regarding the best method of preventing villous atrophy and bacterial translocation. While some human and animal studies suggest that infusing glutamine as an energy substrate to prevent villous atrophy and bacterial translocation has some benefit, other studies have not proven this to be an effective intervention *(Buchman, 1999; Marks et al, 1999)*. In addition, possible contraindications exist, such as liver disease – especially hepatic encephalopathy, and possibly renal disease.

► Adynamic ileus

Adynamic ileus is a common sequela of anorexia, especially in patients supported with parenteral nutritional support. Enteral feeding may decrease this risk as hormonal and neurologic signals are restored by the presence of nutrients in the gut lumen. Adynamic ileus does not always occur, and in many patients normal peristaltic reflexes continue with high pressures being generated during fasted states *(Heddle et al, 1993)*. This point has implications for patients that have undergone intestinal surgery.

The convention of resting the bowel to prevent leakage through enterostomy sites may be flawed. There is evidence that early enteral feeding following major abdominal surgery may be preferable to parenteral support *(Braga et al, 1998 & 2002)*.

Conclusion

- Nutritional support is indicated in canine patients with prolonged anorexia, recent body weight loss unrelated to hydration status, poor body condition and hypoalbuminemia not due to correctable losses.

- Nutritional support can enhance immune function, wound repair, response to therapy, recovery time, and survival.

- Selection of the route and diet for nutritional support should be based on patient tolerance and prevention of adverse side effects.

- Administration of single macronutrients may not be adequate to meet the patient's energy and nutrient requirements and may provide only a limited protein-sparing effect.

- The administration rate of nutritional support should provide the patient's resting energy requirement without increasing the likelihood of volume intolerance or metabolic complications like hyperglycemia, hyperlipidemia and the refeeding syndrome.

- Monitoring of patients on nutritional support should be aimed at preventing adverse complications and to ensure successful management.

References

Alpers DH - Enteral feeding and gut atrophy. Curr Opin Clin Nutr Metab Care 2002 ; 5(6) : 679-83.

Braga M, Gianotti L, Vignali A et al - Artificial nutrition after major abdominal surgery : impact of route of administration and composition of diet. Crit Care Med 1998 ; 26(1) : 24-30.

Braga M, Gianotti L, Gentilini O et al - Feeding the gut early after digestive surgery : Results of a nine year experience. Clin Nutr 2002 ; 21(1) : 59-65.

Buchman AL - Glutamine for the gut : mystical properties of an ordinary amino acid. Curr Gastroenterol Rep 1999 ; 1(5) : 417-23.

Chan DL, Freeman LM, Labato MA et al - Retrospective evaluation of partial parenteral nutrition in dogs and cats. J Vet Intern Med 2002 ; 16 : 440-45.

Chandler ML, Guilford WG, Lawoko CR - Comparison of continuous versus intermittent enteral feeding in dogs. J Vet Intern Med 1996 ; 10(3) : 133-38.

Chandler ML, Guilford WG, Payne-James J - Use of peripheral parenteral nutritional support in dogs and cats. J Am Vet Med Assoc 2000a ; 216(5) : 669-73.

Chandler ML, Guilford WG, Maxwell A et al - A pilot study of protein sparing in healthy dogs using peripheral parenteral nutrition. Res Vet Sci 2000b ; 69 : 47-52.

Davies AR, Froomes PR, French CJ et al - Randomized comparison of nasojejunal and nasogastric feeding in critically ill patients. Crit Care Med 2002 ; 30(3) : 586-90.

De Bruijne JJ - Biochemical observations during total starvation in dogs. Int J Obes 1979 ; 3 : 239-47.

Edney ATB, Smith PM - Study of obesity in dogs visiting veterinary practices in the United Kingdom. Vet Rec 1986; 118: 391-6.

Elliott DA, Riel DL, Rogers QR - Complications and outcomes associated with use of gastrostomy tubes for nutritional management of dogs with renal failure : 56 cases (1994-1999). J Am Vet Med Assoc 2000 ; 217 : 1337-1342.

Fascetti AJ, Mauldin GE, Mauldin GN - Correlation between serum creatine kinase activities and anorexia in cats. J Vet Intern Med 1997 ; 11: 9-13.

Finney SJ, Zekveld C, Elia A et al - Glucose control and mortality in critically III patients. J Am Med Assoc 2003 ; 290(15) : 2041-47.

Heddle R, Miedema BW, Kelly KA - Integration of canine proximal gastric, antral, pyloric, and proximal duodenal motility during fasting and after a liquid meal. Dig Dis Sci 1993 ; 38(5) : 856-69.

Humbert B, Nguyen P, Dumon H et al - Does enteral glutamine modulate whole-body leucine kinetics in hypercatabolic dogs in a fed state? Metabolism 2002 ; 51(5) : 628-35.

Justin RB, Hohenhaus AE - Hypophosphatemia associated with enteral alimentation in cats. J Vet Intern Med 1995 ; 9(4) : 228-33.

Kaneko JJ, Harvey JW, Bruss ML (eds) - Clinical biochemistry of domestic animals. 5th edition. San Diego : Academic Press, 1997 ; 127.

Kotani J, Usami M, Nomura H et al - Enteral nutrition prevents bacterial translocation but does not improve survival during acute pancreatitis. Arch Surg 1999 ; 134 : 287-92.

Kuwahara T, Asanami S, Kubo S - Experimental infusion phlebitis : tolerance osmolality of peripheral venous endothelial cells. Nutrition 1998 ; 14(6) : 496-501.

Laflamme DP, Kealy RD, Schmidt DA - Estimation of body fat by body condition score. J Vet Int Med 1994 ; 8 : 154.

Levene MI, Wigglesworth JS, Desai R - Pulmonary fat accumulation after intralipid infusion in the preterm infant. Lancet 1980 ; 8199: 815-18.

Lippert AC, Fulton RB, Parr AM - A retrospective study of the use of total parenteral nutrition in dogs and cats. J Vet Intern Med 1993 ; 7: 52-64.

Macintire DK - Disorders of potassium, phosphorus, and magnesium in critical illness. Compendium on Continuing Education for the Practicing Veterinarian 1997 ; 19(1) : 41-46.

Marks SL, Cook AK, Reader R et al - Effects of glutamine supplementation of an amino acid-based purified diet on intestinal mucosal integrity in cats with methotrexate-induced enteritis. Am J Vet Res 1999 ; 60(6) : 755-63.

McClave SA, Snider HL - Clinical use of gastric residual volumes as a monitor for patients on enteral tube feeding. J Parenter Enteral Nutr 2002 ; 26(6) : S43-50.

Michel KE - Prognostic value of clinical nutritional assessment in canine patients. J Vet Emer Crit Care 1993 ; 3(2) : 96-104.

Mohr AJ, Leisewitz AL, Jacobson LS et al – Effect of early enteral nutrition on intestinal permeability, intestinal protein loss, and outcome in dogs with severe parvoviral enteritis. J Vet Inter Med 2003 ; 17 : 791-798.

Owen OE, Reichard GA, Patel MS et al - Energy metabolism in feasting and fasting. Adv Exp Med Biol 1979 ; 111 : 169-88.

Phang PT, Aeberhardt LE - Effects of nutritional support on routine nutrition assessment parameters and body composition in intensive care unit patients. Can J Surg 1996 ; 39(3) : 212-19.

Puntis JW, Rushton DI - Pulmonary intravascular lipid in neonatal necropsy specimens. Arch Dis Child 1991 ; 66(1) : 26-28.

Qin HL, Su ZD, Hu LG et al - Effects of early intrajejunal nutrition on pancreatic pathological features and gut barrier function in dogs with acute pancreatitis. Clin Nutr 2002 ; 21(6) : 469-73.

Remillard RL, Darden DE, Michel KE et al - An investigation of the relationship between caloric intake and outcome in hospitalized dogs. Vet Ther 2001 ; 2(4) : 301-10.

Reuter JD, Marks SL, Rogers QR et al - Use of total parenteral nutrition in dogs : 209 cases (1988-1995). J Vet Emerg Crit Care 1998 ; 8(3) : 201-13.

Roongpisuthipong C, Puchaiwatananon O, Songchitsomboon S et al - Hydrocortisone, heparin, and peripheral intravenous infusion. Nutrition 1994 ; 10(3) : 211-3.

Solomon SM, Kirby DF - The Refeeding Syndrome : A Review. J Parenter Enteral Nutr. 1990 ; 14(1) : 90-97.

Steinberg SM - Bacterial translocation : What it is and what it is not. Am J Surg 2003; 186(3) : 301-5.

Toce SS, Keenan WJ - Lipid intolerance in newborns is associated with hepatic dysfunction but not infection. Arch Pediatr Adolesc Med 1995 ; 149 : 1249-53.

Van den Berghe G - Beyond diabetes : saving lives with insulin in the ICU. Int J Obes Relat Metab Disord 2002 ; 26 suppl 3 :S3-8.

Watters JM - Parenteral nutrition in the elderly patient. In Rombeau JL, Rolandelli RH, (eds). Clinical Nutrition Parenteral Nutrition. 3rd edition. Philadelphia : WB Saunders Co, 2001 ; 429-43.

Ziegler TR, Young LS - Therapeutic effects of specific nutrients. In Rombeau JL, Rolandelli RH, (eds). Clinical Nutrition Enteral and Tube Feeding. 3rd edition. Philadelphia : WB Saunders Co, 1997; 112-137.

Diet is an integral part of treatment during the period of hospitalization. Malnutrition hampers the dog's recovery from critical illness.

Key Points
to remember:

Critical care nutrition of dogs

• Ideally, a dog should retain a stable body weight during hospitalization (or gain weight where appropriate). Daily weighing is imperative. **Nutritional support will be needed for a patient with inadequate food intake (real or foreseen) of 3 days or more.**

• **Enteral feeding is by far the best method of nutritional support**: it avoids atrophy of the intestinal villi and facilitates faster recovery. When enteral feeding is impossible, the length of time that food is withheld from the intestine must be minimized.

• **The energy requirement of a hospitalized dog can be compared to that of a resting dog.** Its value is estimated at no less than 70 kcal/kg $(BW)^{0.75}$. It must be understood however that individual variations can increase this requirement by 30%.

• The diet's energy concentration must be maximized, in order to limit meal volumes. The higher the fat content the greater the energy density. Administration of 30-50% of the calories as fat should be the aim. The ideal solution is a diet that has a combination of high energy density and is easy to suspend in water.

• The protein content should be sufficient to maintain a positive nitrogen balance. **Provision of 30-50% of total calories from protein helps combat loss of lean body mass.**

• Be aware that a solution with a high glucose content may promote hyperinsulinemia and hyperglycemia. **Do not exceed 10-25% of total calories as glucose.**

• The fluid-electrolytic balance must be monitored very closely in critically ill dogs: blood potassium, phosphorus and magnesium concentrations are especially important. Rehydration solutions help correct some electrolyte deficiencies.

Pros and cons of different types of enteral or parenteral foods			
Type of food	**Pros**	**Cons**	**Indication**
Hand feeding	- Simple - Not stressful for the dog	- Time consuming - Applicable only in some cases	Very short-term feeding
Appetite stimulants	Few available	Hepatotoxicity possible	Short-term feeding (2-3 days)
Nasoesophageal feeding	- Easy to place tube - Non-invasive - Minimal tranquillization - Few complications	- Tube not always tolerated - Elizabethan collar mandatory - Liquid diet	Short-term feeding (1-2 weeks)
Esophageal feeding	- Easy and fast tube placement - Elizabethan collar not mandatory - No nasal irritation - Does not prevent the dog from eating	- Special equipment required - General anesthetic mandatory	Several weeks of supported feeding
Gastrostomy feeding	- Easy to maintain tube in position - Few complications	- Risk of infection of insertion site	Several months of supported feeding
Jejunostomy feeding	Bypass the pancreas	- General anesthetic mandatory - Delicate tube placement - Intensive care required - Elemental nutritional solutions	Pathology of stomach, duodenum or pancreas
Parenteral feeding	Permits nutritional support during digestive surgery or serious digestive complaint	- Cost - Constant surveillance - Major risks: metabolic complaints, thrombophlebitis, septicemia, atrophy of the intestinal villi, Adynamic ileus	Any situation in which the digestive tract needs rest

Focus on:

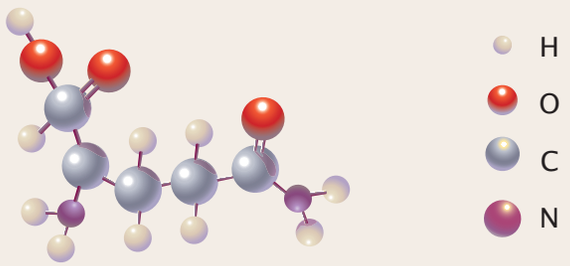
GLUTAMINE

The increased rate of gluconeogenesis accelerates glutamine catabolism in an animal under stress. In the presence of this greater requirement, muscle synthesis of glutamine is often insufficient and the glutamine blood concentration falls. Although glutamine is not an essential amino acid, it may become conditionally essential in some situations.

Glutamine has multiples functions: it participates in maintaining the acid-base balance, it is a precursor of puric and pyrimidic bases, it regulates some hepatic syntheses and it participates in detoxification processes.

Glutamine is a particularly important substrate for rapidly dividing cells such as the cells of the digestive tract and the immune system.

CHEMICAL FORMULA OF GLUTAMINE



Glutamine is used by immunoglobulin A-producing cells of the intestinal mucosa. A low dietary intake combined with a high requirement in critically ill animals may affect the integrity of the intestinal barrier, leading to a greater risk of bacterial translocation and systemic infection.

While glutamine (250-500 mg/kg/day) is recommended for the prevention of atrophy of the intestinal villi, it is not systematically incorporated in parenteral nutrition solutions as preparations for intravenous use are difficult to obtain *(Elliott, 2004)*.

Reference

Elliott D – Parenteral nutrition. Scientific Proceedings WSAVA – FECAVA 2004 ; HVMS World Congress, Rhodes (Greece).

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The social role of food and behavioral pathologies in the dog

1 - Social role of food in canine societies 483
2 - Social role of food in human societies 484
3 - Social role of food in the relationships between humans and dogs 484
4 - Behavioral pathology and food 487

References 489
Royal Canin Nutritional Information 490

The social role of food and behavioral pathologies in the dog

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The feeding behavior of dogs often includes anecdotal evidence or haphazard interpretations. The management of resources, and specifically food, is fundamental in animal societies. Frequently, access to food is ritualized, requiring well developed communication, once the essential needs are covered.
In human societies, when food is abundant, meal access and eating have a social value. This ritualization causes the members of the group to consume the food (or at least to adopt the associated behaviors) for reasons other than hunger. Our domesticated dogs are placed in an identical situation as most of them have sufficient food. The management of their food is therefore more often guided by the needs of communication than by hunger.
Humans and dogs share a number of common points when it comes to communication around food. However, the minor differences are the cause of serious misunderstandings that leads to education problems, dietary disorders and even pathological conditions. It is also conceivable that, beyond their specific characteristics, some diseases or pathological conditions will lead to disruptions in dietary behavior.
Practitioners who observe a dysregulation in food intake must evaluate the type of dysregulation and expect to encounter effects in both communication and behavior.

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A pack of wolves.
In canid societies, the dominant animals control access to the whole group's food supply. The other animals eat very quickly, because access to the food may be refused at any time.

1 - Social role of food in canine societies

Just like many social species that live in hierarchical groups, for dogs access to food resources is based on a precise chain that reflects the hierarchy. The alpha animals that control reproduction have primary access to food resources. This hierarchy means that the resources are reserved for the strongest animals and this results in the selection of the most influential genes *(Goldberg, 1998)*.

The rules established in a given group are maintained and constantly reinforced by the application of rituals that replace and so prevent energy-sapping confrontations.

There is usually a shift between objective and symbolic, as privileges gradually become a symbol of power. In dogs, the control of the food is a symbol of a high hierarchical position, even when the supply is abundant.

It is therefore conceivable that the dog produces a certain number of behaviors aimed at controlling the food in the group without the involvement of appetite or hunger in the determination of these behaviors *(Scott et al, 1965; Fox, 1978)*. So, a dog that begs at the table may be doing so not for taste or hunger reasons, but to show that it has access to the group's resources (in the representative sense).

Besides control of the food, which acquires a ritual function for hierarchization, the behaviors allowing one animal to eat before the others, while others wait and watch, also have a social significance. It is clear that the dominant (alpha) members not only take the best food first, but that they also oblige others to attend the meal and patiently wait their turn *(Muller, 1998a)*.

Domesticated dogs exhibit many of the behaviors that are undoubtedly motivated by the need to impose periods of 'respectful' observation on the master when the dog eats. For example, difficult dogs often love to attract attention when they eat.

A ritual is a behavioral sequence that has lost its initial function, used as a means of communication in a social group. The use of a ritual binds and soothes the group *(Heymer, 1977)*.

© Y. Lanceau

Yorkshire Terrier
Small dogs live more easily in contact with their master (in laps and chairs, etc). As a result, they are more exposed to bad education and dietary errors.

2 - Social role of food in human societies

Managed in the same way as hierarchical animal societies, in highly industrial societies food is also used as a loaded symbol to express notions of equality. The principle is the same as above, but its expression is reversed. Inviting someone to your table is a sign of friendship. This perception should not be misconstrued, it is driven by the same fundamental characteristics as dietary hierarchization in the dog. In the soldiers mess for example, diners are separated according to their rank. At wedding banquets, the seating plan is very important. Placements at the table usually respect hierarchical precedence. Just witness the embarrassment when a group of people sit down to eat after a work meeting when there is no seating plan.

On the other hand, it is good manners for employers to share a drink or a bite to eat with their employees to make it clear that there is not a huge social barrier.

In humans as in dogs, feeding has been ritualized to become a symbol of power or social glue.

Gifts are also a means of power. The person that receives is in debt and the acceptance of a gift is a gesture that can have great social significance. What woman would accept flowers or jewelry from just anyone who offered it, without feeling embarrassed? The gift binds the person who accepts it. One of the ways to possess the animal is to offer it a gift. The gift of food is often the scourge of zoo keepers who are unable to dissuade visitors from trying to give food to the animals they like. For animals, the gift is inevitably food and the stakes are non-acceptance.

3 - Social role of food in the relationships between humans and dogs

© Renner

Young German shepherd after weaning
Dietary ritualization starts at the end of the suckling period and is achieved around the 16th week.

Two factors are intertwined: the necessity of ritualizing the relationships (humans and dogs are social animals) and the need to control this relationship (principally through food). Ignorance of canine ethology and communication often leads owners to content themselves with anthropomorphical interpretations that result in serious aberrations.

The misunderstanding is often established in the first moments of the relationship (the first weeks after adoption), as the master looks to win the dog's affection with gifts of food. In this case the dog will gain the wrong impression of the new family if its development up until that time, has been normal. More seriously, if this attitude is adopted too early in the life of the puppy it may thwart harmonious development by stifling the essential social constraints of self-control in social species *(Moorcroft, 1981)*.

Habits are formed quickly. The master tries to give pleasure to the dog by satisfying its various demands for food, while the dog tries to acquire the highest possible social status.

The social relationship is gradually reduced to these exchanges of food, which allow owners to exonerate themselves from their various breaches. Inviting the dog to the table is a mark of social esteem and a way to win the animal's heart. Gradually, habit will trans-

form the gift of food into a ritual. Besides bad behavior in the relationship, these practices also lead to eating disorders. For these reasons the dog will become difficult and greedy. This is exacerbated when the dog's relationship with its master is based on the ritualized gift of food, which makes change more difficult for both the master and the dog. The notion of guilt plays a large part in this giving of food. The more a master thinks the dog is unhappy the more important he or she will find it to compensate with the gift of food *(Muller, 1998b)*.

Table 1 - Seven helpful tips for the arrival of the puppy

1. Do not change the food the first day the puppy arrives, and only make food available to the puppy for brief intervals: five times a day for five minutes would appear sufficient. Do not linger while the puppy is eating. Subsequently, it is preferable to offer meals for a brief period (five minutes) at regular times. The ideal number of meals for a weaning puppy is five daily and for an adult dog it is two daily.
2. From day one, do not allow your dog to approach the table during your own mealtimes, whatever its age. This rule must never be broken. Remember that breakfast is also a meal.
3. Select kibbles in a rational way, without succumbing to impulse buying. Any changes should be transitional. Do not trust in the preferences of your dog or cat, which are based on flavor and are not always best for the animal's health.
4. Use small pieces of food as a reward after exercise, but ensure that these treats correspond to an effort made or a command learned.
5. Give the dog its meal after you have had your own or at completely different times.
6. Leave the room when the dog is eating. Do not try to take the bowl, as this will provoke a conflict and you cannot be sure that you will come out on top even if you do get the bowl.
7. Contrary to the popular belief, bones do not provide the dog with much in the way of nutrients. It is preferable to give the dog chewing bars. Leave the dog in peace when it is busy with its treat.

You should only give food over and above meals as a reward to help the dog to learn. This means you should give the treat at the end of the sequence of commands you want to reinforce to the dog. Remember you can easily substitute a few kind words or a few pats instead of a treat.

A system of random rewards is recommended to attain a certain type of behavior through training. At first, the desired behavior should be encouraged and reinforced with systematic rewards. When the animal regularly starts to produce the required sequence, the reward may be alternated (once in every two then every three times). After a period of time, it is a good idea to progress to random rewards, which will attain the desired behavior and ensure that it does not disappear when it is no longer reinforced.

Owners inadvertently teach their dogs that they can beg at the table by employing the alternative reward, then stopping providing a reward almost totally, so adopting a random reward model. It is normal for the dog to beg in these circumstances, even when the owner practically never succumbs *(Lorenz, 1978)*.

Table 2 - Ten errors to avoid

1. Giving food from the table: by sharing food you destroy the dog's image of you. The dog admires and feels an attachment to masters that protect their food.
2. Imploring your dog to eat or encouraging it by feeding it with your hand. If you want your dog to respect you, you should not stay in its company when it is eating. By showing that you really want it to eat, you assume a subordinate position and invite the dog to refuse food in its desire to move up the hierarchy.
3. Confusing a good diet with being nice. This may hold for humans, but it does not hold for dogs. A happy dog is a healthy dog that can go for a walk and play with its master. Food should be used only to quell hunger, not as a way of gaining affection. Animals are not capable of managing dietary pleasure in any reasonable way.
4. Do not feed your dog just before you sit down to eat yourself to stop it begging. This will confuse the dog, which will certainly not beg because it is hungry but because it wants to take on the status of master by sharing your food.
5. Giving your puppy different foods to make it feel at ease when it first arrives. The first days in a new home are decisive. It is normal to try to reproduce an environment the puppy understands. You should not modify the image it has of adult humans. It is normal that it does not dare eat when it arrives and exhibits timid behavior. It is also important to impose rules from the beginning.
6. Using small treats to stimulate the dog's appetite for its kibble. There is no point in doing this. If the dog is hungry it will eat its kibble. Otherwise there is a risk of making it eat when it is not hungry, which will cause unwanted weight gain. In addition if you continue with this ritual you increase the risk of the dog not accepting its kibbles.
7. Making up for your absences and shortcomings with food treats. There is a risk you will reduce the dog-master relationship to an exchange of food.
8. Reducing the quantity of food and drink for reasons of cleanliness. This common technique puts the master's desires ahead of the dog's needs. Young puppies must be given at least four meals a day and they must have access to fresh water at all times. There is a risk that irregular distribution will lead to digestive disorders that adversely affect learning.
9. Not worrying about a puppy that eats a lot more than the manufacturer's recommendations. Over consumption can be a sign of satiation, behavioral (hypersensibility-hyperactivity) or digestion problems. It would appear wise not to wait long before discussing it with the veterinarian.
10. Giving a homemade meal once a week. This expresses the master's lack of confidence in a prepared petfood. The master either fears some deficiency or is afraid that the dog will not be happy. Serious discussions with the owner must be used to show the dietary quality of manufactured food.

Practitioners must be aware of these points if they are to eliminate bad habits. A ritual cannot be eradicated without compensation. On the other hand, no guilt should be attributed, as this will involuntarily strengthen the attitude that triggers the gift of food **(Tables 1 & 2)**.

4 - Behavioral pathology and food

► Relational problems

The concept of dietary behavior ritualization enables us to understand the development of relationships in relation to food for the domesticated dog. The ritual must be understood as an essential part of the dog's relationship with the master. To retain contact with our remote friends and acquaintances, at least once a year we succumb to the ritual of sending a greeting card.

The prevalence of rituals increases when the master-dog relationship is weakened and the dog will spontaneously initiate symbolic behavioral sequences. At a certain level, this increase becomes pathological attention-seeking behavior *(Overall, 1997)*.


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Bulimic behavior in a dog may be an expression of anxiety. Eating may have become a displacement activity.

Dietary rituals are clearly involved and the animal may adopt dietary behavior that is contrary to its primary needs (hunger and satiation). The animal may eat even though it is satiated to show its position or to accomplish a ritual act. On the other hand, it may refuse to eat if the circumstances no longer correspond to a ritualized act *(Houpt, 1991)*. These behaviors are governed by strong motivations and are not easy to change. Denouncing them will not be enough to eliminate them. They express the deep unease of the dog, the master and their relationship *(Beaumont et al, 2003)*.

► Anxiety and displacement activity

The animal may become anxious due to relational problems or other reasons. The condition will lead the dog to want to be assuaged more than a normal animal and it will seek to maximize its contacts with its owners (it may be impossible to leave the dog alone). The need for contact (secondary hyper-attachment) may leave the animal unable to feed itself if its masters are no longer present (it will eventually die of starvation). Furthermore, an anxious animal will attempt to regain its emotional stability through repetitive rituals ad infinitum.


© Bouchka

An active Golden Retriever
Recreational therapy is part of the treatment of dietary behavior problems. The goal is to increase exploration activity to create a positive emotional context.

Unfortunately, such automatic excessive behaviors (stereotypes) lose their primary function and especially their comforting power. Only a considerable increase in number can compensate for the loss of this function. The ritualized sequence gradually becomes displacement activity.

If feeding is part of the behavior adopted by the dog to regain a calm attitude, disproportional ingestion and a spectacular weight gain can be expected.

Such behavior cannot be eliminated without specific etiological treatment (antidepressant and restoration of a socially-adapted environment).

► Sick animals

Owners often tend to wrongly interpret their animal's lack of appetite as a sign of developing illness and encourage the dog to eat even though it is in good health.

It is true that a sick animal – especially one with a fever – will typically lose its appetite. This behavior has been described as an adaptive response *(Hart, 1990 & 1991)*. Interleukin will play a role in the sick animal's demotivated behavior *(Dantzer, 1999)*. Conversely, it is not sufficient to explain a clear lack of motivation to eat without a visible organic cause by saying that the disease is behavioral. Such a default diagnostic often leads to unproductive treatments.

► Satiation problems

The dog's relationship with its owner is not the source of all behavioral diseases. Some dogs are abnormally adapted or may even be suffering from an illness. Some of these conditions are expressed through satiation problems.

> Two-phase hypersensibility-hyperactivity syndrome (HSHA)

In the worst cases, hypersensibility-hyperactivity or a lack of self-control is accompanied by a lack of satiation. The animal becomes unable to adapt its behavior to the internal messages it receives. The sight of food triggers feeding and the sight of water triggers drinking. The dog only stops when he is incapable of continuing or when a more inspiring event attracts its attention *(Pageat, 1995)*.

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Knowing that such behavioral disorders exists can help the practitioner to show greater patience in helping to deal with the difficult issues.

These dogs are seldom obese, because they expend more energy than healthy dogs. They are often insomniacs and their hypersensitivity leads them to react to stimulation with great energy. Their dietary needs are generally not at all consistent with the recommendations of manufacturers of commercial foods, which are not geared to such energy expenditure.

This disorder rarely resolves without treatment. Anxiety ultimately develops, modifying the initial clinical presentation *(Dehasse, 1996)*. These animals have difficulties learning. It is fairly uncommon for dietary rituals to be established in the master-dog relationship here.

> Primary and secondary dissocialization

Dissocialization is the result of bad developmental conditions *(Muller, 2000)*. This disorder can be primary when it is the consequence of major initial deficiencies and it can be secondary when it is due to unfavorable early and late conditions *(Arpaillange, 2000)*.

Patients present various symptoms, which boil down to a poor or even non-existent knowledge of canine social rules. For these dogs, of course, dietary rituals are absent or frustrating. The desired food is consumed and every obstacle against satisfying this craving is fought against. These dogs are sometimes capable of jumping on the table to steal their master's plate. This condition has a wide spectrum of severity, from very poor education to the most violent psychotic behavior.

> Depression

Emotional problems can sometimes bring about mood disorders. The best known is depression, which can be acute or chronic in dogs. The distinction between these two forms is centered on appetite and sleep. There would appear to be a correlation between the two.
In a chronic depression, sleep increases while feeding decreases *(Habran, 1998)*. An irregular appetite may be the first sign of this chronic form.
The acute form is more alarming: the dog stops eating and sleeps excessively. In puppies it represents an emergency.

Conclusion

The study of dietary behavior goes well beyond the confines of nutrition. Conversely, you cannot hope to come to grips with canine nutrition without a good knowledge of the psychological value of food and meals, for both humans and dogs.

Clinicians that deal with problems of dietary behavior must consider the elements of behavior to be symptoms of disease. The consultation is used to identify the food-related symptoms and other components to arrive at a systematic description of the disease.

The prescription depends on the disease, and incorporates every etiological aspect of it. An exclusively symptomatic prescription will not have the same impact. If it is to be effective, nutrition alone can target only some of the problems of dietary behavior and the prescription must include all psychological and organic aspects.

References

Arpaillange C - Comportement du chien : responsabilité du maître ? Point Vét 2000 ; 31(207) : 93-94.

Beaumont E, Beata C, Diaz et al - Pathologie comportementale du chien, Paris, Masson 2003, 319 p.

Dantzer R - Éléments d'éthologie cognitive (du déterminisme biologique au fonctionnement cognitif) dirigé par Gervet J et Pratte M ; Editions Hermes, Paris, 1999.

Dehasse J - Le développement de l'inhibition et de l'autorégulation physiologiques, XVII^e congrès SAVAB, 1996.

Fox MF - The dog: its domestication and behaviour. Garland STMP Press, 1978.

Goldberg J - Les sociétés animales. Paris, Delachaux 1998 : 345 p.

Habran T - La dépression chez le chien et le chat. Réflexion à partir de modèles animaux. Mémoire pour le diplôme de Comportementaliste des Écoles vétérinaires françaises ; 1998.

Hart BL - Behavioral adaptation to pathogens and parasites: five strategies. Neurosci Biobehav Rev 1990 ; 14(3) : 273-294.

Hart BL - The behavior of sick animals: In: Veterinary clinics of North America 1991 ; WB Saunders company, Philadelphia: 225-237.

Heymer A - Vocabulaire éthologique. PUF Paris 1977: 235 p.

Houpt KA - Feeding and drinking behavior problems. Advances in companion animal behaviour. Vet Clin North Am Small Anim Pract 1991 ; 21(2) : 281-298.

Lorenz K - Les fondements de l'éthologie. Paris, Flammarion 1978: 427 p.

Moorcroft WH - Heightened arousal in 2-week-old rat: the importance of starvation. Dev Psychobiol 1981 ; 14 (3) : 187-199.

Muller G - Présentation de quelques cas cliniques de sociopathies chez le chien et de quelques conflits territoriaux chez le chat. Mémoire pour le diplôme de Comportementaliste des Écoles vétérinaires françaises ; 1998a.

Muller G - Distinction mauvaise famille, mauvais développement, mauvaise éducation. Congrès spécialisé du GECAF, Morzine 1998b.

Muller G - La prévention des troubles comportementaux à l'élevage. Point Vet 2000 ; 31:109-116.

Overall KL - Clinical behavioral medicine for small animals. Boston, Mosby, 1997: 544 p.

Pageat P - Pathologie du comportement du chien. Ed. Point Vét.1995 : 367 p.

Scott JP, Fuller JL - Canine Behavior ; University of Chicago Press, 1965.

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The palatability of a food depends on how the dog consumes it, as this translates its perception of the food's organoleptic qualities. A highly palatable food will be consumed with great pleasure, while an unpalatable food may be underconsumed or even refused.

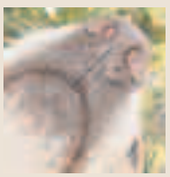
Key Points
in the analysis of:

The dietary behavior sequence

Generally speaking, food intake follows the following sequence.

The search, identification and selection phases

The dog uses its sense of smell to capture the aromas emitted by the food and its sense of touch to judge the food's temperature. **Smell is the most discriminating sense in this phase.** The dog has 70-200 million olfactory receptors, compared with a human's 5 to 20 million receptors *(Vadurel & Gogny, 1997)*.



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When a dog sniffs, the airflow is 1 l /sec, which is ten times faster than in normal respiration *(Vadurel & Gogny, 1997)*. Olfactory acuity is at a maximum when the dog is hungry and falls when the dog is satiated.

The sense of smell declines with age.

The oral phase

The dog now perceives the size, shape, texture and taste of the food.

The sense of taste is centered in the gustatory papilla on the tongue, palate and pharynx. Dogs have around 1700 tastebuds, compared with 9000 tastebuds in humans.

Dogs distinguish five distinct flavors: bitter, sweet, acidic, salty and umami, which is the recognition of an essential amino acid, glutamate. Dogs tend to reject bitter flavors and be attracted to sweet flavors. It should be remembered that wild canids also eat fruits and berries.

Conditioning starts before birth, as the puppy's gustative system starts to function just before whelping *(Ferrel, 1984)*. It is sensitive to certain molecules in the mother's food, which are conveyed through the placental circulation and the amniotic liquid *(Thorne, 1995)*. This intrauterine exposure influences the future preferences of the puppy *(Doty, 1986)*.

Digestion phase

If the dog associates negative sensations with the ingestion of a food (e.g. if it is ill just after it has eaten), it may develop a process of aversion that will lead it to avoid this food the next time *(Cheney & Miller, 1997)*.

COMPARISON OF OLFACTORY PERFORMANCE IN DOGS AND HUMANS
(from Vadurel & Gogny, 1997)

	Dog	Human
Surface of the olfactory mucosa (cm^2)	60 to 200	3 to 10
Number of receptor cells (millions)	70 to 200	5 to 20
Part of the olfactory brain/total brain	35 times greater	
Detection threshold for certain molecules	concentration 10^6-10^8 times weaker	

Focus on:

FOOD FLAVORS

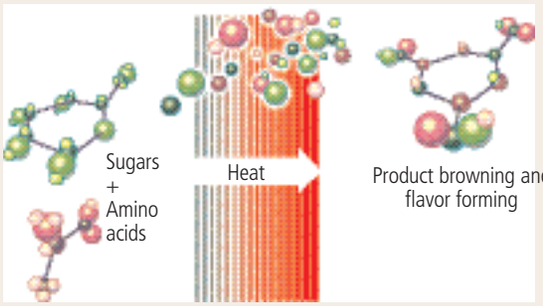
The dog is naturally attracted to food with a high fat content. Increasing the quantity of fat in the kibble's coating is the simplest way of increasing palpability, although this strategy may be counterproductive to the nutritional strategy. There is a danger that high fat food will encourage obesity if the owner fails to properly control the quantities given.

The more you try to limit the fat content, the more important flavor is to palatability. Flavors were limited until new ones started to be produced by traditional methods like enzyme hydrolysis and Maillard reactions, as used in the manufacture of cookies. A technological breakthrough has enabled the development of a third generation of flavors, with even better results. The effect is much improved as it is the synergy of the two flavor types that were formerly used for dogs.

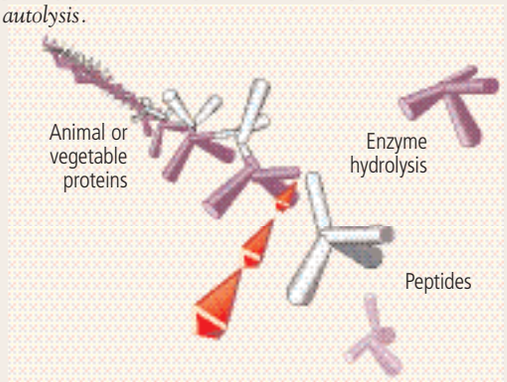
The work on flavors involves following their development in time. Palatability must remain satisfying until the final date of consumption stated on the packaging.

THE MAIN TECHNOLOGIES USED UN DEVELOPING FLAVORS

1. ***Maillard reactions*** *are used to flavor various products (coffee, rusks, roasted meat, etc).*



2. ***Hydrolyzates*** *are often obtained from heated and acidified poultry proteins. Enzymes are used to produce protein autolysis.*



References

Cheney CD, Miller ER – Effects of forced flavor exposure on food neophobia. Appl Anim Behav Sci 1997 ; 53: 213-217.

Doty RL - Odor-guided behavior in mammals. Experientia 42, 1986 ; Birkhaüser Verlag, Basel, Switzerland: 257-271.

Ferrell F - Taste bud morphology in the fetal and neonatal dog. Neurosci Biobehav Rev 1984 ; 8(2): 175-83.

Thorne CJ - Sensory and experiential factors in the design of foods for domestic dogs and cats. In: Recent Advances in Animal nutrition, 1995 ; Nottingham University Press, Loughborough, UK: 51-167.

Vadurel A, Gogny M - L'odorat du chien: aspects physiologiques et facteurs de variation. Point Vét 1997 ; 28 (181): 1037-1044.

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Integration of nutrition into clinical practice

1 - Maximizing space 495
2 - Feeding hospitalized patients 498
3 - Advice on diets 500
4 - Dietary training 503

References 505
Royal Canin Nutritional Information 506
Table of composition of the main ingredients
used for the preparation of home-made diets 508

Integration of nutrition into clinical practice

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In the past, when veterinary medical knowledge was limited, husbandry issues including diet were the predominant focus for patient care. As new diseases were described, nutritional issues did not become any less vital to successful patient care, but their importance was slowly diluted by the sea of new diagnostics and therapeutics that became available to veterinary medicine. Fortunately, our knowledge of nutrition has not remained static as the rest of veterinary medicine has advanced, and thus, the wisdom of integrating diet into a patient's therapeutic management has been proven in a growing number of disease states. Given the importance of nutrition in veterinary medicine, the goal of this chapter is to illustrate how nutrition can be successfully integrated into any clinical practice.

Veterinary medicine is transitioning into a two tier system of providing medical care. The first tier in this system is the primary care provider (PCP). The second tier in the system is the referral practice (RP). In addition, it is assumed that a RP inherently sees more complex and refractory cases as a percentage of its caseload.

Size is not necessarily related to the type of activity; some of the recommendations in this chapter for a RP may be more appropriate for a PCP with a large number of veterinarians. However, this assumption may not hold across all practices, and therefore the reader is encouraged to review and consider all of the following recommendations.

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Veterinary caduceus of the Netherlands.

Veterinary caduceus in France.
Below, from top to bottom:
- Veterinary caduceus of United States
- Veterinary caduceus of South Africa
- Veterinary caduceus of Germany.

Every veterinary practice is different whether that be due to geographic, socioeconomic or practice style differences. Therefore, any guideline that is created cannot anticipate every specific need that a particular practice may have. However, certain significant differences between practices are likely to be universal based on practice size and type.

Regardless of practice type or size, there is an inherent need to dedicate space to nutrition. The ability to store and provide more dietary options is somewhat dependent on the quantity of space that a practice allocates for that purpose. Since a significant percentage of a practice's earnings are frequently from food sales, this allocation of space is most likely economically justified. As there are always limitations on the amount of space available, the following section discusses strategies to maximize available space and recommends the minimum inventory necessary to treat the majority of cases.

1 - Maximizing space

If space is limited, the amount of stock on hand will inherently need to be limited. A small inventory demands either one of two management strategies – frequent delivery or limited sales.

Clearly, limiting sales either intentionally or unintentionally is less than desirable. Limited sales can frequently mean that the importance of nutritional management in patient care is under-recognized. This can have a deleterious effect on both patient and practice health.

Orders cannot be placed once a week or month, but rather may need to be made daily in order to prevent prohibitively long delays in providing patients or clients with needed diet. Inevitably, there is a cost associated with having a small inventory. The cost of a small inventory may not be realized if the only cost recognized is the expense associated with the additional square footage and not lost sales or increased labor costs.

A large inventory allows a practice the luxury of having infrequent deliveries and/or high diet demand. This system allows the workload to reduce due to frequent ordering. The downside to this is the added space that such an inventory requires.

► Managing incoming stock

Several companies have developed control systems that allow product sales to be tracked in addition to assisting with inventory management. This type of sales data allows the practice manager to better assess the practice's needs and to stock a practice-specific diet inventory. Whatever management tool is used, it is necessary to decide:
- the quality offer available to clients;
- the minimum volume to be stocked for each reference.


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A practice that deals with many obese patients may wish to carry a higher percentage of diets designed for weight loss than a practice that focuses on oncology.

> Selecting available products

In an effort to address space limitations a priority should be placed on stocking diets that are used frequently. Diet selection should be based on disease prevalence and the proven importance of nutrition in disease prevention and treatment **(Table 1)**.

TABLE 1 - THE LIST OF MAIN THERAPEUTIC FOODS AVAILABLE TO VETERINARIANS

DIET TYPE	INDICATION
Low energy diet	Obese prone/obesity
High moisture diet/diet that induces thirst with adjusted concentrations of crystallogenic precursors	Urolithiasis
Protein hydrolysate diet or novel antigen diet(s)	Adverse reactions to food
Low phosphorous/low protein diets	Acute/subacute/chronic renal failure; hepatic encephalopathy
High energy density diet	Volume intolerance, unintended weight loss, inappetance
Low fat diet	Pancreatitis, reduction of delayed gastric emptying, fat intolerance
Highly digestible diet	Non-specific acute gastroenteritis, fiber non-responsive constipation/diarrhea
Liquid diet	Enteral feeding through a feeding tube
Dry diet targeting oral hygiene	To help reduce the development of plaque and calculus
Low carbohydrate OR high fiber diet*	Diabetes mellitus
High energy density diet with concurrent sodium restriction*	Third space fluid accumulation secondary to heart failure or decreased oncotic pressure
Parenteral nutrition solutions*	Intractable vomiting or diarrhea, pancreatitis when it is impossible to place a jejunostomy tube, recovery from gastrotomy or enterotomy

The list above of therapeutic diets should meet the canine dietary needs of most practices.
** If space permits, it is also possible to stock these kinds of diets.*

The list of therapeutic diets should meet the canine dietary needs of most practices.

Other diets are available for growth and maintenance, degenerative joint disease support, hepatic and cardiac disease support that are not listed in the table, but may be useful depending upon the practice preferences and demographics.

Although a single commercial diet for each category above may be adequate for the majority of patients, there are times when palatability, learned aversions or other qualities will necessitate the use of a diet that is not in stock. To facilitate identifying diets that may serve as adequate surrogates, practices should keep up-to-date product guides for all available manufacturers. These product guides can also serve as references for nutrient data for patients with extensive diet histories.

Almost all patients can be managed through the use of commercial diets; however, a small subset of patients may require specially formulated, home-cooked diets. In these cases special training in veterinary nutrition is recommended to ensure all situations can be handled correctly.

> Keeping inventory at a minimum

The minimum inventory is equal to the quantity that will theoretically be sold between the order date and the delivery date. If orders are made daily and the delivery time is 24 hours, the minimum inventory must constitute 1/6 of weekly sales. This inventory can of course be supplemented by a safety margin to offset a delay in delivery or increased consumption for a limited period.

An order must be triggered when the stock reaches a minimum threshold. The quantity to be ordered depends on the quantity of products that can be put on the shelves. For various references, it is also important to take into account the potential growth of the sales.

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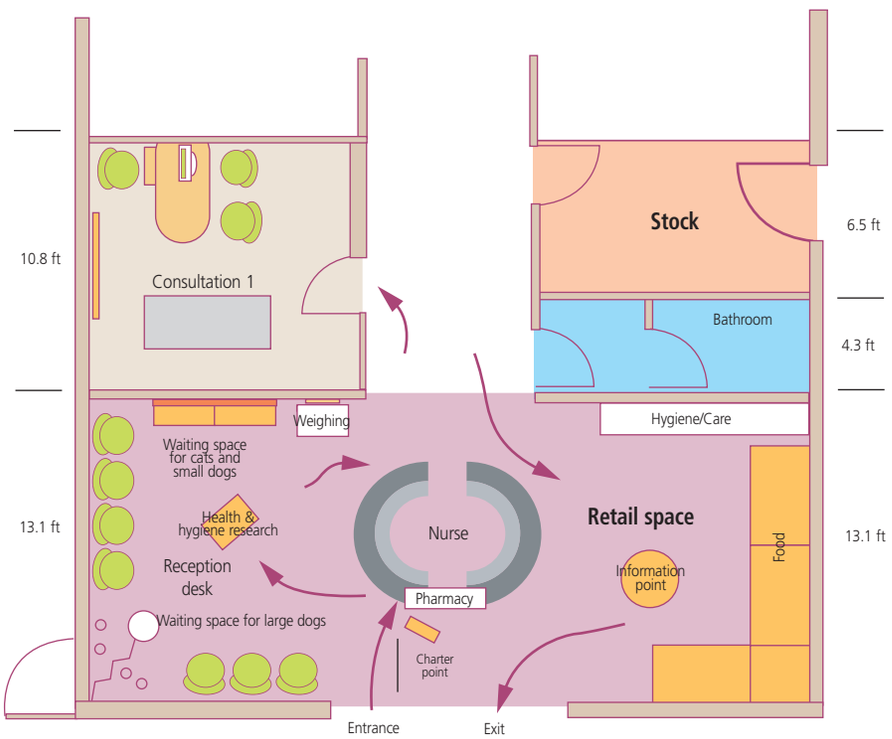
Consistent product usage has the benefit of allowing product performance for a particular disease state to be determined and adjustments in recommendations to be made when indicated. Usage that is too inconsistent may limit the practitioner's ability to recognize a product's effectiveness.

► Storage

> Retail space

Stock must be arranged neatly, separate from the storage zone **(Figure 1)** and as clearly as possible for the client. Arrange according to species (with a visual for fast identification), then by brand and lastly by product family to help clients find what they want. Labels to the front will make them easier to read.

FIGURE 1 - EXAMPLE OF THE FLOOR PLAN FOR A VETERINARY CLINIC



Storage and retail spaces must be separate. The retail space must be visible throughout the veterinarian's prescription talk. It must facilitate the replenishment purchases and attract the attention of owners that usually buy food through other channels.

Large packs mean you have to have a lot of space between shelves. Since the number of diets that a practice wishes to stock will often exceed the amount of available space, stocking smaller sized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Frequent replenishment will facilitate a rapid response to the request of owners, but will increase the workload for staff.

bags can allow for increased storage. Using small bags for dietary trials allows the hospital to need less space for food storage and a larger bag can be subsequently special-ordered when the diet's palatability and performance has been proven. Moreover, due to the decreased mass of smaller bags, higher (and easier) shelving can be employed, increasing storage capacity.

Initiating a policy that encourages clients to bring their pet's typical diet from home when the dog is to be hospitalized can also limit the amount and variety of maintenance foods that need to be stocked and prevent the risk of aversion.

> The storage zone itself

There are four must-dos to use the storage zone optimally:
- **Space optimization:** reduce the distance between shelves by laying large packs flat;
- **Product accessibility:** label the shelves to make products easier to find. Large bags should be nearest to the ground.
- **Respect storage conditions:** products must be kept dry and must not be subjected to extreme temperatures or humidity
- **Respect expiration dates:** new stock should be placed behind older stock on the shelves.

► Managing outgoing stock

Outgoing stock should normally trigger three actions:
- Billing and payment or charging
- Stock is updated automatically by the computer system
- A new order to replenish the stock at required levels.

2 - Feeding hospitalized patients

► Preparation of the meals

Space dedicated solely for diet preparation is vital to facilitating the application of nutrition in clinical practice. This area can be as simple as a small counter to allow cans to be opened and bowls to be filled, along with an adjacent sink equipped with a garbage disposal. A few additional items can increase the efficiency of a food preparation/kitchen area. A brief list of items that all practices should consider is provided in **Table 2**.

TABLE 2
BASIC EQUIPMENT FOR THE PREPARATION OF MEALS FOR HOSPITALIZED DOGS

- Refrigerator dedicated to diet storage
- Blender
- Microwave
- Can opener
- Measuring cups
- Knives
- Bowls
- Plastic lids to cover opened cans
- Gram scale
- Rice cooker

Additional Equipment to Consider
- Sterile hood or admixture compounder for parenteral nutrition
- Commercial dishwasher

► Choice of diet

A fundamental question in the management of every hospitalized patient is whether to feed or not. If the answer is to feed the patient, the next decision concerns the route of administration and the type of food. This topic is explored further in Chapter 14; however, the subject will be discussed as it relates to the logistics of providing nutritional services to the client and patient.

As a policy, clients should be encouraged and instructed to bring the patient's typical diet for feeding during hospitalization. Clearly there are exceptions which should be considered based on the underlying disease and the reason for hospitalization. However, when practical and not contraindicated, feeding the patient's own diet should minimize any potential gastrointestinal distress that may occur due to sudden dietary changes.

When the patient's typical diet is not available, another diet will have to be selected. Highly digestible diets are usually well accepted and tolerated; however, care should be taken to ensure that the diet is not concurrently too high in fat. Although fat can increase palatability and the likelihood of acceptance, it is the experience of the authors that sudden increases in dietary fat appear to be one of the most consistent and least recognized causes of gastrointestinal distress. In addition, although diets higher in moisture are often found to be more palatable, this

is not always the case and the patient may have a texture preference for dry food and will reject diets higher in moisture. Therefore, a highly digestible and low fat diet may be the best food to use as a standard hospitalized diet and should be stocked in an amount to meet this need.

> Meeting a hospitalized patient's energy needs

For many hospitalized patients, voluntary consumption of food will adequately meet a patient's energy needs. However, nutritional support may become necessary and, thus, should be an available procedure at all practices. A variety of enteral feeding tubes to meet diverse patient needs can be placed without special equipment beyond the appropriate feeding tubes and diet (i.e. nasoesophageal, esophagostomy or jejunostomy feeding tubes).

Percutaneous endoscopic gastrostomy (PEG) tubes require the use of more expensive and advanced equipment, but all practices should be able to provide adequate nutritional support to their patients without the use of an endoscope.

The use of parenteral nutrition may not be practical at many clinics and, thus, may be limited to RPs. However, as peripherally administered parenteral nutrition solutions with lower osmolarity and higher energy density become more common place and more proven, the use of parenteral nutrition may be more widely used in the future. For further discussion on critical care nutritional support please see **Chapter 14**.

How to ensure owner compliance after a diet prescription in dogs

A recent study commissioned by the American Animal Hospital Association (AAHA) reviewed client compliance in a variety of clinical areas, including the use of veterinary therapeutic diets. More than 350 veterinary practices throughout the United States participated through interviews and medical record reviews. The goals were to determine compliance levels, identify opportunities to provide better health care for pets through compliance, understand the barriers to compliance and lastly, how to promote compliance.

The report determined that 27% of pets with a medical condition that would have benefited from a therapeutic diet did not receive or follow such a recommendation from the veterinary provider. These findings equated to 11.6 million dogs with one of six diagnosed conditions that could have been helped by the use of a prescription diet that were not fed a therapeutic diet at all, or were not fed a therapeutic diet for an appropriate amount of time.

There are a number of factors that may contribute to a reduction in compliance when it comes to the use of therapeutic diets in our patients:

- The veterinarian's misconceptions about the client's willingness to act
- Cost of the diet
- Convenience
- Willingness of the pet to eat the food
- The owner's nutritional philosophies
- The veterinarian's lack of confidence in their own recommendations
- The possibility that the client may not clearly understand the benefits of the recommendation.

There are steps that we can take to increase compliance when it comes to ensuring that our clients follow a recommendation to use a therapeutic diet:

1. Ensure that you and your staff have confidence in your recommendations.
2. Create understanding and shared expectations through client communication and education.
3. Make the solution easy.
4. Continuous communication.

Compliance with respect to a diet prescription begins with the veterinarian and their staff. When there is a universal understanding and consistency with regard to ensuring client compliance, the patient, client and your veterinary practice all benefit.

References:

- *AAHA Compliance Study. Available at: www.aahanet.org.*
- *Client Compliance. DVM Best Practices, July 1, 2003. Available at: www.dvmnewsmagazine.com/dvm*

3 - Advice on diets

► Nutritional advice at every appointment

At the very least, a diet history should be collected and a brief discussion of the patient's performance on its current diet should be completed at every appointment. A diet history must be detailed enough that the patient could be fed the correct diet and amount with the recorded information.

The veterinarian should strive for a diet history that would enable tracking of every calorie consumed by the patient (i.e. main diet, secondary diets, dog treats, human treats, etc.), but often this level of detail is reserved for patients that have undergone unintentional weight loss or gain. The use of a standardized form **(Table 3)** may prove useful in collecting detailed and accurate information on a patient's diet. Having a form available for clients to take

TABLE 3 - DIET HISTORY FORM

Patient Name: …	**Client Name: …**	**Date**: …

Features: …

Below to be completed by client

Is your pet fed in the presence of other animals? ☐ Yes ☐ No
If so, please describe: …

Does your pet have access to other unmonitored food sources
(i.e. food from a neighbor, cat food etc.)? ☐ Yes ☐ No
If so, please describe: …

Who typically feeds your pet? …

How do you store your pet's food? …

Please list below the brand or product names (if applicable)
and amounts of ALL foods, snacks, and treats your pet eats: …

Amount Fed

Brand/Product/Food:
Form:
Per Meal:
Number of Meals:
Fed Since:

Please list other diets your pet has received in the past,
indicating the approximate time period when they were fed:
- Brand/Product/Food
- Form:
- Quantity served per meal:
- Number of meals per day:
- Reason Stopped:

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

Numerous services can be provided on an outpatient basis to the client and patient. These services vary in their complexity and the amount of effort that is required to provide them.

home enables them to complete the diet history at home where the specific diet name and amount can be more readily determined. The form also can easily be filed into the patient's medical record for later review and comparison. It has been the experience of the authors that such forms elicit more truthful and complete answers than simply questioning the client.

► Commercial diet recommendations

Every veterinarian should feel comfortable making recommendations to clients regarding commercial diets for healthy patients. As veterinarians focus more on preventative medicine, dietary recommendations will play a more important role in every patient's overall wellness plan. When recommending a diet, two important aspects to consider are nutritional adequacy and the ability of the diet to maintain the patient in an appropriate body condition.

The veterinarian's product range must be split into three distinct groups: Health Nutrition (for healthy animals), Feed & Secure Nutrition (to address specific risks) and Clinical Nutrition, to support the treatment of some pathologies.

Nutritional adequacy is constantly evolving as nutrient requirements are defined and refined. In the U.S., the non-profit organization, Association of American Feed Control Officials (AAFCO), has developed testing protocols and nutrient profiles in an effort to ensure nutritional adequacy of animal feeds including commercial pet foods. Diets that have undergone feeding trials are often preferred since they may provide better evidence that a diet's nutrients are available. In comparison, diets that simply meet nutrient profiles have not established that their nutrients are available and, thus, may not perform as anticipated based solely on recommendations.

Ideally, all food producers should have feeding test results for the food they are selling. Product quality also depends on the producer's vigilance with respect to the raw ingredients used and the end products sold.

One approach to help ensure the likelihood that a particular product is nutritionally adequate is to recommend feeding commercial diets that have a long-term history of use. Smaller companies often lack the same level of experience and expertise in diet formulation, employ few, if any, full-time nutritionists, and rarely have active research and development programs. Larger companies have many more "sentinels" for potential diet problems due to the increased number of dogs fed their products. Thus, if problems do arise, they are less likely to be missed or overlooked as an isolated incident.

The only intervention proven to delay the onset of disease and extend lifespan is maintenance of an optimal body condition *(Kealy & al, 2002)*. Therefore, it is important that each client be counseled on the importance and health benefits of maintaining a lean body condition in their pet. It is also important to remember that in every feeding equation there are three major factors that affect the final outcome; the animal, the diet and the husbandry/environmental conditions in which the animal is maintained. Therefore, the ability of the client to use a diet to maintain a lean body condition in their pet is an important indicator of how that diet performs in any given situation. In many instances, diets designed for maintenance or all life stages can be used successfully. However, sometimes a diet that is less energy dense may be necessary. At the same time, a less energy dense diet should have increased concentrations of all nutrients per unit of energy, as the delivery of nutrients may be artificially limited when fed to maintain a lean body condition.

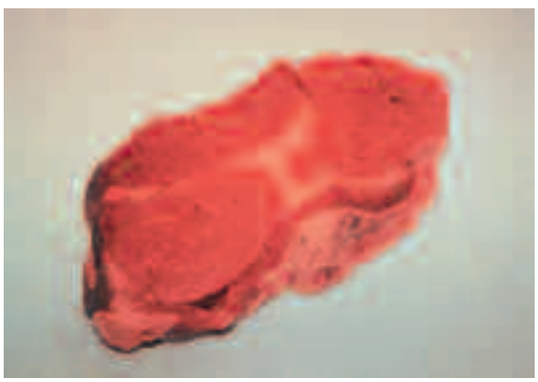
► Nutritional supplements

The act of selecting a diet that is nutritionally adequate should negate the need for additional supplementation. Veterinary medicine suffers from anthropomorphism in many areas, and one of the most extensive areas where this occurs is nutritional supplementation. Clients are inundated by the media and the human medical community about the beneficial effects of increasing their own intake of selected nutrients. Many of these beneficial effects would be blunted or lost if the daily diet of the client was as balanced as their pet's commercial food. Unfortunately, this point is often lost on clients and the perception that additional supplementation is in the best interest of their pet continues. This perception is difficult to counter, especially when supplementation is seen as innocuous and only beneficial. This is clearly not the case, and the client may need to be educated on the potential risk of adding nutrients into an already complete and balanced diet.

Beyond education, the veterinarian should provide guidance regarding the proven efficacy of the product. Efficacy studies rarely exist in the veterinary literature. Any research that has been done is often not in vivo studies, but rather in vitro work where the concentrations used exceed the amount physiologically possible. Alternatively, the amount of the nutrient being supplemented is quite possibly a fraction of the amount already in the diet and thus of little additional benefit. Clients' energies and finances may be better spent on the selection and purchase of a complete and balanced maintenance diet that maintains optimal body condition. Additional supplementation of any nutrient should only be advised in conditions where an increased requirement has been shown and where the amount provided in the diet is known in order to avoid dietary excesses. If a diet is found to be low in a particular nutrient, selection of an alternative diet with appropriate levels of the nutrient in question is a more prudent course of action rather than supplementation.

► Home prepared diets

An all-meat diet is imbalanced and especially leads to calcium deficiency.



Some clients choose to prepare food at home out of a concern that commercial pet foods are not as wholesome or nutritious as a diet they make themselves. Others have allowed their dogs to develop a fixed-food preference, usually based around home-cooked ingredients. Some clients are required to prepare their dog's meals out of medical necessity. Some dogs have multiple concurrent disease states, which cannot be managed using a commercially available pet food.

Whatever the underlying cause, all of these clients are equally at risk of feeding a diet that is inappropriate, incomplete or unbalanced. Although these diets are unlikely to cause a problem in the short term (2-3 months), there is a risk of clinical signs developing over the long term in the healthy adult and

most likely sooner in the growing or unhealthy dog. Evaluation of the client's home prepared diet should be offered and recommended.

Initiating a successful consultation with a board-certified nutritionist usually requires that a very detailed and accurate diet and medical history be provided, along with the patient's current weight and body condition score, as well as the client's goals and concerns regarding the patient's diet. For puppies, the owner should be encouraged to regularly update the weight gain curve.

If specific, but uncommon ingredients (for which little nutrient data is known) are utilized by the client, determining their willingness to change the ingredient or their reason for using the ingredient can be very useful. It can be quite difficult to determine the overall caloric distribution, let alone specific nutrient concentrations, by simply looking at the ingredients. However, the veterinarian should feel comfortable identifying simple and obvious nutrient deficiencies in home prepared diets.

The following items should be identifiable in every home prepared diet:

- **Protein source** – usually from an animal or a concentrated vegetable protein (i.e. tofu);
- **Essential fatty acids** – especially linoleic acid – animal-source proteins rarely provide adequate levels of this fatty acid, thus a vegetable oil should be included;
- **Calcium and phosphorus** – these minerals are required in high concentrations and therefore are often provided in the form of bone meal or a calcium supplement;
- **Other minerals and vitamins** – unless liver or whole egg is provided in relatively high amounts, a source of other minerals and vitamins is necessary;

The presence of each of these components does not guarantee completeness or balance, but their absence can serve as an easy indicator to the practitioner and client that the diet should be evaluated.

Proteins are composed of twenty or so amino acids, only half of which are indispensable to the dog and must be provided in the food.

Essential fats are polyunsaturated fatty acids. They are more sensitive to oxidation and must therefore be stored with care.

The calcium and phosphorus requirement is particularly important in growth and lactation. These two minerals should be properly balanced.

4 - Dietary training

► Training for veterinarians

The importance of expertise in this field cannot be overemphasized. Competency requires extensive training in nutrition, and in cases where the diet will be used therapeutically, veterinary medical training is a must. Caution should be exercised when consulting individuals who do not have the appropriate training and credentials to formulate diets. Diplomates of the ACVN or ECVCN that provide this service have the necessary skills and training, and should be consulted.

Most veterinary nutritionists reserve the use of a home-cooked diet for:
- clients that cannot be dissuaded from home preparing their pet's food
- and for patients with multiple, concurrent disease processes that cannot be appropriately managed using commercially available diets.

Home-cooked diets have the disadvantage of being more expensive than commercially prepared food, labor intensive and prone to "diet drift". "Diet drift" refers to the tendency of some clients to slowly adjust diets over time without realizing, or considering the consequences of adding more of a particular ingredient or eliminating a necessary supplement. These concerns aside, home-cooked diets are often the only option in instances where a commercial product is unacceptable to the patient, or there is not one product that can meet that animals needs. In

addition, home-cooked diets also allow for the use of novel ingredients, can be formulated to take advantage of recent research that has not found its way into a commercial formulation, or that may not be economically practical to mass produce.

It may be difficult enough evaluating the total calorie content, never mind conducting a nutritional analysis of the diet solely on the basis of a list of ingredients. A veterinarian must however be able to identify nutritional deficits in home-made diets to recognize the need to enlist the assistance of a trained veterinary nutritionist.

Technicians and nurses can also be trained to provide client education on the specific nutrient differences between therapeutic and maintenance diets.

► Training for clinical staff

Integration of nutrition into clinical practice is dependent on fully utilizing a practice's support staff. Support staff can assist beyond stocking diet, feeding hospitalized patients and selling food. Technicians and nursing staff should be trained to monitor daily food intake in all patients. This requires that feeding orders be clearly provided for each animal. An American study showed that in 22% of hospitalized dogs presenting an undernourished condition, the problem is simply due to a poor understanding of written recommendations *(Remillard et al, 2001)*.

Follow-up monitoring of dietary performance can become the responsibility of the technical staff. Many support staff would welcome the additional responsibility of weigh-ins for weight loss programs or monitoring urine pH or specific gravity in patients with a history of urolithiasis. Receptionists should be trained to recognize the appropriate use of therapeutic diets so that client purchase inconsistencies can be quickly identified and addressed.

Conclusion

Without question, nutrition is a vital component to providing optimal patient care. Clinics that have not already integrated nutritional management, monitoring and counseling into the care of each animal, must begin to do so in order to provide the highest standard of care. Additional resources and expertise that can help any practice achieve these goals may be found in the references listed in **Table 4**.

TABLE 4 - SOURCE OF POTENTIAL INFORMATION IN CANINE NUTRITION

American Academy of Veterinary Nutrition	www.aavn.org
American College of Veterinary Nutrition	www.acvn. org
Association of American Feed Control Officials	www.aafco. org
Center for Veterinary Medicine at the FDA	www.fda.gov/cvm/default.html
Comparative Nutrition Society	www.cnsweb.org
European College of Veterinary and Comparative Nutrition	http://datamartcomputing.hopto.org/EBVS/colleges/ecvcn.htm
European Society of Veterinary and Comparative Nutrition	www.vet-alfort.fr/esvcn/esvcn.html
National Research Council	www.nas.edu/nrc
Pet Food Association of Canada	www.pfac.com
Pet Food Manufacturer's Association	www.pfma.com
Pet Food Institute	www.petfoodinstitute.org

References

Kealy RD, Lawler DF, Ballam JM et al - Effects of diet restriction on life span and age-related changes in dogs. J Am Vet Med Assoc 2002; 220-1315-20.

Remillard RL, Darden DE, Michel KE et al - An investigation of the relationship between caloric intake and outcome in hospitalized Dogs. Vet Ther 2001; 2(4): 301-10

In a veterinary clinic, the organization of the food storage shelves should help clients understand the nutritional goals, highlight all exclusive veterinary diets, and facilitate management by the clinic's staff.

Key Points
to remember:

Selected basic merchandising concepts in the veterinary clinic

The goal of merchandising is to grow sales to clients. In quality terms, merchandising should also:

- **Improve the client's impression of the clinic**

A sober, discreet and rational presentation of the products is a significant benchmark for owners that expect personalized advice.

- **Underscore the difference between a clinic and a retailer**

Owners expect the veterinary clinic to differentiate itself from other dog food outlets by offering high-end specialist products.

- **Recruit new clients**

Whatever the reason for the consultation, nutritional recommendations are always welcome. They are especially appreciated:

- when the patient is a very young puppy, a puppy at the end of growth or a dog that starts to show signs of aging.
- when the reason for consultation must entail a nutritional prescription, like obesity or neutering.
- during routine visits: Health Nutrition helps accentuate the food's preventive role and increases visits to the clinic.

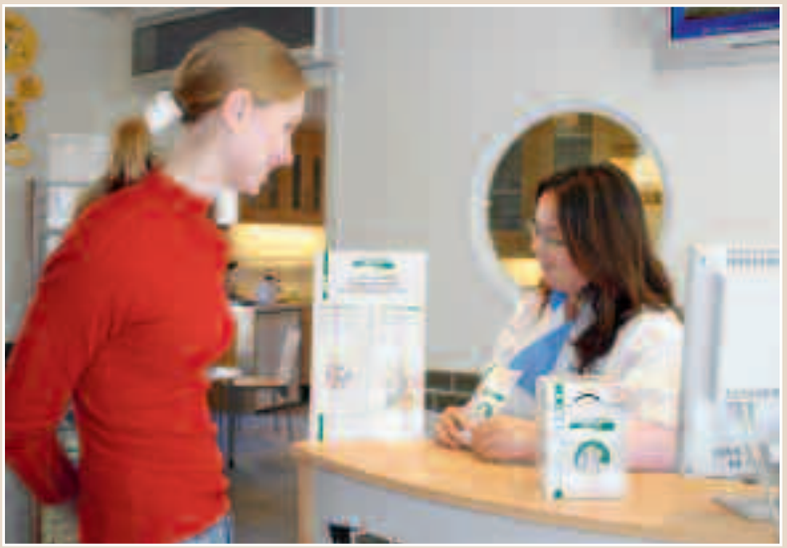
- **Reassure owners and develop their loyalty**

All communication tools should focus on the major arguments: a well nourished animal is healthy and a good diet has a positive effect on the animal's longevity. Samples or small trial packs encourage the owner to try a food without risk.

Goals of retail space and shelf organization

If the clinic's staff has a key role in providing nutritional advice, the products' placement in the shelves should help owners understand the indications. The four keys points are:

- **The species**
- **The aim:** preserving the health of the dog, preventing selected specific risks or adapting to a specific pathological state
- **The brands**
- **The segmentation criteria by brand:** age, size, breed, lifestyle, etc



It is preferable for the owner to have ready access to brochures that convey the veterinarian's instructions.

To summarize, merchandising is about:	
The right product	carry a range of nutritional products
In the right place	organize your space to present the products optimally
At the right time	take account of the seasonal nature of sales
At the right price	be consistent in your pricing policy
In the right quantity	avoid gaps in stock
With the right information	make instructional material available

Ideally, the space should be organized in such a way that owners are led to buy a new supply of food for their dog, and even to buy new products for the dog that they have not seen before (e.g. chewing bars for dental hygiene).

TABLE OF COMPOSITION USED FOR THE PREPARATION

A home-made diet is subjected to the variation of the composition of the ingredients. Depending on their origin, the nutritional analysis of the ingredients can be different and the final balance of the diet will vary.

		Metabolizable energy (kcal/100 g)	Protein-calorie ratio (g/1000 kcal)	Dry matter (%)	Protein (%)	Fat (%)	Digestible carbohydrates (%)	Total Dietary Fibre (%)	Calcium (mg/100 g)	Phosphorus (mg/100g)	Sodium (mg/100g)	Magnesium (mg/100g)	Potassium (mg/100g)
Meat	Beef, minced meat, 5% fat	115	191	26.2	22.0	3.0			*7*	*197*	*74*	*27*	*439*
	Beef, minced meat, 10% fat	172	114	33.4	19.5	10.4			7	186	64	21	342
	Beef, minced meat, 15% fat	208	99	34.8	20.5	14.0			*9*	*186*	*62*	*19*	*300*
	Beef, minced meat, 20% fat	252	68	39.1	17.0	20.4			7	140	68	18	270
	Mutton, shoulder	194	97	33.3	18.7	13.2			9	140	75		295
	Veal, muscle	92	230	23.6	21.3	0.8			13	198	94	16	358
	Veal, brisket	131	142	26.3	18.6	6.3			11	237	105		329
	Veal, shoulder	107	195	25.1	20.9	2.6			12	204	87	15	395
	Pork, shoulder	219	80	35.0	17.5	16.5			9	149	74		291
	Chicken, breast with skin	145	154	29.6	22.2	6.2			14	212	66		264
	Chicken, boiled	257	72	40.0	18.5	20.3			11	180		17	180
	Turkey, breast without skin	105	229	26.3	24.1	1.0			26	238	46	20	333
	Duck	132	148	26.7	19.6	6.0			11	202	90	19	262
	Ox liver	128	152	29.7	19.5	3.4	5.3		6	352	116	21	330
	Hare	113	190	26.7	21.6	3.0			14	210	44	24	276
	Venison, haunch	97	221	24.3	21.4	1.3			5	220	60		309
	Venison, back	309	184	27.8	22.4	3.6			25	220	84		342
	Wild boar meat	162	121	29.8	19.5	9.3			10	167	94	22	359
Fish	Alaskan hake	74	226	188	16.7	0.8			8	376	100	57	338
	Cod	77	231	19.5	17.7	0.6			26	194	72	24	352
	Sardine	118	164	25.5	19.4	4.5			85	258	100	24	
	Mullet	120	170	25.9	20.4	4.3			53	217	69	29	404
	Halibut	96	210	23.9	20.1	1.7			14	202	67	28	446
	Herring, Atlantic	233	78	37.6	18.2	17.8			34	250	117	31	360
	Mackerel	182	103	32.0	18.7	11.9			12	244	84	30	386
	Haddock	77	232	19.8	17.9	0.6			18	176	116	24	301
	Tuna	226	95	38.5	21.5	15.5			40	200	43	50	363
Egg	Hard-boiled egg	156	82	25.7	12.8	11.3	0.7		54	214	144	12	147
Oils and fats	Sunflower oil	900	0	100		100.0							
	Rapeseed oil	900	0	100		100.0							
	Linseed oil	900	0	100		100.0							
	Bacon	759	5	87	4.1	82.5			2	13	21		14
	Margarine	722	0	80.8	0.2	80.0	0.4				101		
	Butter	751	1	84.7	0.7	83.2			13	21	5	3	16
	Lard	900	0	100	0.0	100.0							

OF THE MAIN INGREDIENTS OF HOME-MADE DIETS

		Metabolizable energy (kcal/100 g)	Protein calorie ratio (g/1000 kcal)	Dry matter (%)	Protein (%)	Fat (%)	Digestible carbohydrates (%)	Total Dietary Fibre (%)	Calcium (mg/100 g)	Phosphorus (mg/100g)	Sodium (mg/100g)	Magnesium (mg/100g)	Potassium (mg/100g)
Dairy products	Quark, fresh cheese, 0% fat	71	190	18.7	13.5	0.3	4.0		*92*	*160*	*40*	*12*	*95*
	Quark, fresh cheese, 20% fat	109	115	22.0	12.5	5.1	3.4		85	165	35	11	87
	Quark, fresh cheese, 40% fat	159	70	26.5	11.1	11.4	3.3		*95*	*187*	*34*	*10*	*82*
	Acid curd cheese	124	237	36.0	29.4	0.7			125	266	787	13	106
	Cheddar cheese	398	64	63.7	25.4	32.2	1.7		752	489	675	30	102
	Cottage cheese	100	123	21.5	12.3	4.3	3.3		95	150	230		88
	Cow's milk, UHT	66	51	12.8	3.3	3.8	4.9		120	92	48	12	157
	Cow's milk, reduced fat, UHT	47	72	10.7	3.4	1.6	5.0		118	91	47	12	155
	Yoghurt, low fat	36	95	10.2	3.5	0.1	5.8		143	109	57	14	187
Carbo-hydrate sources	Rice	344	21	87.1	7.4	0.6	77.7	1.4	6	114	4	32	109
	Rice, cooked	119	19	29.6	2.3	0.2	26.3	0.5	4	37	1	8	34
	Pasta made with eggs	336	37	89.3	12.3	2.8	69.9	3.4	23	153	17	42	219
	Pasta made with eggs, cooked	91	47	23.2	4.3	0.9	17.5		9	62	7	14	53
	Pasta, wheat whole-meal	318	46	90	14.5	2.3	63.7	6.7	46	300	3	87	460
	Potato, cooked, with skin	67	30	22.2	2.0	0.1	15.5	1.7	12	50	3	21	416
	Tapioca	357	1	87.0	0.5	0.2	94.3	0.4	11	20	4	3	20
Vegetables & Fiber sources	Carrots (boiled, drained)	18	45	8.8	0.8	0.2	3.4	2.5	30	29	42	10	180
	French beans	32	76	10.5	2.4	0.2	5.3	1.9	60	37	2	24	238
	Leek	24	93	12.1	2.2	0.3	3.3	2.3	63	48	4	16	267
	Tomato	15	62	5.8	1.0	0.2	2.6	1.0	9	22	3	12	242
	Lentils, dry	260	90	88.5	23.4	1.5	40.6	17.0	65	411	7	129	837
	Lentils, cooked	73	101	23.4	7.4	0.4	10.7	4.5	23	130	1		255
	Wheat bran	172	93	88.5	16.0	4.7	17.7	45.1	67	1143	2	490	1352
	Rolled oats	337	40	90.0	13.5	7.0	58.7	10.0	48	415	7	134	374
	Wheat germ	312	92	88.3	28.7	9.2	30.6	17.7	49	1022	5	285	993
	Pectin			100				100					
	Cellulose			100				100					
Vegetable protein source	Tofu	82	98	15.4	8.1	4.8	1.9		87	97	4	99	97
Miscel-laneous	Brewer's yeast	229	209	94.0	47.9	4.2			50	1900	77	230	1410
	Honey	302	1	81.4	0.4		75.1		6	5	2	2	45

In red: ingredients used in the different examples of home-made diets presented in this book

Sources

Food Composition and Nutrition Tables. 6th rev. ed. Boca Raton: CRC Press, 2000.

Répertoire général des aliments - Table de composition. J.-C. Favier, J. Ireland-Ripert, C. Toque, M. Feinberg, Ciqual-Regal. Tec & Doc Lavoisier, 1995.