Encyclopedia of Feline Clinical Nutrition

"Knowledge is only of value when it is shared!"

As with the book dedicated to dogs, this Encyclopedia deliberately pushes the boundaries of what is generally expected of the genre. Its presentation, breezy and richly illustrated, will have everyone who flicks through wanting to immerse themselves in its contents. It is quite simply the most up-to-date reference work on the subject.

Each chapter is set out in the same way:
- Author biographies
- Clinical and dietary facts
- Frequently asked questions
- Bibliography
- Nutritional information
  - Focus on a specific nutrient
  - Key dietary points for each pathology
  - Extracts from other publications and research of Royal Canin

First and foremost, this Encyclopedia is intended for veterinarians practicing feline veterinary medicine and students. All told, twenty three authors participated in this project. Clinicians and nutritionists were involved in each chapter to ensure the harmonious combination of veterinarian medicine and nutrition. It is the first time that so many foreign contributors, from ten countries in all, have been assembled by Royal Canin to produce a book that will be distributed to its partners in the veterinary world.

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ROYAL CANIN

Pascale Pibot
Vincent Biourge
Denise Elliott

Encyclopedia of Feline Clinical Nutrition

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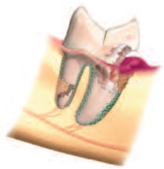

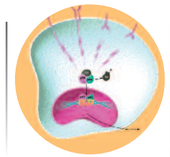

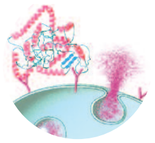

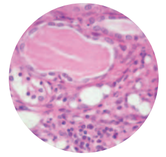

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The book is the result of a collaboration with international authors who are specialized in different areas of veterinary medicine. Our warmest thanks to all those who have been involved in producing this Encyclopedia.

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... and of course, the whole team of Diffomédia/Paris for their wonderful job!

Health and nutrition; more closely related than ever before

Feeding a cat may appear ar first glance to be a straightforward exercise. However, this assumption requires some qualification, because cats are strict carnivores with nutritional requirements that differ from those of dogs. In addition, cats generally have very clear dietary preferences that need to be considered. Furthermore, if the cat is ill or has a higher pathological risk, things can sometimes get really complicated.

This Encyclopedia of Feline Clinical Nutrition endeavors to answer the main questions of our time about feline clinical nutrition. The authors were asked first and foremost to summarize the current state of knowledge about cats. When the published data was too succinct, it was sometimes necessary to cite results obtained from other species, while always clarifying where their studies come from and utilizing them in the specific context of feline nutritional characteristics, to avoid incorrect extrapolations.

The following list of questions does not pretend to be an incisive tool to test your knowledge, but you may be interested in how many questions you can answer – without looking at the book.

1. How do you determine the body weight of an obese cat?
2. Which cat breeds are most likely to present dietary sensitivity?
3. What are prebiotics?
4. In the absence of clinical sign of hepatic lipidosis, which blood parameter is used to evaluate hepatic lipid accumulation?
5. What two characteristics should be prioritized in a diet for a diabetic cat?
6. What is the most common cause of hyperlipidemia in cats?
7. Should severe sodium restriction always be recommended in cats with chronic kidney disease?
8. How do you combat both struvite and calcium oxalate stones at the same time?
9. How do you definitively diagnose taurine deficiency?
10. What are the agents active against the development of dental calculus?
11. What are the essential criteria for selecting food for cats with cancer?
12. What is the best feeding route for a cat in intensive care?
13. Why can't cats distinguish sweet taste?
14. What effect is produced by a dramatic increase of omega-3 fatty acids versus omega-6 fatty acids in the diet?

Each of the 14 chapters of the Encyclopedia is filled with information that will enable you to check, correct, refine and perhaps improve your answers.

We hope that during your reading you will find many other subjects of interest and that nutrition will become an even more important aspect of your diagnostic and therapeutic approach.

Pascale Pibot, Denise Elliott, and Vincent Biourge

1. How do you determine the body weight of an obese cat?
a. It's a simple calculation based on the condition of the body
b. By bioelectrical impedance analysis
c. By indirect calorimetry

2. Which cat breeds are most likely to present dietary sensitivity?
a. The Persian
b. The Maine Coon
c. The Siamese and related breeds

3. What are prebiotics?
a. Non-digestible carbohydrates that are fermented in the gut by bacteria
b. Microorganisms that have a beneficial effect on the intestinal flora
c. Sources of non-fermentable fiber

4. In the absence of clinical sign of hepatic lipidosis, which blood parameter is used to evaluate the lipid accumulation level in the liver?
a. Bilirubin
b. Cholesterol
c. Alkaline phosphatase

5. What two characteristics should be prioritized in a diet for a diabetic cat?
a. High fiber content and low starch content
b. High protein content and low starch content
c. Low protein and starch content

6. What is the most common cause of hyperlipidemia in cats?
a. Primary idiopathic hyperlipidemia
b. The animal is not fasted before the sample is taken
c. Diabetes mellitus

7. Should a severe sodium restriction always be recommended in cats with chronic kidney disease?
a. Yes, it helps prevent hypertension
b. Yes, it activates the renin-angiotensin-aldosterone system
c. No, it can activate the renin-angiotensin-aldosterone system

8. How do you combat both struvite and calcium oxalate stones at the same time?
a. By encouraging diuresis
b. By acidifying the urine pH
c. By limiting the dietary consumption of phosphorus

9. How do you definitively diagnose taurine deficiency?
a. By dosing taurine based on the results of muscle biopsy
b. By measuring the taurine level in the plasma
c. By measuring the taurine level in the whole blood

10. What are the agents active against the development of dental calculus?
a. Polyphosphate salts
b. Omega-3 fatty acids
c. B-group vitamins

11. What is the essential criteria for selecting food for cats with cancer?
a. High glutamine concentration
b. Palatability
c. High protein content

12. What is the best feeding route for a cat in intensive care?
a. The parenteral route
b. A combination of parenteral and enteral route
c. The enteral route

13. Why can't cats distinguish sweet taste?
a. Because cats do not have any salivary amylase
b. Because the sweet taste receptors are deactivated
c. Because cats rarely consume sweet food

14. What effect is produced by a dramatic increase of omega-3 fatty acids versus omega-6 fatty acids in the diet?
a. Immunostimulant effect
b. Immunosuppressant effect
c. No effect

1-a, 2-c, 3-a, 4-c, 5-b, 6-b, 7-c, 8-a, 9-c, 10-a, 11-b, 12-c, 13-b, 14-b

How did you do?
- *More than 10 correct answers: well done, you're going to enjoy this book*
- *7-10 correct answers: not a bad score, but you can do better*
- *Fewer than 7 correct answers: this book could teach you a lot!*

"Let food be thy medicine"

Hippocrates (460-377 BC)

© Romuald Fernand

It is a long time since cats moved from being the irregular and unwelcome frequenters of farms and alleyways to pampered companions kept for their beauty, gentleness and mystery. With every day that passes their place in western homes becomes more and more assured. Indeed, the cat population now even outstrips the dog population.

Their relationship to humans has developed remarkably and their behavior has adapted to these contacts: this wild animal has become so well adapted to life indoors that its life expectancy has increased significantly, from an average of four years for outdoor cats to 18 years for those that live indoors. This comfortable life does have a downside: obesity for one is a major and growing threat. Nowadays, cat owners are very concerned about the health of their animal. Vaccination, neutering and tattooing or microchipping are all ways to try to extend its life and as such they have become a very important part of the daily routine of veterinarians.

Cats have been the subject of numerous veterinarian studies and in the field of feline nutrition, for one, great – even crucial – advances have been made over the past fifteen years. The range of dedicated food available today makes it easier to control or prevent many diseases (urolithiasis, food allergies, chronic kidney disease to name but a few). For many years Royal Canin has made it a matter of honor to find effective, targeted solutions to the specific problems affecting cats. This species is actually more of a challenge to care for than dogs. They are more demanding and fully capable of starving themselves to death even when they have access to plenty of food, so they demand very precise responses to make up for an 'enzymatic toolbox' that is not really suited to compensating for nutritional deficiencies.

The advancements in knowledge have had a recent but real impact on nutrition courses at veterinary colleges, schools and universities. It is important that clinicians are able to draw on the latest, most complete knowledge on the subject. That is the aim of this encyclopedia, conceived by the Royal Canin research teams, which sets a new standard in feline clinical nutrition.

Twenty-three global specialists have contributed to its 14 chapters, 10 of them are based on a collaboration between a clinician and a nutritionist. I am proud to be able to say that seven of those 23 authors are employees of Royal Canin, which is proof of the commitment of everyone at the company to working as hard as possible and using their know-how to benefit both dogs and cats.

I sincerely hope that this book, like its sister publication about dogs, will prove a useful tool for you and your team and facilitate the employment of nutrition in your daily practice.

Jean-Christophe Flatin
President of Royal Canin

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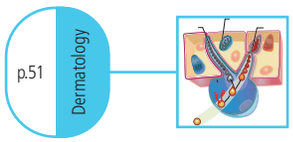

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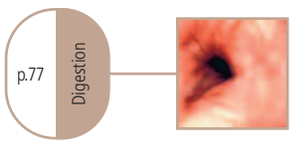

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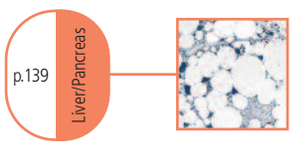

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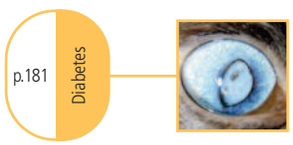

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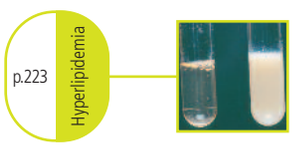

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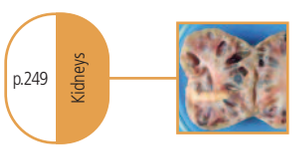

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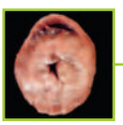
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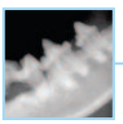
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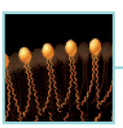
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ABBREVIATIONS USED IN THIS CHAPTER

ARA: arachidonic acid
BCM: body cell mass
BCS: body condition score
BMI: body mass index
BMR: basal metabolic rate
BW: body weight
CCK: cholecystokinin
CKD: chronic kidney disease
CLA: conjugated linoleic acid
CP: crude protein
DF: dietary fiber
DEXA: dual energy x-ray absorptiometry
DMB: dry matter basis
DM2: diabetes mellitus type 2
ECW: extracellular water
FFM: fat free mass
FLUTD: feline lower urinary tract disease
FM: fat mass
FBMI™: feline body mass index
GLP (1,2): glucagon-like peptide (1, 2)
GRP: gastrin releasing peptide
HDL: high density lipoprotein
IBW: ideal body weight
ICW: intracellular water
IGF 1: insulin-like growth factor 1
LA: linoleic acid
LBM: lean body mass
LIM: leg index measurement
ME: metabolizable energy
MRI: magnetic resonance imaging
MTPI: triglyceride transfer protein inhibitor
OA: osteoarthritis
PYY: peptide tyrosine-tyrosine
RER: resting energy requirement
SCFA: short chain fatty acid
TBW: total body water

Feline obesity: epidemiology, pathophysiology and management

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Obesity is considered to be the most common form of malnutrition in small animal practice. It has been suggested that as many as 40% of pets are obese. The significance of obesity pertains to its role in the pathogenesis of a variety of diseases and the ability to exacerbate pre-existing disease. Obesity has been associated with an increased incidence of osteoarthritis, cardiorespiratory problems, diabetes mellitus, constipation, dermatitis, anesthetic risk, and reduced life-expectancy.

1 - Definition of obesity

Obesity is defined as an accumulation of excessive amounts of body fat *(Bray, 1999)*. In humans, a wealth of epidemiological data demonstrate that morbidity and mortality risk correlates with increasing body fat mass. Criteria are usually based on indirect measures of adiposity such as the body mass index (BMI; weight [kg] divided by height^2 [m]), and definitions exist for "overweight" (25 < BMI < 30 kg/m^2) and "obese" (BMI > 30 kg/m^2). A recent large-scale epidemiological study suggested that the optimal BMI for non-smoking 50 year-old adult Caucasians was 20-25 *(Adams et al, 2006)*, and many other studies concur with these findings. In contrast, data on what represents an optimal feline body weight are more limited; cats are classified as being overweight when their body weight is more than 10% above their "optimal body weight", and classified as "obese" when their body weight exceeds 20% of optimal *(Lund et al, 2005)*. In the largest epidemiological studies of their kind, increasing risk of associated diseases is seen with increasing levels of adiposity, as judged by body condition score (BCS) *(Scarlett et al, 1998; Lund et al, 2005)*. This suggests that, like in humans, excessive weight confers a mortality and morbidity risk (see below) and support the need to strive for optimal body condition.

OVERWEIGHT OR OBESE?
Cats are classified as being overweight when their body weight is more than 10% above their "optimal body weight", and classified as "obese" when their body weight exceeds 20% of optimal.

2 - Epidemiology of obesity

► Prevalence and time trends

Obesity is an escalating global problem in humans *(Kopelman, 2000)*, and current estimates suggest that almost two thirds of adults in the United States are overweight or obese *(Flegal et al, 2002)*. Prevalence studies of companion animal obesity are more limited; reports from various parts of the world, have estimated the prevalence of obesity in the dog population to be between 22% and 50% *(McGreevy et al, 2005; Colliard et al, 2006; Holmes et al, 2007)*. In cats, information is limited to a handful of studies over a time-frame of over thirty years, using a variety of definitions of overweight/obesity and techniques to estimate body condition *(Sloth, 1992; Robertson, 1999; Russell et al, 2000; Harper, 2001; Lund et al, 2005)*. From this work, estimates of obesity prevalence range from 19 to 52% **(Table 1)**.

One of the most recent studies was from the USA, and utilized 1995 records of the National Companion Animal Study *(Lund et al, 2005)*. The results suggested that approximately 35% of adult cats were classed as either overweight or obese (overweight 28.7%; obese 6.4%). However, prevalence of overweight and obesity varies amongst age groups with middle age cats (between 5 and 11 years of age) particularly at risk (overall prevalence 41%; overweight 33.3%, obese 7.7%). Of particular concern was the finding that a clinical diagnosis of obesity was only recorded in 2.2% of cats (despite the BCS findings), suggesting that veterinarians do not consider the condition to be of clinical significance.

Whatever the true figure for feline obesity, it is clear that the condition is one of the most important medical diseases seen by veterinarians, especially for middle-aged adults. Furthermore, studies have reported that owners tend to under-estimate the body condition of their cats, compared with the estimates of their veterinarians *(Kienzle & Bergler, 2006)*; and these individuals may not be presented for assessment.

► Risk factors for feline obesity

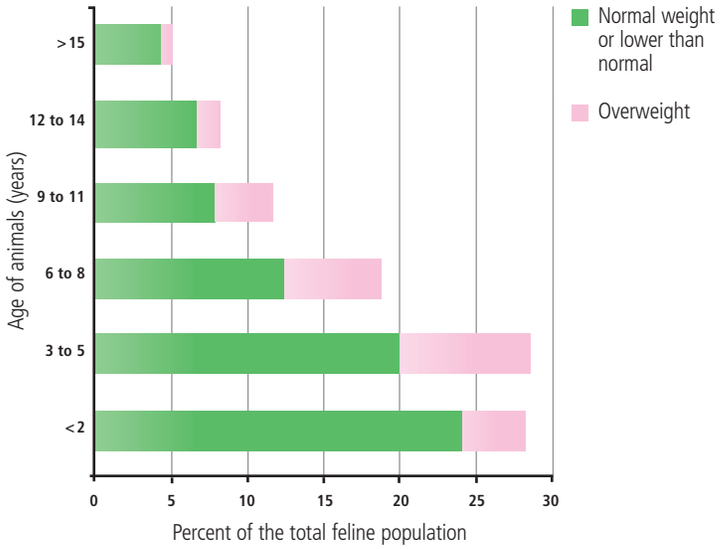
Obesity prevalence is influenced by numerous factors. Individual factors that have been identified include gender and neuter status, age, and breed; environmental factors include accommodation, presence of dogs in the household, and the feeding of certain types of diet; additionally, some factors may be the combination of both individual and environmental influences e.g. inactivity. Other studies have implicated owner factors and feeding behavior as risk factors for overweight and obesity in cats *(Kienzle & Bergler, 2006)*.

TABLE 1 - ESTIMATION OF THE PREVALENCE OF FELINE OBESITY

Reference	Country	Incidence rate
Sloth, 1992	UK	40%
Robertson, 1999	Australia	19%
Russel et al, 2000	UK	52%
Lund et al, 2005	USA	35%

Figure 1 - Prevalence of feline obesity according to age

(from Scarlett, 1994 and Robertson, 1999; study on 2671 cats)



In absolute terms, the highest number of overweight cats is found in the 3-5 years of age category. Relatively speaking, cats aged 6-8 years are most affected: one in three cats in this age group are overweight.

> Age

Middle age is a particular risk factor for overweight and obesity in cats **(Figure 1)**. One study identified that body condition was significantly higher in cats <13 years of age compared with those >13 years *(Russell et al, 2000)*. In another North American study, the prevalence for overweight and obesity was greatest in cats between 5 and 11 years of age *(Lund et al, 2005)*. Such data are critical to veterinarians since they help to identify the population most at risk, and would suggest that prevention strategies, if instigated early (e.g. ~2 years of age) might have the greatest impact on satisfactory management of the condition.

> Neuter status and gender

Neutering is the major cause of obesity in cats with numerous studies confirming the link *(Scarlett et al, 1998; Robertson, 1999; Allan et al, 2000; Russell et al, 2000; Lund et al, 2005; Martin et al, 2001; 2006a)*. Metabolic consequences of neutering will be developed in the pathophysiology section.

Gender itself is also a predisposing factor in some but not all studies, with males over-represented in recent work *(Lund et al, 2005)*. The reasons for such a gender association have not been fully elucidated, not least given that one study has shown that fasting metabolic rate declines in female but not male cats that were neutered *(Fettman et al, 1997)*.

> Endocrine abnormalities

Compared with dogs, obesity in cats is less likely to result from endocrine abnormalities such as hypothyroidism and hyperadrenocorticism. However, the use of progesterones for contraceptive management has been associated with the development of obesity.

In cats, obesity is most of the time associated with increased plasma concentration of prolactin, leptin and insulin-like growth factor (IGF)-1 *(Martin et al, 2006a)*. The hormonal profile is thus completely different from that of the obese dog *(Martin et al, 2006b)*. All these hormones have a direct role in the onset of insulin-resistance *(Melloul et al, 2002)*.

> Breed

A handful of studies have examined the influence of breed on the prevalence of feline obesity. Two studies identified that "crossbred" or mixed-breed cats were approximately twice as likely to be overweight as purebred cats *(Scarlett et al, 1994; Robertson, 1999)*. *Lund et al* (2005) also found mixed breed cats (domestic shorthair, domestic medium hair, domestic longhair) to be at greater risk; Manx cats were also predisposed.

> Environment

Environmental factors reported to influence the prevalence of obesity include the type of accommodation, the number of cats and or the presence of dogs in the household *(Scarlett et al, 1994; Robertson, 1999; Allan et al, 2000)*. With regard to accommodation, both indoor dwelling and living in an apartment have been shown to predispose in some *(Scarlett et al, 1994; Robertson, 1999)* but not all *(Russell et al, 2000)* studies, probably because this type of environment does not respect the normal ethogram of the cat. It is likely that inability to maximally exercise and boredom may play a part.

One study demonstrated that the presence of dogs in the household significantly reduced the odds of developing obesity *(Allan et al, 2000)*, possibly due to the behavioral traits of the cats or dogs.

Finally, the type of owner that own exclusively cats might differ from those who own both cats and dogs; in this respect, people who own both might be less inclined to dote upon their cats and less likely to provide premium foods for their pets (see below).

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A cat may eat less when it lives with a dog:
- *it might be intimidated by the presence of a dog, reducing its drive to eat*
- *a dog may drive the cat away from the food bowl*
- *the cat can be stimulated by the dog to play. Its physical activity is thus overall more important than if it only lives alone.*

> Activity

Activity is one of the factors influenced both by individual and environmental variables. It is possible that the principle influence of type of accommodation relates to ability to exercise outdoors. Numerous studies have identified inactivity as a major risk factor for both overweight and obesity *(Scarlett et al, 1994; Allan et al, 2000)*, although not all studies have confirmed this finding *(Russell et al, 2000)*.

> Dietary factors

Some studies have suggested that feeding premium pet foods *(Scarlett et al, 1994)* conveys an increased risk compared with the risk whilst feeding a grocery store diet. The increased palatability may overcome normal appetite control leading to overeating, but in the 1990's, the main reason proposed for such an association was that premium food tended to have a higher fat, and hence energy, content than grocery products; today, many moderate fat-diets (10-14% fat on dry matter basis [DMB]) are available.

Kienzle and Bergler (2006) conducted a study of owner attitudes and compared cats that were overweight with those that were normal weight or thin. The owners of overweight cats tended to offer food on a free-choice basis, but there was no difference in the type of food fed.

Many veterinarians typically feed cats with high-fat diets specifically formulated to prevent FLUTD. These high-fat calorically dense diets are a frequent cause of obesity.

> Owner factors and behavior

Some studies have indicated a number of owner factors in the development of obesity *(Kienzle & Bergler, 2006)* and it is interesting to make comparisons with dogs. For instance, the owners of obese cats tend to "humanize" their cat more, and cats have a potential role as a substitute for human companionship. Over-humanization was also associated with overweight in a dog study, but a close human-dog relationship was not *(Kienzle et al, 1998)*. The owners of overweight cats spend less time playing with their pet and tend to use food as a reward rather than extra play. Further, the owners of overweight cats watch their cats during eating more often than owners of cats in normal body condition; this is similar to findings for dog owners. The owners of both overweight cats and dogs have less of an interest in preventive health than those of pets in ideal body condition. Unlike the owners of overweight dogs who tend to have a lower income, there are no demographic differences amongst owners of overweight and normal weight cats. Finally, the percentage of female owners is higher in overweight than in normal weight cats.

Further, many owners misread signals about the behavior of their cat with regard to eating. It is important to remember that:

For cats, possible factors involved in the development of obesity include anxiety, depression, failure to establish a normal feeding behavior, and failure to develop control of satiety.

- Cats in the wild are designed to be trickle feeders and would typically consume numerous small meals. Despite this, many owners choose to feed their cats in 2-3 large meals per day.
- In contrast to humans and dogs, cats do not have any inherent need for social interaction during feeding times. When the cat initiates contact, owners often assume that they are hungry and are asking for food when they are not. Nevertheless, if food is provided at such times, the cat soon learns that initiating contact results in a food reward. If larger amounts or energy-dense foods are offered, it has the potential of leading to excessive food intake and obesity;
- Play is necessary throughout life **(Figure 2)**. Dog owners are usually conditioned to provide regular exercise through both walks and play; in contrast, most cat owners do not engage in play sessions with their pets.

3 - Medical significance of obesity

It has long been known that dietary restriction can increase longevity in a number of species including dogs *(McCay et al, 1935; Kealy et al, 1992, 1997, 2000, 2002; Lane et al, 1998; Larson et al, 2003; Lawler et al, 2005)*. It is probable that a similar association is present for cats, although data to support such a supposition are lacking.

Whilst it is generally accepted that overweight and obesity increases the risk of suffering from a number of associated diseases in cats **(Table 2)** limited scientific peer-reviewed data are available to support these associations. There have been two large-scale studies assessing disease associations in overweight and obese cats. In a study by *Donoghue and Scarlett* (1998), the major associations recognized were diabetes mellitus, dermatoses, lameness and diarrhea **(Figure 3)**.These authors also noticed that overweight cats have a shorter lifespan.

A subsequent study *(Lund et al, 2005)* assessed disease associations in a population of 8159 cats. For overweight and obesity, the major disease associations included oral cavity disease, urinary tract disease, diabetes mellitus, hepatic lipidosis, dermatopathy and neoplasia.

TABLE 2 - DISEASES ASSOCIATED WITH FELINE OBESITY

Metabolic abnormalities
- Hyperlipidemia/dyslipidemia
- Insulin resistance
- Glucose intolerance
- Hepatic lipidosis

Endocrinopathies
- Hyperadrenocorticism
- Diabetes mellitus

Orthopedic disorders

Dermatologic diseases

Oral cavity disease

Cardiorespiratory disease
- Hypertension

Feline asthma?

Urogenital system
- Feline lower urinary tract disease
- Urolithiasis

Neoplasia

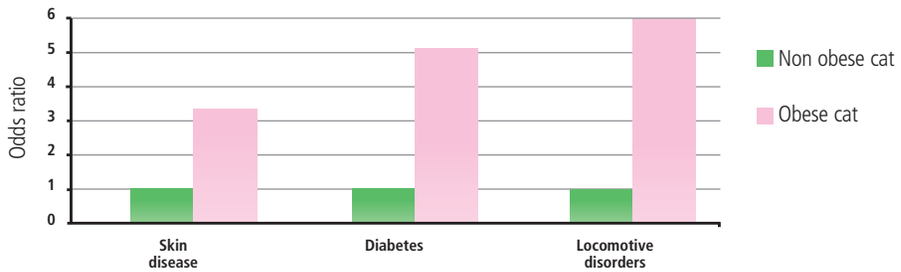
Functional alterations
- Joint disorders
- Respiratory compromise e.g. dyspnea
- Dystocia
- Exercise intolerance
- Heat intolerance/heat stroke
- Decreased immune functions
- Increased anesthetic risk
- Decreased lifespan

FIGURE 2 - A CAT'S LIFE: ETHOGRAM*

Eating represents less than 1hour per day for the cat but sleeping is the most time-demanding activity: 14-18hrs/24hrs, i.e. 60-75% of the time.

FIGURE 3 - INFLUENCE OF FELINE OBESITY ON THE INCIDENCE OF SKIN DISEASES, DIABETES MELLITUS AND LOCOMOTIVE DISORDERS

(from Scarlett & Donoghue, 1998)



► Association between excessive weight, insulin resistance and diabetes mellitus

Insulin secreted by pancreatic β cells controls the uptake and use of glucose in peripheral tissues (see chapter 5).

Cats most often suffer from diabetes mellitus that resembles "type 2" diabetes mellitus in man (DM2), and, therefore, obesity is a major risk factor in this species *(Nelson et al, 1990)*. Of all disease associations, diabetes mellitus is by far and away the most well-known. Indeed, epidemiological studies have confirmed an increased risk of diabetes mellitus in obese cats; in the study by *Lund et al* (2005), an odds ratio of 2.2 was reported for obese cats versus those in ideal body condition. This supports the work of older studies which have also reported an association *(Panciera et al, 1990; Scarlett & Donoghue, 1998)*. Finally, it has been proven that diabetic cats have significantly reduced sensitivity to insulin than cats without DM2 *(Feldhahn et al, 1999)*.

► Dermatoses

Both the *Scarlett and Donoghue* (1998) and the *Lund et al* (2005) studies suggested a link between obesity and dermatoses. Diseases represented included feline acne, alopecia, various forms of dermatitis, scale formation, and dermatophytosis. Diffuse scale is commonly observed, most likely due to reduced ability to groom efficiently.

Similar, one of the authors has observed numerous obese cats with fecal soiling; an association with grooming is suggested by the fact that such problems commonly resolve or improve after weight reduction. A single case report has also been published of perivulvular dermatitis associated with obesity; whilst the authors reported that episioplasty was required for resolution of this problem *(Ranen & Zur, 2005)*; unfortunately, there was no mention of an attempt at weight management in this case. Finally, extreme obesity can lead to physical inactivity and to the development of pressure sores **(Figure 4)**.

Figure 4 - 9 year old neutered male Siamese cat with gross obesity (body weight 12.95 kg, condition score 5/5).
The obesity had led to inactivity, inability to groom and pressure sores on the ventral abdomen.

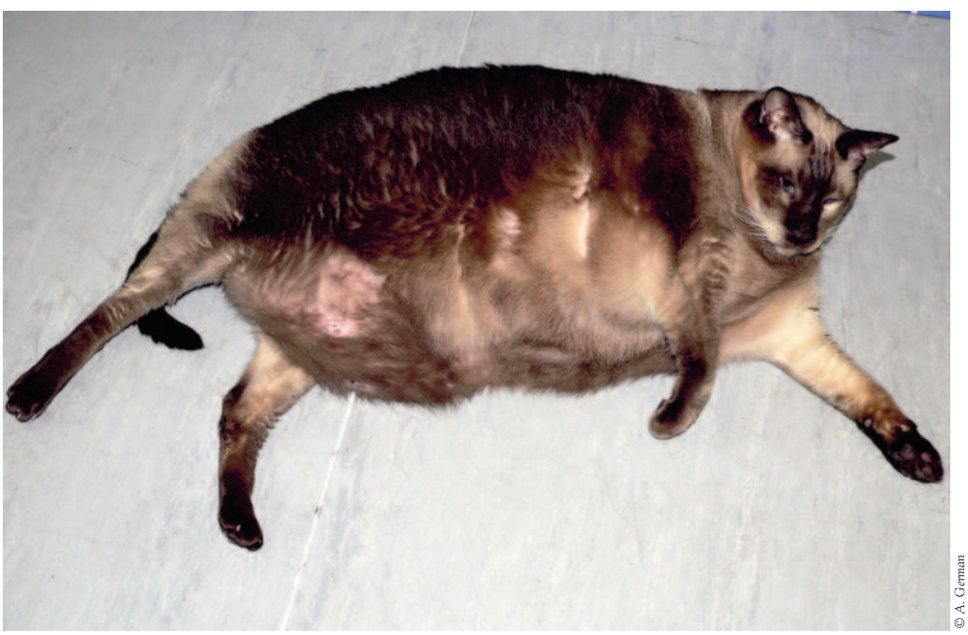


Figure 5a - Hip dysplasia in a cat

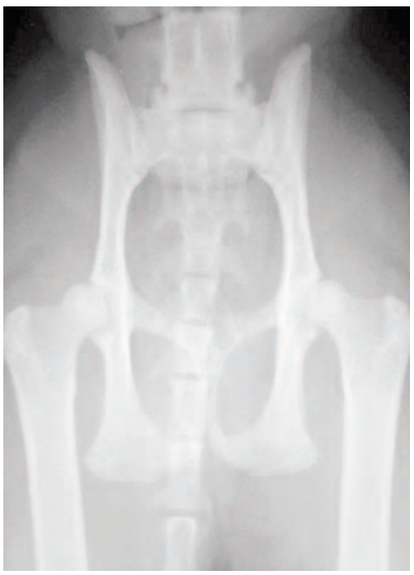
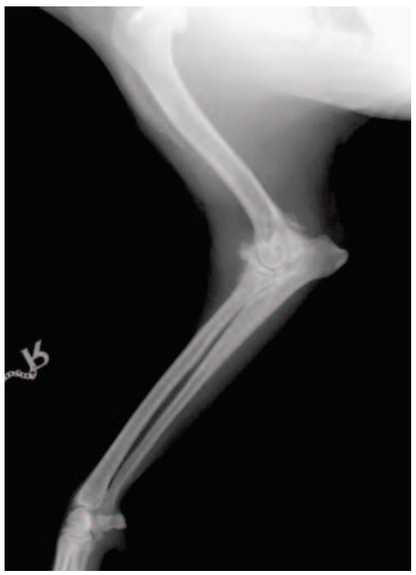


Figure 5b - Elbow osteoarthritis in a cat



Elbow and coxofemoral joints are commonly affected by osteoarthrosis in obese cats.

► Orthopedic diseases

Similar to dogs, obesity may be a risk factor for orthopedic disease in cats, with one study suggesting that obese cats were five times more likely to limp than cats of normal body condition *(Scarlett & Donoghue, 1998)*. However, not all reports have confirmed this association *(Lund et al, 2005)*. Orthopedic pain may be a reason why obese cats are less likely to groom and hence suffer from dermatoses (see later).

One of the major hurdles with confirming such an association is the fact that the prevalence of orthopedic disease is likely to be under-recognized in this species, compared with dogs. This is likely to be due to differences in behavior between cats and dogs; dogs are commonly taken for walks on a regular basis, such that it will rapidly become evident to the owner if their pet is stiff or lame. In contrast, cats tend to be self-sufficient such that, if orthopedic disease is present, cats rest themselves and it may not be readily evident to the owner that there is a problem. A study examined the prevalence of feline osteoarthritis (OA), by examining radiographs taken to examine other regions (e.g. thorax) *(Godfrey, 2005)*. In this study, there was radiographic evidence of OA in 22% of radiographs from adult cats. These results are particularly concerning in light of the fact that the population examined were not necessarily suspected to have orthopedic disease in the first place. In fact, a recent prospective study of OA in cats has identified the most prominent signs are reduction in the ability to jump and decreased height of jumping *(Clarke and Bennett, 2006)*. This study also demonstrated that the elbow and coxofemoral joints are most commonly affected **(Figure 5)**. In the experience of one of the authors, many cats limp at the time of presentation, and mobility improves markedly after weight loss. Thus, like dogs, weight reduction should be pursued in obese cats who limp.

► Gastrointestinal disease

An association between gastrointestinal disease and feline obesity has been previously reported; *Scarlett and Donoghue* (1998) reported that obese cats were more likely to suffer from diarrhea than those in normal body condition. *Lund et al* (2005) reported gastrointestinal diseases included anal sac disease, inflammatory bowel disease, colitis, megacolon and constipation in overweight or obese cats. However, even if the link between constipation and body weight has been studied in human medicine *(De Carvalho et al, 2006)*, the reasons for such a potential association are not clear and would require further study in cats. Very high fiber diets are suspected to increase the risk of constipation in cats.

► Hepatic lipidosis

The association between feline obesity and hepatic lipidosis is well-known. More information on hepatic lipidosis is presented in chapter 4. Concerns over inducing hepatic lipidosis are often cited as a reason why veterinarians are reluctant to instigate weight management in obese cats. How-

ever, it is not clear how real this concern actually is. In this respect, even marked dietary energy restriction (e.g. 25% [*Biourge et al, 1994*] or 45% [*Watson et al, 1995*] of maintenance energy requirements) did not lead to the development of hepatic lipidosis. Thus, it would appear that for hepatic lipidosis to develop, complete fasting for five to six weeks may be required *(Biourge et al, 1993)*. Clinical hepatic lipidosis is probably associated with other inciting factors e.g. concurrent illness.

► Neoplasia

A link between obesity and cancer has been widely reported and, if this link is entirely causal, one in seven cancer deaths in both men and women in the USA, might be the direct result of being overweight or obese *(Calle & Thun, 2004)*. Similarly, studies in cats have reported an association with neoplasia *(Lund et al, 2005)*; reported tumors included adenocarcinoma, basal cell carcinoma, fibrosarcoma, lipoma, lymphoma, mammary tumor, mast cell tumor and squamous cell carcinoma.

Whilst a global association with neoplasia may be present, the risk of developing specific neoplasia would require additional prospective studies. An association between mammary carcinoma and obesity has been reported in some *(Sonnenschein et al, 1991)*, but not all *(Perez Alenza et al, 2000a, 2000b)*, canine reports. Overweight dogs have also been reported to have an increased risk of developing transitional cell carcinoma of the bladder *(Glickman et al, 1989)*, but such a risk has not been reported for cats.

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The association between FLUTD and obesity may be a consequence of orthopedic problems: the painful cat may be reluctant to move and position itself for urination. The reduced frequency of urination can be a cause of lower urinary tract disease.

► Urinary tract diseases

The *Lund et al.* study (2005) identified that cats which were overweight were more likely to suffer from urinary tract diseases. Diseases reported included acute cystitis, urolithiasis, idiopathic feline lower urinary tract disease, urinary obstruction, and urinary tract infection. As with neoplasia, additional prospective studies are required to determine the exact risk for urinary tract. Of most note is the association with feline lower urinary tract diseases e.g. idiopathic FLUTD and urolithiasis. It is important to remember that obese cats are also most likely to live indoors, which is known as a risk factor for FLUTD.

An association between obesity and diseases of the feline kidney is less clear and, currently, there have been no studies to demonstrate such a link in client-owned cats. However, circumstantial evidence for such a link exists given that there is evidence from dogs that the onset of obesity is associated with histologic changes in the kidney; reported changes include an increase in Bowman's space (as a result of expansion of Bowman's capsule), increased mesangial matrix, thickening of glomerular and tubular basement membranes, and increased number of dividing cells per glomerulus *(Henegar et al, 2001)*. Functional changes were noted in the same study, including increases in plasma renin concentrations, insulin concentrations, mean arterial pressure, and plasma renal flow. As a consequence, the authors speculated that these changes, if prolonged, could predispose to more severe glomerular and renal injury.

► Oral cavity disease

Obesity was shown to be a risk factor for oral cavity disease in a large scale study of cats in North America *(Lund et al, 2005)*, with an odds ratio of 1.4. However, the reasons for such an association are not clear and, to the authors' knowledge, have not been reported in other species. Further work would be required to determine why obesity, per se, is a predisposing factor.

► Cardiorespiratory issues

In many species, increased body weight can result in effects on cardiac rhythm, increased left ventricular volume, blood pressure and plasma volume. The effect of obesity on hypertension is con-

troversial since studies have suggested that the effect is only minor *(Bodey et al, 1996; Montoya et al, 2006)*. Whilst it could be hypothesised that similar effects may be seen in cats, there are no published scientific studies reporting such a link.

► Risks during anesthesia and clinical procedures

Overall, obesity makes clinical evaluation more difficult. Techniques that are more problematic in obese patients include physical examination, thoracic auscultation, palpation and aspiration of peripheral lymph nodes, abdominal palpation, blood sampling, cystocentesis, and diagnostic imaging (especially ultrasonography). Anesthetic risk is reportedly increased in obese dogs, most likely given recognized problems with estimation of anesthetic dose, catheter placement, and prolonged operating time *(Clutton, 1988; Van Goethem et al, 2003)*. Although no published data exist, it is likely that similar problems exist in cats. Finally, decreased heat tolerance and stamina have also been reported in obese animals *(Burkholder & Toll, 2000)*.

4 - Pathophysiology of obesity

► Energy balance: intake versus expenditure

The control of body weight requires the accurate matching of caloric intake to caloric expenditure over time. Despite dramatic fluctuations in caloric intake, normal animals are able to maintain a very stable body weight. Long-term regulation of energy balance is dependent on the coordination and interpretation of peripheral signals indicating the level of energy stores. The best known signals are leptin and insulin. Short-term regulation depends on meal-related signals such as cholecystokinin (CCK) or gastrin related peptide (GRP) *(Strader & Woods, 2005)*. Therefore, the central nervous system receives uninterrupted information about body energy stores through metabolic, neural and endocrine factors. Some are from central origin; some originate from the gastrointestinal tract or adipose cells. However, the elementary distinction between central and peripheral mechanisms tends to give way to a more integrated concept. In fact, each peripheral factor acts independently from central control and central factors modulate the secretion of peripheral factors by adjusting the response to ingested nutrients and modifying appetite behavior.

► Weight gain and appetite control

A wide range of central neuroendocrine factors have been linked to the control of energy balance. At a mechanistic level, identification of those factors that control appetite remains a challenge and is an important physiological basis to develop new pharmacological treatment strategies. Among new strategies developed against obesity, appetite manipulation is one of the most attractive. The aim is to block endogenous signals that stimulate appetite.

Hunger has cognitive and environmental components, such that the feeling of hunger could develop despite physiological satiety. In this circumstance, there is disruption of the relationship between appetite and food intake and abnormal appetite control is common in obese subjects. Among factors leading a cat to eat in the absence of hunger, there is boredom, availability of palatable food, or emotional stress *(Mattes et al, 2005)*.

Many pharmacologic approaches have been considered to control hunger and to modify the secretion of peptides implicated in its regulation **(Table 3)**.

One of the most recently identified signals of food intake is the gut peptide ghrelin *(Cummings et al, 2006)*. Ghrelin is the unique enteric peptide known to increase food intake. There is a net rise of plasma ghrelin concentration after a period of fasting and it declines in the post-prandial period. In addition, it appears that ghrelin is not only a short-term signal of hunger since, in obesity, its concentration was increased by 24% in a group of subjects who had lost weight *(Cummings et al, 2002)*. Thus, the increased concentration of ghrelin, an orexigenic signal, counteracts the effect

Appetite is composed of three phases: **hunger, satiation and satiety**.
Hunger is defined as a biological drive impelling the ingestion of food.
"Satiation" and satiety are defined by some investigators as intra- and inter-meal satiety, respectively:
- **satiation** refers to processes that promote meal termination. A sensation of fullness develops, thus limiting meal size;
- **satiety** refers to postprandial events that affect the interval to the next meal, so regulating meal frequency, which is also influenced by learned habits *(Cummings & Overduin, 2007)*. Satiety is considered a motivation not to eat between episodes of eating. The state of satiety delays the onset of a meal and may reduce the amount of food consumed in a forthcoming meal.

of the regimen and tends to promote the regain of lost weight after a period of energy restriction. Future research should focus on dietary interventions that could reduce ghrelin concentration and food intake.

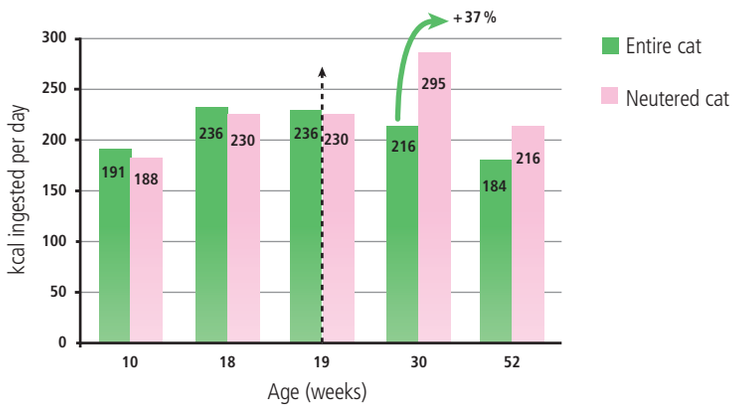
CCK controls satiety. It is released in response to the ingestion of fat and protein in the diet, although its appetite suppression effect is strongly increased by stomach distension *(Kissileff et al, 2003)*. Central administration of CCK reduces meal size in animals including humans. However, despite promising results showing that CCK acts to limit energy intake, it appears that long-term chronic administration has no effect on body weight loss. Therefore, the best method to control CCK release seems to be modifying the composition of the diet via protein levels. In cats, it has been demonstrated that dietary protein and amino acids raise plasma CCK concentration *(Backus et al, 1997)*. Among amino acids, tryptophan, phenylalanine, leucine and isoleucine were found to be the most effective.

Administration of amylin, bombesin and related-peptides (GRP, neuromedin B, glucagon-like peptide [GLP]-1, glucagon and related peptides (glicentin, GLP-2, oxyntomodulin), peptide tyrosine-tyrosine (PYY) and related peptides (pancreatic polypeptide, neuropeptide Y), gastric leptin and apolipoprotein A-IV reduces food intake. Leptin is an orexigenic factor that leads to glucose intolerance, insulin resistance and hyperinsulinemia; further, chronic hyperleptinemia induces obesity *(Kopelman, 2000)*. With the exception of the pancreatic hormones and leptin, all such peptides are synthesized in the brain. This underlines the complexity of the system and shows how difficult it is to understand all the mechanisms implicated in food intake. Therefore, the use of pharmacologic therapies should be extremely cautious and may have strong side effects due to the high complexity of the regulation on a long-term basis.

TABLE 3 - GASTROINTESTINAL HORMONES IMPLICATED IN APPETITE REGULATION
(from Strader and Woods, 2005)

Hormone	Effect on food intake
Cholecystokinin	Decreased
Amylin	Decreased
Glucagon like peptide-1 (GLP-1)	Decreased
Peptide tyrosine-tyrosine (3-36) (PYY)	Decreased
Apolipoprotein A_4	Decreased
Enterostatin	Decreased
Bombesin/gastrin releasing peptide (GRP)	Decreased
Glucagon	Decreased
Gastric leptin	Decreased
Ghrelin	Increased

FIGURE 6 - EFFECT OF NEUTERING ON FOOD INTAKE
(from Calvert, 2003)



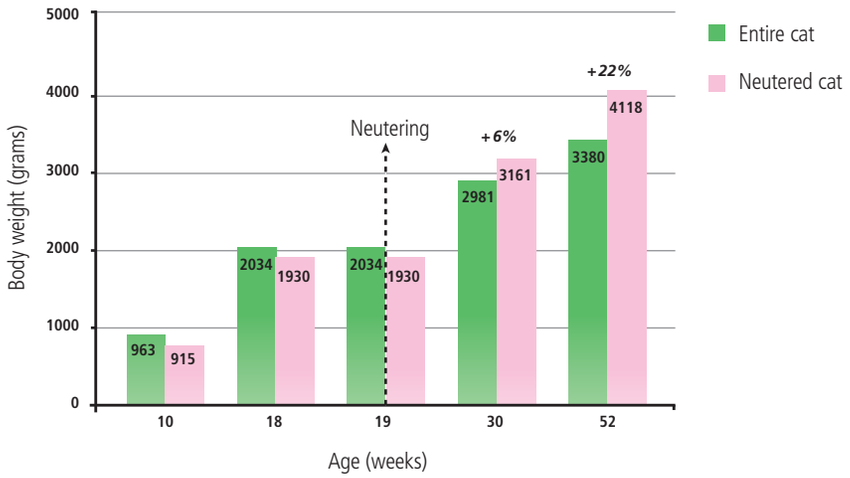
After neutering, cats are less capable of regulating their food intake. This leads to a gain in weight.

► Neutering and obesity

How neutering leads to weight gain has been the subject of some debate. The main factor seems to be an alteration in feeding behavior leading to increased food intake (*Flynn et al, 1996; Fettman et al, 1997; Harper et al, 2001; Hoenig & Ferguson, 2002; Kanchuk et al, 2003*; see also **Figure 6**), and decreased activity *(Flynn et al, 1996; Harper et al, 2001)*.

The metabolic consequences observed after neutering are likely to be secondary to the specific hormonal changes that occur after this procedure. Studies in other species have shown that estrogens can suppress appetite *(Czaja & Goy, 1975)*. Thus, removal of the metabolic effects of estrogens and androgens by gonadectomy may lead to increased food consumption. However, the exact mechanism by which this occurs is not known and, in this respect, a recent study has refuted the hypothesis that gonadal hormones may interact with CCK, the gastrointestinal hormone that can

Figure 7 - Effect of neutering on body weight
(from Calvert, 2003)



influence appetite *(Backus et al, 2005; Asarian & Geary, 2006)*. Ghrelin is probably implicated in this mechanism.

In studies conducted by one of the authors, plasma concentrations of various hormones were monitored in seven male and six female cats, before and after neutering *(Martin et al, 2004; 2006a)*. All cats were neutered after they had reached sexual maturity, at 11 months of age. By modifying endocrine homeostasis, neutering induces a new state of equilibrium in which the hormones involved in obesity and the dysregulation of glucose metabolism predominate. The earliest hormonal change was a rapid increase in the plasma concentration of IGF-1. This increase was noticeable as soon as the first week after neutering and tended to stabilize over time. Although studies about the regulation of the somatotropic axis in obesity report contradictory results on the secretion of IGF-1, receptors for this molecule have nevertheless been identified in pre-adipocyte and adipocyte cells lines *(Louveau & Gondret, 2004)*. Thus, the increase in IGF-1 secretion following neutering may have a primary role in the onset of obesity in the cat, since it promotes the multiplication and even the growth of adipocytes.

Increase in prolactin concentration varied between the males and females ($p < 0.0001$) *(Martin & Siliart, 2005)*.

- Female cats (with the exception of one cat) demonstrated hyperprolactinemia prior to neutering, that was probably linked to their sexual activity at the time of neutering (heat period). Hyperprolactinemia was maintained over time and by 24 weeks post-neutering, the mean concentration was about 60 ng/mL.
- In male cats, results were markedly different. Prior to castration, the mean plasma concentration was below 20 ng/mL; after 12 weeks it reached about 30 ng/mL.

Two years after castration, the mean prolactin concentration was about 70 ng/mL for both gender. We conclude that neutering induces a persistent hyperprolactinemia, regardless of gender and initial concentrations.

Prolactin has a role in the production and maintenance of adipose tissue *(Flint et al, 2003)*. Additionally, it is possible that an elevated prolactin concentration could also have a deleterious effect on glucose metabolism in the cat in the short or long term.

When energy expenditure is expressed on a lean mass basis, no difference in metabolic rate was noted between entire individuals and individuals that are neutered *(Fettman et al, 1997; Martin et al, 2001; Kanchuk et al, 2003; Nguyen et al, 2004)*. However, neutered cats are more obese than intact ones **(Figure 7)** and they are reported to have resting metabolic rates 20-33% below those of intact cats *(Flynn et al, 1996; Root et al, 1996; Harper et al, 2001; Hoenig & Ferguson, 2002)*. Coupled with reduced physical activity, this lower metabolic rate highlights the necessity to decrease the caloric intake of neutered cats to limit the increase in body weight.

5 - Clinical evaluation of the obese patient

► Quantifying obesity in cats

Obesity is defined as an excess accumulation of body fat and all measures of adiposity involve defining body composition. The main conceptual division of importance is between:

Table 4 - Composition of fat mass and fat free mass

Body weight	**Fat free mass** - Heterogenous - Water content 72-74% - Density of 1.1 g/mL	**Minerals** (Potassium 50-70 mmol/kg)	
		Intracellular water Extracellular water	**Water**
		Glycogen and proteins from muscles	**Energy**
	Fat mass - Homogenous - Anhydrous - Potassium free - Density of 0.9 g/mL		

- fat mass (FM): the adipose tissue
- fat-free mass (FFM) *(Pace & Rathbun, 1945)*. The major constituents of the FFM are presumed to be present in fixed ratios and include the intracellular (ICW) and extracellular water (ECW), minerals, and protein. The FFM contains the body cell mass (BCM) which is the metabolically active part of the body responsible for determining most of the resting energy expenditure. BCM encompasses those lean tissues most likely to be affected by nutrition or disease over relatively short periods. Further, since FFM is an index of protein nutrition, changes in FFM likely represent alterations in protein balance.

Table 5 - Techniques available to measure body composition

Clinically relevant techniques	Research relevant techniques
Body weight Body condition score Morphometric measurements Feline Body Mass Index Dilutional techniques Bioelectrical impedance analysis Dual energy x-ray absorptiometry	Densitometry Computed tomography Magnetic resonance imaging Total body electrical conductivity Total body potassium Neutron activation analysis

Thus, assessment of FM and FFM provides valuable information about the physical and metabolic status of the individual; the FM represents an energy storage depot, whilst FFM represents the actual health of the animal **(Table 4)**.

Various techniques are available to measure body composition **(Table 5)**, and these differ in applicability to research, referral veterinary practice and first-opinion practice. Broadly speaking, a number of techniques are available to assess the degree of adiposity, including:
- clinical assessments (e.g. morphometric measurements, body condition scoring, sequential body weight measurement, sequential photography)
- experimental procedures (e.g. chemical analysis, dilution techniques (e.g. deuterium determination of total body water), total body potassium, densitometry, total body electrical conductivity, and neutron activation analysis).
- techniques that have potential for application in clinical work (e.g. dual energy x-ray absorptiometry, bioelectrical impedance analysis, computed tomography, magnetic resonance imaging).

Only those of greatest relevance to clinical practice will be discussed in detail.

The body weight recorded at the end of the first year can usually be a good reference of the optimum body weight of the cat during the rest of its life.

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► Established clinical measures of body composition

> Body weight measurement

It is the simplest technique available and should be included in the examination of every patient, especially in very young cats, at the end of the growth period. However, work by one of the authors has suggested that this remains an infrequent part of the routine examination of companion animals *(unpublished observations)*. It provides a rough measure of total body energy stores and changes in weight parallel energy and protein balance. In the healthy animal, body weight varies little from day to day.

Figure 8 - Indicative weight for several feline breeds

Source: Royal Canin Encyclopedia of the Cat

1. Singapora: < 3 kg
2. Siamese: 2,5-4 kg
3. Persian: 3-6 kg
4. Chartreux: 4-7 kg
5. British Short Hair: 4-7 kg
6. Norwegian Forest Cat: 3-9 kg
7. Maine Coon: 5-10 kg

The ratio between the heaviest and the lightest cats of well-known breeds is 1 to 4, which represents a relative homogeneity compared with the canine species where the ratio is 1 to 100.

There can be wide variation between scales though, so it is important to use the same scale for an individual animal each time to avoid inter-scale variation. Body weight can be falsely altered by dehydration or fluid accumulation. Edema and ascites may mask losses in body fat or muscle mass. Likewise, massive tumor growth or organomegaly can mask loss in fat or lean tissues such as skeletal muscle. Further, breed influences can also lead to variability in body weight for cats in similar condition **(Figure 8)**. Body weight correlates only moderately with body fat mass *(Burkholder, 2001)*.

As a result, sporadic measurements at single time points are of only limited use (if not coupled with concurrent assessment of body condition -**see below**). Nevertheless, sequential body weight measurements (e.g. throughout life in an individual cat, instigated at the time of young adulthood) can provide a sensitive indicator of subtle changes in body composition and could provide a vital tool for the prevention of obesity.

Figure 9 - Body condition scoring in cats

Grades	Criteria
1 Emaciated 	- Ribcage, spine, shoulder blades and pelvis easily visible (short hair) - Obvious loss of muscle mass - No palpable fat on rib cage
2 Thin 	- Ribcage, spine shoulder blades and pelvis visible - Obvious abdominal tuck (waist) - Minimal abdominal fat
3 Ideal 	- Ribcage, spine not visible but easily palpable - Obvious abdominal tuck (waist) - Little abdominal fat
4 Overweight 	- Ribcage, spine not easily palpable - Abdominal tuck (waist) absent - Obvious abdominal distension
5 Obese 	- Massive thoracic, spinal and abdominal fat deposits - Massive abdominal distension

> Body condition scoring

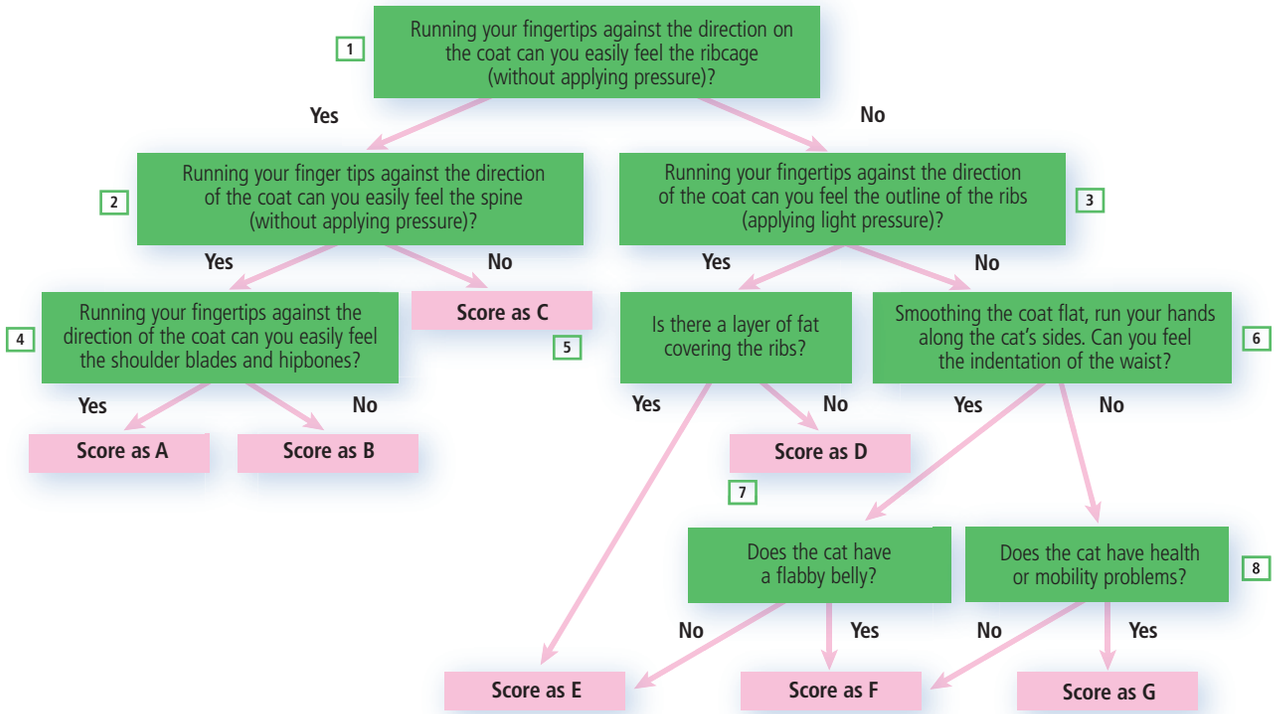
Body condition scoring is a subjective, semi-quantitative method of evaluating body composition that is quick and simple to perform. All systems assess visual and palpable characteristics to assess subcutaneous fat, abdominal fat and superficial musculature (e.g. ribcage, dorsal spinous processes and waist). The technique of body condition scoring does depend on operator interpretation and does not provide any precise quantitative information concerning alterations in fat free or lean body mass relative to fat mass.

Different scoring systems have been described but the most common scoring systems used are the 5-point system (where a BCS of 3 is considered ideal, see **Figure 9**) or the 9-point system (where a BCS of 5 is considered ideal) *(Laflamme, 1997; McGreevy et al, 2005)*. Given that half points are often employed in the 5-point system (giving a total of 9 categories), these two systems are virtually equivalent. A 7-point algorithm-based approach **(Figure 10)** is specifically designed to be used by owners to assess their own pets. A study has demonstrated a good correlation between the system and body fat measurements made by Dual Energy X-Ray Absorptiometry (DEXA) with excellent agreement between experienced operators *(German et al, 2006)*. Most importantly, good agreement was found between measurements by operators and owners, suggesting that the method may be reliable when used without prior training. However, such data are preliminary and further validation would be required before it is used by owners.

Limitations of the BCS include the subjectivity inherent in the scoring system and inter-observer variation. Finally, like body weight, BCS gives an overall assessment of body condition; it cannot differentiate between body compart-

The BCS in conjunction with body weight gives a clinician a more complete perspective on a patient's body condition and should be recorded at every visit.

Figure 10 - Waltham S.H.A.P.E.™ Guide for Cats



S.H.A.P.E.™ Score	Description
A - Extremely thin	Your cat has a very small amount or no total body fat. > **Recommendation:** seek veterinary advice promptly.
B - Thin	Your cat has only a small amount of total body fat. > **Recommendation:** seek veterinary advice to ensure your cat is offered the appropriate amount of food. Reassess using the S.H.A.P.E.™ chart every 2 weeks.
C - Lean	Your cat is at the low end of the ideal range with less than normal body fat. > **Recommandation:** increase food offered by a small amount. Monitor monthly using the S.H.A.P.E.™ chart and seek veterinary advice if no change.
D - Ideal	Your cat has an ideal amount of total body fat. > **Recommendation:** monitor monthly to ensure your cat remains in this category and have him/her checked by the veterinarian at your next visit.
E - Mildly overweight	Your cat is at the upper end of the ideal range with a small amount of excess body fat. > **Recommendation:** seek veterinary advice to ensure your cat is offered the appropriate amount of food and try to increase activity levels. Avoid excessive treats and monitor monthly using the S.H.A.P.E.™ chart.
F - Moderately overweight	Your cat has an excess of total body fat. > **Recommendation:** seek veterinary advice to implement safety an appropriate weight loss plan including increasing activity levels. Reassess using the S.H.A.P.E.™ chart every 2 weeks.
G - Severely overweight	Your cat has a large amount of excess total body fat that is affecting its health and well being. > **Recommendation:** seek veterinary advice promptly to introduce a weight loss plan to reduce your cat's weight, increase activity levels and improve health.
NB Some breeds and different life-stages may have different ideal S.H.A.P.E.™ scores.	

S.H.A.P.E™ (Size, Health And Physical Evaluation) is a new 7-point flow-diagram for measuring body condition, designed to allow owners to assess the body condition of their pets. It correlates well with body fat: all subjects were scanned in dorsal recumbency with a fan-beam DEXA (Lunar Prodigy Advance; GE Lunar; Madison, USA). *There is also a good agreement between owner scores and those of experienced operators* (German et al, 2006).

Figure 11A - Measurement of the length of the lower limb (LIM) from the middle of the patella to the calcaneus.

Figure 11B - Measurement of the rib cage circumference.

ments and does not provide any precise quantitative information concerning alteration in fat free or lean body mass relative to fat mass.

> Morphometric measurements

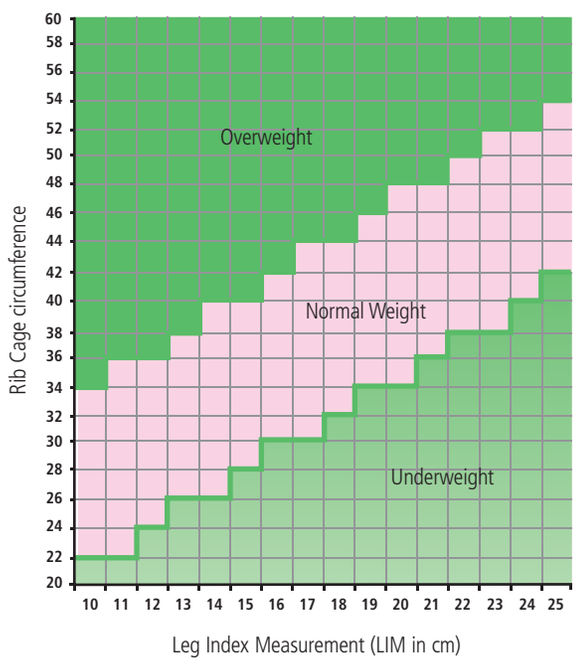
Morphometry (more appropriately "zoometry" for veterinary species) is defined as the measurement of "form" and, in relation to body composition analysis, refers to a variety of measured parameters that are used to estimate body composition. The three main approaches are:
- dimensional evaluations (where various measures of stature are combined with weight)
- measurement of skin fold thickness
- ultrasound technique.

Dimensional evaluations

Dimensional evaluations are usually performed by tape measure, and a number have been reported in cats. Measurements of "length" (e.g. head, thorax and limb) are correlated with lean body components *(Hawthorne & Butterwick, 2000)*, whilst circumferential measurements have been shown to correlate both with lean body mass (LBM) *(Hawthorne & Butterwick, 2000)*, and body fat *(Burkholder, 1994)*. Segmental limb measures and (likely) truncal length are thought to be better measures of stature and thus correlate best to LBM. By combining more than one measure (usually one that correlates with FM, and one correlating with LBM), equations can be generated to predict different body components.

The best example of such a measure is the feline body mass index (FBMI)™ *(Hawthorne & Butterwick, 2000)*. The FBMI™ is determined by measuring the rib cage circumference at the level of the 9th cranial rib and the leg index measurement (LIM), which is the distance from the patella to the calcaneus **(Figure 11)**.

TABLE 6 - FELINE BODY MASS INDEX CHART



The percent body fat can be calculated as:
- % fat = (1.54 x ribcage circumference) – (1.58 x leg index measurement) – 8.67 (rib cage circumference and LIM in cm)
- or, more simply: 1.5 (ribcage – LIM)/ 9
- or determined by consulting a reference chart **(Table 6)**.

The FBMI™ is a very simple, yet objective tool to determine the body fat content of the cat. In addition, it is particularly valuable for convincing clients that their cat is indeed overweight and in need of weight loss.

Measurement of skin fold thickness

This technique has been used extensively in people to determine the percent body fat using equations derived for various populations. Unfortunately, these measurements cannot be used in cats because feline skin is easily detached from underlying fat tissue which makes skin-fold measurement impractical and unreliable.

Ultrasound

Another method of measuring the subcutaneous fat layer is by ultrasound. This technique has been used in Beagles and equations have been derived to predict percent body fat from the subcutaneous fat thickness *(Wilkinson & McEwan, 1991)*. These regression equations do not work in other dog breeds but future research may allow investigators to develop new, more accurate equations for this simple technique.

> Bioelectrical impedance analysis (BIA)

Bioelectrical impedance analysis (BIA) is a safe, noninvasive, rapid, portable, and fairly reproducible method of assessing body composition in companion animals. This method has the potential of quantifying total body water (TBW), ECW, ICW, BCM, FFM and FM.

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Bioelectrical impedance analysis (BIA) is a safe, noninvasive, rapid, portable, and reproducible method of assessing body composition in healthy cats.

Electrical conductance is used to calculate the composition of the body by measuring the nature of the conductance of an applied electrical current in the patient. Body fluids and electrolytes are responsible for conductance whilst cell membranes produce capacitance. Since adipose tissue is less hydrated than lean body tissues, more adipose tissue results in a smaller conducting volume or path for current and larger impedance to current passage. The FFM contains virtually all the water in the body and thus if bioelectrical impedance is measured a value for FFM can be determined.

Two types of BIA systems are currently available; single frequency which applies a 50 kHz current, and multi-frequency which utilizes frequencies from 5 kHz to 1000 KHz. A BIA test is performed by placing four small electrodes on the body. The electrical current is introduced into the patient from the distal electrodes. As the current travels through the body it experiences a slight delay due to cells, and the current is then detected by proximal electrodes. The proportion of the current in the ICW and ECW is frequency dependent:

- low frequencies (e.g. 5kHz) pass primarily through the ECW because of high cell membrane capacitance
- in contrast, at higher frequencies the effects of cell membrane capacitance is diminished so the current flows through both the ICW and ECW environments (or TBW).

BIA allows estimation of body composition in healthy dogs, cats, and humans *(Scheltinga et al, 1991; Stanton et al, 1992; Patel et al, 1994)*. However, BIA may be affected by hydration status, consumption of food and water, skin and air temperature, recent physical activity, conductance of the examination table, patient age, size, shape and posture in addition to electrode positioning. Reliable BIA requires standardization and control of these variables. BIA requires further evaluation and validation in disease states, especially those associated with major disturbances in water distribution and states such as sepsis which may alter cell membrane capacitance.

Calculation of ECW-ICW takes approximately 1 minute, hence BIA provides instantaneous on line information of body composition that has never before been available.

> Deuterium (D_2O) dilution technique

The water content of the FFM is among the best used techniques for determining body composition due to the relative stability of the FFM hydration between species. Briefly, TBW can be measured by several stable labelled isotopes dilution methods including D_2O and the following relationship has been validated:

$$\text{Fat mass} = \text{body mass} - \text{TBW}/0.73$$

The first study on cats was published in 1950 by *Spray and Widdowson*.

In practice, after a 24h fasting period, a sub-cutaneous injection of D_2O in an isotonic saline solution is administered (500 mg D_2O/kg). The mass of the syringe (and needle) before and after injection should be accurately weighed to determine the exact quantity of labelled-isotope that will dilute in body water. The first blood sample is taken before injection, the second about 3-4 hours after D_2O injection. Until recently, this technique was limited due to technological problems but

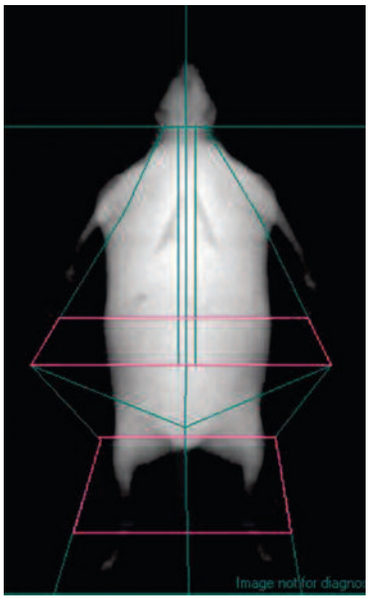


Figure 12 - DEXA examination in an obese cat.
DEXA prior to weight loss shows a body fat content of 54.4% (reference range 18 to 25%).

today a new method of analysis has been developed which makes this technique less expensive and more widely available.

> Dual energy X-ray absorptiometry (DEXA)

This technique originally developed for precise measurement of bone mineral content (BMC). However, it is now also used to measure both body fat and non-bone lean tissue. DEXA uses photons of two different energy levels (70 and 140 kVp) to distinguish the type and amount of tissue scanned. The X-ray source is positioned underneath the table supporting the patient, with the detector housed in an arm above the patient.

During a scan the source and detector move together over the patient. The detector measures the amount of X-rays that pass through the subject. The X-rays of the two different energy levels are impeded differently by bone mineral, lipid and lean tissue. Algorithms are used to calculate both the type and quantity of tissue in each pixel scanned. DEXA calculates bone mineral density, bone mineral content, fat mass, and lean body mass.

DEXA's low coefficient of variation for measuring BMC (~1%) makes it a very precise technique but a few constraints have to be noted:
- equipment is still expensive
- short sedation is required
- standardization of the technique is very important *(Raffan et al, 2006)*.

DEXA is safe and quick; with the more modern fan-beam DEXA scanner, it takes under five minutes for a whole body scan in a cat **(Figure 12)**. Similar to other body composition techniques, DEXA relies on the assumption that lean body mass is uniformly hydrated at 0.73 mL water/g.

► Determination of basal metabolic rate (BMR)

Precise knowledge of energy expenditure is important in obese animals to determine the exact amount of energy needed to loose weight. Energy expenditure is the result of internal and external work and of heat yields. Energy originates from nutrients that are converted to various energy forms that can be used by the body. Most chemical reactions in the body need oxygen and produce water and carbon dioxide. So relationships have been established between respiratory and energy expenditure.

Among methods available, indirect calorimetry allows the determination of the basal metabolic rate by measuring only oxygen consumption and carbon dioxide production. In practice, the cat is placed in a specific cage for about 4-h and gas exchanges are measured. The formula used to calculate BMR was validated by *Weir* (1949). An abbreviated Weir formula has also been developed:

$$BMR\ (kcal/day) = [3.9\ (kcal/L) \times V\ (O_2\ (L)) + 1.1\ (kcal/L) \times V\ (CO_2\ (L))]$$

6 - Prevention of feline obesity

The goal of any weight-loss program is to facilitate a progressive decrease of body fat stores without detrimental effects on health. However, success is variable and, since long-term follow-up of weight loss programs is often poor, relapse is frequent. Consequently, it is preferable to prevent obesity occurring in the first place, rather than attempting to cure it once it has developed. As mentioned above, obesity has a number of health and welfare implications, most notably by decreasing both quality and quantity of life.

► Weigh and perform a body condition score on every cat at every consultation

Both of these assessments should form part of a standard physical examination. They enable subtle body composition changes to be noted, and increases in body weight (suggesting over feeding) can therefore be picked up and rectified early on. However, these assessments also have wider health

implications, because subtle weight loss might be recognized as the first component of another significant medical disease.

► Communicate the message of obesity prevention early on

Advice on healthy eating and exercise should be included in all kitten consultations and continued for all cats whenever they are seen at the practice.

► Be alert to weight gain in middle-aged cats

Strategies to prevent obesity from developing should be implemented most aggressively in cats between 6 and 10 years of age. Most important is to prevent the onset of obesity in young (adult) cats, since these animals are the ones that will benefit most from avoiding excess adiposity (in terms of effects on longevity and reduced disease risk).

► Be alert to weight gain after neutering

Like with age, neutering is a major predisposing factor for overweight and obesity **(Figures 13 & 14)**. It is advisable to schedule 2-3 weight-checks in the first 6-12 months after neutering to identify those cats at risk of weight gain and correct it before it becomes a problem.

FIGURE 13 - WEIGHT GAIN AFTER NEUTERING

(from Harper, 2001)

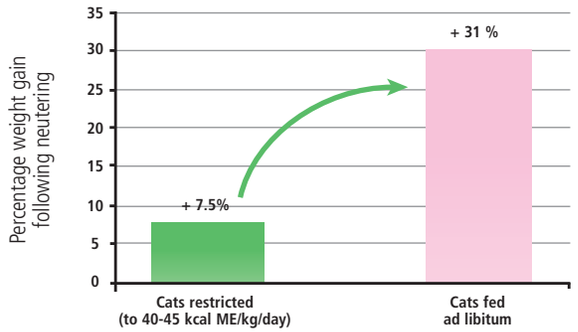
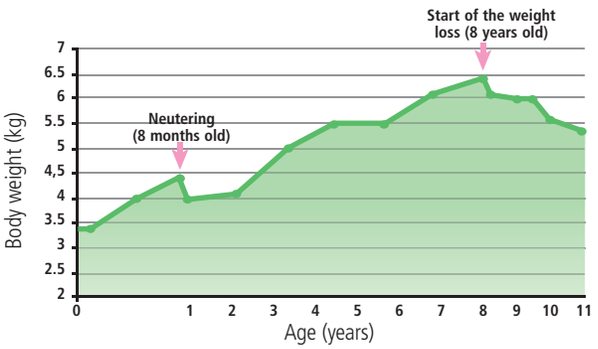


FIGURE 14 - SERIAL BODY WEIGHT MONITORING OF A CAT



The initial body weight was obtained at the time of neutering at 8 months of age. A weight loss program was not implemented until until the cat was 8 years old and 28% overweight.

► Promote the benefits of a healthy lifestyle for all cats

Encourage responsible feeding behaviors, which utilize many of the strategies discussed for the treatment of obesity (see lifestyle alterations). This includes weighing and recording food intake, avoiding the feeding of extras, and promoting regular physical activity through exercise and play sessions. Ideally, all practice staff should be encouraged to promote these concepts, and waiting room literature and other forms of education and support should be available to all owners.

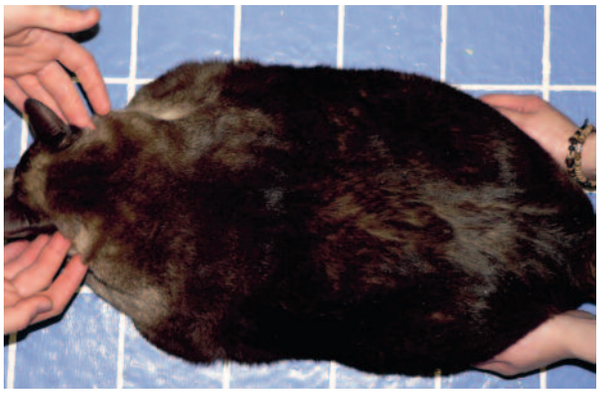
► Target new pet owners

It goes without saying that people who have only recently taken on a new pet, will have limited experience with pet ownership. Hence, it is important to make sure all new owners have the education and support necessary to prevent obesity problems from developing.

7 - Five components to a successful weight management strategy for feline obesity

It is relatively easy to diagnose obesity and to prescribe a specific diet. The challenge lies in convincing the owner to introduce the necessary changes in the feeding and lifestyle of the animal in order to induce and maintain significant weight loss.

1. Initial assessment
2. Establishing pet owner understanding and commitment
3. Setting and managing owner expectations
4. Intervention
5. Maintenance.



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When a clinician is presented with an obese cat for the first time, it is essential to perform a thorough assessment of the patient.

► Initial assessment

The aims of the first examination are:

- to quantify the level of obesity. Whilst the language should be positive and constructive, the risk of allowing a cat to continue to be overweight should be firmly stressed. Owners are more likely to want to intervene if the perceived health benefits for their pet are clear;
- to identify predisposing factors for obesity in this cat
- to determine the current health status. This will enable weight loss to be instigated in the safest and most effective manner for the cat:
  - obesity-associated diseases
  - other, potentially unrelated diseases which may affect the way in which the case is investigated and treated.

The recommended components of the initial assessment follow several stages.

History. This should include details of environment, lifestyle, diet and exercise regimes, as well as a complete medical history including previous or current therapy.

Physical examination. The goal is to identify signs of associated diseases (either causing or contributing to weight gain), and any concurrent diseases.

Weight measurement. The use of a single set of electronic weigh scales is recommended which are, ideally, regulated validated for precision and accuracy.

Body condition score. Condition scoring the patient is not only a key diagnostic tool for establishing the degree of obesity but is also an invaluable tool for discussion with owners. Whilst the exact system used is not critical, clinicians should use the same one for all of their patients, since familiarity is likely to lead to more accurate scoring. The 5 or 9-point BCS (discussed earlier) have been validated against body fat measurements made by DEXA, and thus are known to correlate with the degree of adiposity if performed by a trained operator.

General laboratory investigations. Laboratory investigations may be necessary to verify the health status of the cat. These should include routine hematological examination, clinical chemistry, and urinalysis. Additional investigations may be required in some circumstances.

Additional investigations. Additional investigations will depend on the presence or suspicion of any associated disease. Examples include:

- measurement of blood pressure if facilities are available
- fructosamine measurement for diabetes mellitus
- survey radiography for orthopedic and respiratory disease
- hepatic ultrasonography, fine needle aspiration cytology and/or liver biopsy for suspected hepatic lipidosis
- urine culture, ultrasonography, radiographic contrast studies for lower urinary tract diseases.

Exactly what tests are recommended in each circumstance is beyond the scope of these guidelines and are at the discretion of the individual veterinarian. If other conditions are identified, specific therapy should be implemented at an appropriate time (before, during or after the weight management regime). Obviously, weight loss may be a major factor in the treatment of any obesity-associated disease.

► Establishing owner understanding and commitment

Successful treatment of obesity depends above all on the motivation of the owner and their compliance with the weight loss program. Success is most likely when the client understands and

accepts the reasons why weight loss is necessary. The clinician must be aware of the reason that the cat was presented for evaluation, as the level of client motivation will vary. There are three main scenarios: presentation for obesity itself, for an obesity-associated disease or for an unrelated reason.

> Presentation for obesity

The owner seeks advice about the weight problem. Client management will be easiest because these owners are already motivated and have accepted the need for intervention. Therefore, they should be most receptive to appropriate veterinary advice. This is the least common presentation.

> Presentation for an obesity-associated disease

The cat presents with a condition that is due to obesity. The clinician can communicate to the client that the obesity is a medical, rather than cosmetic, problem. It is important to explain that the excess weight caused or contributed to the disease, and how it is an essential part of maximizing response. If such arguments are made in a convincing manner, client motivation should not be a problem.

> Presentation for an unrelated reason

The obesity is an incidental observation during a consultation for an unrelated reason. This typically occurs during an annual vaccination or routine health check.

Initiating discussion in these cases is difficult because the reaction of the owner is not predictable. Some may refuse to believe that a problem exists, some may believe that the veterinarian's recommendation is financially-motivated, whilst others believe that they are to be blamed for the problem. An additional problem arises with owners who have obesity or health problems of their own. The approach is to focus on the health of the cat, including any existing morbidity and the potential for future health problems as a result of continuing obesity. The veterinarian should use sensitive language, such that the owner can accept their pet is overweight without being made to feel guilty.

If they believe that their cat is currently healthy and an obvious co-morbidity does not exist, the owner may not be convinced by an argument structured around the potential future health problems that may arise. Instead, it may help to focus on detrimental effects on current quality of life e.g. fitness, physical activity and grooming. Before and after testimonials from previous clients, highlighting the health benefits of weight loss, may help in convincing these owners.

Some owners may still not be convinced of the need for intervention at the initial consultation, and may require several visits before the argument is accepted. Since owner motivation and compliance are essential pre-requisites for successful weight management, there may be little point in embarking upon a weight reduction program without them. However, providing information leaflets for owners to read may help to improve their understanding of the need to intervene.

► Setting and managing owner expectations

Once the veterinarian is happy that the owner is fully committed, treatment of obesity can be started. There are two phases of the program:
- intervention (when the weight loss occurs): this first phase can take many months
- maintenance (when body weight is stabilized and then maintained): the second phase is lifelong.

Given that successful weight loss depends mainly on owner commitment, it is vital to ensure that the owner has realistic expectations from the outset.
The timescale of treatment, the level and rate of weight loss, cost of therapy, potential side-effects of treatment, behavioral changes in the pet, time commitment for lifestyle changes (e.g. exercise),

behavior of other family members and any other potential pitfalls should be discussed. The aim should be to make sure that the owner is fully informed of all eventualities and has no unexpected surprises. The problems which are most likely to be encountered include:
- difficulty in adapting to the new diet (palatability)
- difficulty in adapting to a reduced amount of food
- behavioral troubles due to permanent hunger with inopportune vocalizing, aggressiveness, stealing food
- very slow loss of weight.

Every step of the way, the veterinarian should remind the owner of the goals of therapy, success so far, future expectations and how long-term success can be achieved. This should help to ensure that the client remains committed to each stage of therapy.

► Intervention

When it comes to management of obesity in any species, there are four potential options:
- surgery
- pharmaceutical intervention
- lifestyle alterations
- dietary management

The usual methods generally lead to a reduction of adipose tissue mass either by reducing energy intake (e.g. dietary management, pharmaceuticals, bariatric surgery) or by increasing energy expenditure (e.g. increasing physical activity through lifestyle changes). In reality, whilst the latter may assist in weight loss, it is rarely successful if used as the sole component. Thus, some form of dietary caloric restriction is usually necessary, although a combination of strategies is likely to be most successful. Finally, for any intervention to be successful, close monitoring is vital. The approach chosen for any one case may vary and, as a result, the following guidelines are deliberately general.

> Surgical procedures

In addition to the ethical concerns, surgical procedures are unlikely to be a viable treatment option for obesity in pets because these procedures are complex, expensive and morbidity is likely to be high (e.g. 23% to 55% of patients have a short- or long-term complication) *(Powers & Pappas,*

LIPOSUCTION

This common cosmetic surgery technique in humans aims at reducing adipose tissue mass. However, only subcutaneous fat is removed, which carries little metabolic risk, and does not modify dietary behavior. A single canine case study reports the use of liposuction for the treatment of a large subcutaneous lipoma *(Bottcher et al, 2007)* but it is unlikely that this technique will be an ethically justifiable option in companion animals.

BARIATRIC SURGERY

This term is used to describe surgery for the management of obesity through the control of food intake. One of the most successful treatment is the Roux-en-Y gastric bypass *(Strader and Woods, 2005)*, which both reduces the stomach volume and allows a rapid delivery of the stomach contents to the small intestine. Compulsory restriction of meal size, decreased digestibility and changes in endocrine signals of the gut contribute to the weight loss.

PHARMACEUTICAL AGENTS AVAILABLE FOR THE TREATMENT OF OBESITY

Sibutramine

Sibutramine is the only centrally-acting anti-obesity drug approved for use in humans in most countries *(Halford, 2006)*. It works as an inhibitor of the reuptake of serotonin, noradrenaline and dopamine. Sibutramine acts on both satiety and thermogenesis to induce weight loss. The efficacy of sibutramine has been demonstrated in rodents and humans. Numerous side effects may be seen on cardio-vascular function with studies showing increases in both heart rate and blood pressure.

Orlistat, or tetrahydrolipstatin

Orlistat is the saturated derivative of lipstatin (potent inhibitor of pancreatic lipases isolated from *Streptomyces toxytricini*). Its primary function is to prevent intestinal absorption of fat. It is intended for use in conjunction with a supervised low fat calorie diet. Orlistat is minimally absorbed into the systemic circulation and its effect is local. The efficacy of Orlistat has been demonstrated in type 2 human diabetes patients. Orlistat induces a significant decrease in blood cholesterol and triglyceride concentrations, and it minimizes cardiovascular risk factors *(Leung et al, 2003)*. Simultaneous administration of soluble dietary fiber (psyllium) significantly reduces the gastrointestinal side effects (steatorrhea and flatulence). Long-term orlistat use may reduce absorption of vitamins A, D, E and beta-carotene and supplementation is necessary.

Microsomal triglyceride transfer protein inhibitors (MTPI)

These drugs are only currently licensed for use in dogs, and block the assembly in the enterocytes and the release of lipoprotein particles into the bloodstream. Dirlotapide can be used as sole therapy for obesity for a maximum period of 12 months. It prevents lipid absorption and it reduces the appetite, the latter effect being the major contributor to weight loss *(Li et al, 2007)*. The most common side effect is vomiting, which can occur in up to 20% of dogs using the drug.

Mitratapide

Mitratapide has recently been approved to aid in weight loss in dogs *(Re, 2006)*. It is designed to be used short-term in conjunction with dietary management and behavioral modification. The drug is given for two 3-week periods punctuated by a 14-day period off the medication. Predominant side effects reported are vomiting and diarrhea. Elevations in liver enzymes can also be seen, although there is no clear evidence of long-term hepatic dysfunction.

1989). Gastric outlet obstruction, vomiting, dumping, gastric leaks and wound infections are common complications. Dietary deficiencies may also result from malabsorption.

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Methods to increase physical activity in cats include:
- increasing play activity
- encouraging the cat to exercise itself
- increasing movement through the use of food treats.

> Pharmacologic treatment

For a number of years, pharmaceutical agents have been available for the treatment of obesity in humans. The drugs which are licensed in most countries are sibutramine and orlistat, although other drugs (e.g. rimonabant) are available in some countries. All available agents are successful in producing weight loss in the majority of patients, although the effect is modest at best (~5-10% weight loss). They can reduce obesity-associated diseases but side effects are common and can be problematic. In addition, a predictable rebound effect often occurs when the drug is discontinued.

With the ever-increasing global obesity epidemic, pharmaceutical management is a growth area, with many companies investing in the development of newer and more effective pharmaceuticals. Pharmaceutical agents have been recently licensed for treatment of canine obesity: the available agents are from a novel group of drugs, the microsomal triglyceride transfer protein inhibitors (MTPI). At the current time, these pharmaceutical agents are not suitable for use in cats. It is not known whether or not similar drugs will be developed for cats in the future.

> Lifestyle alterations

These changes must be implemented during the intervention phase of the weight loss program but need to be maintained lifelong in order that there is permanent success e.g. a healthy lifestyle has been adopted.

The aim should be to increase the level of activity in gradual steps and to make it a regular feature of the pet's life. In practice, exercise has many advantages:
- it increases energy expenditure during training and in the post-exercise period
- it stimulates fat oxidation
- it protects lean body mass
- it has the potential to reverse the decrease in BMR induced by a low calorie diet.

If possible, cats should be encouraged to spend time outdoors. Activity in cats can also be encouraged by using cat toys. For some cats, encouraging walking activity prior to meal times by moving the feeding bowl can also help. Many obese outdoor cats may voluntarily increase their activity levels once their fitness improves during weight loss. The exact exercise program recommended must be tailored to the individual and take into account medical concerns, existing capabilities, breed and age of the patient, as well as the age, and owner circumstances.

Dangling toys are usually appreciated by cats.

© J. Newton

The benefits of exercise go beyond the fact that it burns calories: it builds muscle mass and thus increases the resting metabolic rate, improves mobility, is beneficial for the cardiovascular system in general, enhances the pet/owner bond, provides mental stimulation and generally improves welfare and quality of life. It also enhances compliance and improves the outcome.

In domestic cats, hunting and eating behaviors are independently motivated. Thus, cats have a physiological need to hunt (or perform some alternative to this such as play activity) even when their daily energy requirements are already fulfilled. Although play behavior

The best-designed stations are those that provide many and varied levels and climbing options (thus making full use of 3-dimensional space), include dangling toys and scratch posts. Scratching is an additional means by which cats can expend energy; posts which allow the cat to stretch at full stretch are best.

may be more pronounced in juvenile cats, most owners do not realize that it is necessary throughout life.

When implementing regular play activity, it is best to start with short (~2-3 minutes) sessions each day. This will not overburden the owners, and allow the cat to become accustomed to the activity. Once a regular level of activity is established, and as weight loss progresses, it is possible to increase the duration and intensity of the exercise/play sessions.
A number of toys designed specifically for cats are now available; some features of good cat toys include:
- ability to produce rapid and unpredictable movement
- emission of a high-pitched sound
- small "prey" size
- ability to supply a food reward.

Some home-made objects can work equally well (e.g. rolled up paper, tin foil etc). Feline play stations are another means by which cats can both exercise and fulfill their natural behaviors. These incorporate the opportunity to climb, balance, scratch and hide.

Food can also be a useful motivator for physical activity. Hollow toys can be purchased or constructed, which contain small amounts of kibbles **(Figure 15)**. The cat must then play with the toy (thereby expending energy) to receive the reward. This solution diverts the cat, decreases its boredom when living exclusively indoors, and helps to reduce overall food consumption.

Modifying feeding behavior

Long-term modification of the owners approach to feeding the cat is the second component to a successful program. The following points should be considered.
- Always weigh out food on weigh scales; measuring cups are unreliable.
- Record the amount fed and eaten throughout the weight program.
- Offer the daily food ration in divided meals (2-4 per day) rather than as a single meal.
- Consider methods of slowing food intake at meal times. This can include the use of feeding toys, diets with a larger kibble size (that require more chewing before swallowing), relocating the feed bowl before or during meal times, and activity related rewards e.g. food ration only given after an activity has been performed.
- Avoid feeding additional food in the form of treats or table scraps. Occasional (ideally nutritionally-balanced) treats are acceptable as long as they are factored into the feeding strategy e.g. count towards total daily intake.
- Make certain that all members of the family, friends and neighbors are aware of and are committed to the program.
- If scavenging and begging behavior is seen, do not offer a food reward but encourage another form of positive owner-pet interaction e.g. play session. This will distract the cat from the behavior at the same time as increasing energy expenditure.

> Overview of dietary management

In theory, dietary management can be achieved in three ways:
- using a standard maintenance diet, but reducing the amount of food offered daily
- using a diet which has a lower energy density
- using a food which has low palatability.

It is inadvisable to use a standard maintenance ration and simply restrict the amount of food given. Most nutrients are balanced to the energy content of the ration and, when this is restricted, malnutrition states may develop. For similar reasons, using diets with low palatability are also not an

Although formulations may vary, most weight loss diets for cats have some or all of the following characteristics:
- **Reduced energy density,** usually through a reduction in fat content and an increased fiber content
- **Increased protein content relative to energy content.** This ensures that protein malnutrition does not occur when energy intake is restricted. This strategy does not increase the rate of weight loss, but minimizes the amount of lean tissue lost during weight management.
- **Increased micronutrient** (vitamins and minerals) contents relative to energy content. This ensures that malnutrition does not occur when energy intake is restricted.
- **L-carnitine supplementation.** This compound is an essential co-factor of lipid oxidation and assists in the transport of long-chain fatty acids into mitochondria. Thus, it facilitates fatty acid oxidation maximizing the amount of fat (and thus minimizing the amount of lean tissue) lost on a weight management program.
- **Fiber supplementation.** Higher dietary fiber content increases the bulk of the diet and may improve satiety.

answer; cats will remain hungry, can develop behavioral problems and may become malnourished. Therefore, using diets with a reduced energy density is the key strategy during dietary intervention and additional dietary modifications can help to produce optimal weight reduction with minimal loss of the body fat free mass.

A variety of diets are available, all of which work through caloric energy restriction. Detailed information on the formulation of weight loss diets for cats can be found in future sections. The current information is a summary.

► Maintenance

Although the main medical benefit of a weight reduction program is a long-term reduction in adipose tissue mass, of greater importance is the permanent switch to a healthy lifestyle. As such, success ultimately depends not only on reaching the target, but in avoiding any rebound. In short, a permanent change in the attitude and behavior of the owner is required to ensure so that any weight loss is maintained long term.

The first challenge is to change the cat from a protocol designed for weight loss, to one designed to maintain body weight. The passage to the stabilization diet should be gradual, e.g. the hypoenergetic food should be substituted with a maintenance ration in a step-wise fashion, without provoking any weight gain. The energy level required can be determined in various ways:
- one method is to increase the food intake by 10% every two weeks until no further weight loss occurs. This will enable the veterinarian to set the exactly daily caloric requirement to prevent a rebound;
- alternatively, if food intake was recorded throughout the period of weight loss and, at some point, no weight was lost between consecutive visits, the caloric consumption at this stage may be a suitable estimate of maintenance requirements.

Once target weight has been achieved, regular check-ups should be continued, as well as the support and encouragement for the owner: there should be revisits every 2-4 weeks until the veterinarian is satisfied that weight is being maintained. Thereafter, the interval can gradually be extended but should not be less frequent than once every 3-6 months.

The choice of diet for the maintenance phase is less critical than that used for weight loss. There should be no need to feed a diet specifically formulated for weight loss, long term. However, it may be necessary for the cat to continue on a hypoenergetic diet, albeit consuming larger (i.e. maintenance) quantities. Purpose-formulated diets are available for use in the post-weight loss phase, and contain many desirable characteristics, including reduced energy content and increased fiber level (to promote satiety).

Any strategy that is implemented must aim to put in place a healthier relationship between the cat and the owner. The weight loss program is doomed to failure if no such change is made. For long-term effectiveness, it is essential that the patient does not return to the former situation. The owners should be counseled to the fact that modification of lifestyle is a lifelong (but difficult) process, and that they will need to continue to manage dietary intake for life.

8 - Dietary management of pre-existing obesity

The goal of the treatment is to lose body fat with minimal loss in lean tissue and without negative effects on health. Loss of adipose tissue depends on many factors: the initial body composition, the degree of energy restriction required, the rate of weight loss, the level of protein intake, the metabolic adaptations and the intensity of exercise. Recent work by one of the authors has

Figure 15 - Examples of good cat toys include devices that encourage the cat to play with the toy to receive its food.

© C. Arpaillange

The toy releases a few kibbles when the cat makes it move.

© C. Arpaillange

During a play session, cats must be given the opportunity to catch the "prey" object.

FIGURE 16 - BALANCE BETWEEN ENERGY SUPPLY AND ENERGY EXPENDITURE

Energy supply
Food intake through feeding, titbits and any successful hunting expeditions

Energy expenditure
Short bursts of energy consuming exercise when awake

suggested that cats that lose a higher percentage of body weight overall, tend to lose a greater proportion of lean tissue during weight loss *(German, in press, 2008)*.

In theory, the strategy is simple: in order to achieve weight loss the cat must be fed less energy than it requires **(Figure 16)**. In practice, this means feeding at a level below maintenance energy requirements. This is done by first calculating the energy requirement at ideal body weight and then feeding a proportion of this figure. It is essential to base the calculations on the target body weight and not the current weight.

► How do I determine the ideal body weight?

In order to make a correct calculation of maintenance energy requirements for an obese cat, the ideal body weight must already be known or be estimated.

> When ideal body weight is known or can readily be determined

The ideal body weight may have been recorded during a previous visit when the cat was a young adult in ideal body condition (e.g. a condition score of 3/5 or 5/9). It is by far the most accurate guide to optimal body weight in any individual.

> Estimation of ideal body weight from current body weight and body condition*

In the absence of historical information, an estimate of ideal weight can be made from the current body weight and condition. Assuming that each point above 5 (on a 9-integer condition score) or half point above 3 (on a 5-integer condition score) correlates with 10-15% increase in body weight, a simple mathematical equation can then be used to estimate ideal weight e.g.:

Current weight = 8 kg
Current condition score = 5/5 or 9/9 (~ 40% overweight)
Ideal weight = 100/140 x 8 kg = 5.7 kg

► Recommending an optimum rate of weight loss

If correct energy restriction is applied, obese cats do lose weight *(Butterwick et al, 1994; Butterwick & Markwell, 1996)*. However, the progress of weight loss must be carefully evaluated. A further question is: what rate of weight loss is best? Is rapid weight loss better than slow weight loss?

Many studies have focused on the ideal rate of weight loss because, for owners, rapid weight loss is more satisfactory. In a study *(Szabo et al, 2000)*, obese cats lost 7 to 10% of their obese body weight (BW) during the first week, 3 to 5% during the second week and 2 to 4% for the remainder of the weight loss period. They were fed 25% of their maintenance energy requirement based on the target ideal body weight. However, at the end of the weight loss period, there was an increase in insulin and glucose concentration suggesting that glucose intolerance may be developing in these cats. Therefore, this level of energy restriction appears to be too strict and the authors concluded that the rapid weight loss might increase risk factors associated with the development of diabetes mellitus.

The recommended rate of weight loss remains a controversial issue in veterinary medicine. The weight loss rate must be consistent with relative sparing of lean tissue. Marked energy restriction (down to 45% of maintenance energy requirement at target weight) leads to more rapid weight loss (~1.3% per week) than moderate energy restriction (60% of maintenance energy requirements leading to ~1% body weight loss per week), but lean tissue loss is greater (18% compared with 8%) *(Butterwick et al, 1994)*. Even if the optimal target rate of weight loss seems to be 1.0 to 1.5% of initial BW per week, the exact rate should be tailored to the exact needs of each individual case and slower rates of weight loss are acceptable if tolerated by the client and veterinarian **(Figures 17 A & B)**.

FIGURE 17A - CLINICAL CASE N°1

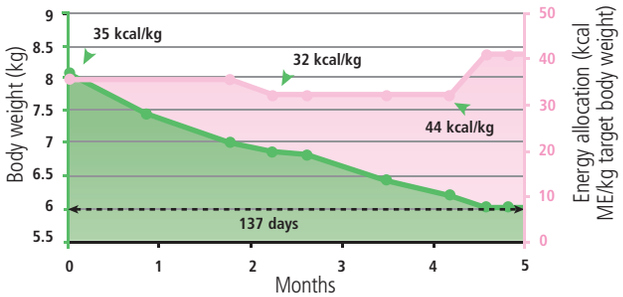
Before: 8 kg

Dr A. German et S. Holden, Weight Management Clinic, University of Liverpool.

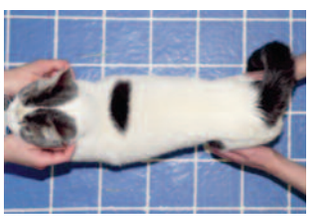
- Breed: DSH
- Age: 8 yrs 10 mths
- Sexual status: neutered male
- Body fat: 40.4%
- BCS: 4.5/5
- Lifestyle: indoor cat

Since body weight has increased, the cat has become far less active. He has problems with grooming behavior, especially in the perineal area. Poor skin and coat condition.

Weight loss summary



After: 6 kg



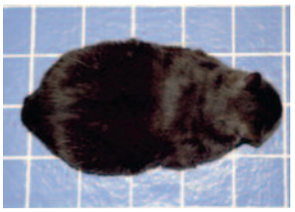
Dr A. German et S. Holden, Weight Management Clinic, University of Liverpool.

- Weight loss duration: 137 days
- Mean average loss: 1.1%/week
- Average allocation: 36 kcal/kg of target body weight
- Body fat: 18.8%
- BCS: 3/5

The cat has become much more mobile with weight loss: he climbs fences, jumps on kitchen units and initiates play sessions. He is better able to groom, therefore his coat condition has greatly improved.

FIGURE 17B - CLINICAL CASE N°2

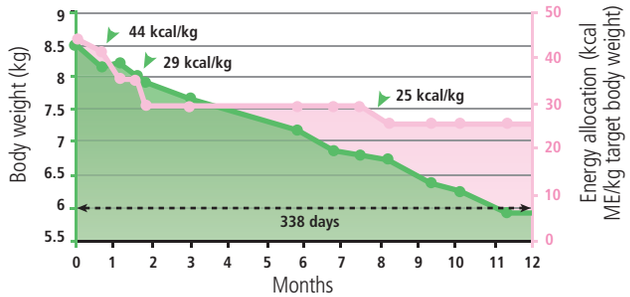
Before: 8.5 kg



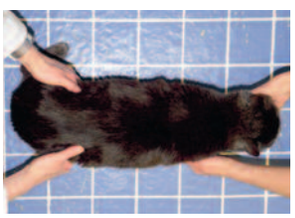
- Breed: DSH
- Age: 13 yrs
- Sexual status: neutered female
- Body fat: 44.5%
- BCS: 5/5
- Lifestyle: indoor cat

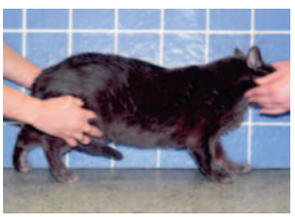
The owners acquired her at approximately 3 years of age and as that time she was already overweight. However, the problem has deteriorated since then. The cat has now decreased mobility, and inability to groom efficiently. She is a very lazy cat. She has a greasy coat, with coarseness to the hair on the caudo-dorsal body.

Weight loss summary



After: 5.5 kg





- Weight loss duration: 338 days
- Mean average loss: 0.75%/week
- Average allocation: 30 kcal/kg of target body weight
- Body fat: 31.3%
- BCS: 3/5

Since her weight loss, the cat can jump up and down off chairs. She follows the owners around the house throughout the day. Her ability to groom has improved. She looks better, her coat condition has improved. According to the owner, she looks definitely happier.

At this rate, the majority of tissue lost is body fat and no adverse metabolic effects were noted in 14 cats *(Center et al, 2000)*. Blood glucose and alkaline phosphatase significantly decreased between week 0 and week 18, but cholesterol, alanine aminotransferase and aspartate aminotransferase significantly increased. Nevertheless, absolute changes were small and within reference ranges for all the parameters except blood cholesterol concentrations. Nine cats developed hypercholesterolemia during the weight loss program *(Center et al, 2000)*; this effect was also observed in another study *(Szabo et al, 2000)*. Further, in a concomitant study *(Ibrahim et al, 2000)*, changes in cholesterol concentration were found to be due to increased production of high density lipoproteins (HDL). This study also demonstrated that blood cholesterol concentration could be reduced by a diet containing corn oil, thereby confirming that the type of dietary fat could influence lipoprotein metabolism in cats.

FIGURE 18 - RESTING ENERGY REQUIREMENTS IN CATS BEFORE AND AFTER WEIGHT LOSS

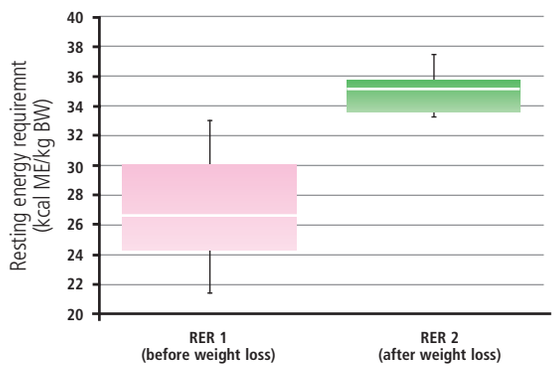


TABLE 7 - RER IN OBESE CATS BEFORE AND AFTER WEIGHT LOSS

	Obese state	After weight loss
Mean BMR (kcal ME/kg $BW^{0.65}$)	58	57
Min	39	49
Max	68	64

TABLE 8 - ENERGY REQUIREMENTS FOR LEAN AND OBESE CATS
according to NRC 2006

Equation	NRC 2006 recommendation
Lean cat (BW* = 4 kg)	100 kcal ME/kg $BW^{0.67}$ = 253 kcal ME/d *(i. e: ≈ 63 kcal/kg BW)*
Obese cat (BW* = 5 kg)	130 kcal ME/kg $BW^{0.4}$ = 247 kcal ME/d *(i. e: ≈ 50 kcal/kg BW)*
According to the experience of the authors, at a maintenance state, this energy allowance is too high for an obese cat who will maintain his body weight. The equation must be based on the ideal body weight and a 40% restriction is necessary to induce weight loss in a obese cat.	
Obese cat (IBW** = 4 kg)	0.6 x 100 kcal ME/kg $BW^{0.67}$ = 152 kcal ME/d *(i. e: ≈ 38 kcal/kg IBW)* 0.6 x 130 kcal ME/kg $BW^{0.4}$ = 136 kcal ME/d *(i. e: ≈ 34 kcal/kg IBW)*

* body weight **ideal body weight

ENERGY INTAKE RECOMMENDED FOR OBESE CATS

Body score	Daily caloric intake per kg of ideal body weight/day
3.5 or 4.0	30 kcal ME
4.5 or 5.0	35 kcal ME

► How do I determine the daily energy allocation to achieve weight loss

> Physiological consequences of energy restriction

Decrease in energy expenditure is a universal response to energy restriction in all species. This adaptation is a survival strategy to protect the organism when the central nervous system detects a state of starvation; therefore, when body weight decreases, BMR decreases. In humans, changes in BMR when in negative energy balance vary between -5% to -25% depending upon the level of energy restriction *(Prentice et al, 1991)*. Such reductions in BMR can make smooth and uniform weight loss difficult.

For humans, there are strong relationships both between the severity of energy restriction and the rate of weight loss, and also between energy restriction and suppression of resting metabolic rate. As a consequence, the greater the level of energy restriction applied, the greater the suppression of BMR. Hence, there may be a threshold below which the perceived advantages of rapid weight loss may, in the longer term, be counterbalanced by a more pronounced physiological defence against weight loss *(Prentice et al, 1991)*. Therefore, the decrease in metabolic rate can be counterbalanced by using either pharmacological approaches or by increasing physical activity.

> Optimum energy intake to achieve weight loss

A study has determined the level of energy intake required to achieve an expected rate of BW loss of 1 to 2% per week in 7 neutered obese cats *(Nguyen et al, 2002)*. In this study, energy expenditure was assessed by indirect calorimetry. The level of energy consumption during the weight loss period to obtain the desirable rate was 40 ± 2 kcal ME/kg ideal body weight e.g. approximately 66% of the energy requirement for an adult cat in optimal BW. Unexpectedly, resting energy requirement (RER) expressed as related to kg BW significantly increased whilst BW and body fat decreased. RER was measured during weight loss **(Figure 18)**. Cats lost 37± 3% of their initial body weight, and the rate of weight loss varied along the study from 0.1 to 3.0% per week and was never linear. Mean RER was 32 kcal ME/kg BW [min 21- max 39] but RER was significantly lower in the obese state (27 ± 2 kcal ME/kg BW) than after weight loss (35 ± 1 kcal ME/kg BW, p=0.028).

According to the current recommendations of the National Research Council (NRC 2006), an allometric coefficient was suggested to calculate the daily energy requirement for cats. The rela-

tionship between resting energy expenditure and body weight was best described with a coefficient of 0.65. When RER was expressed as kcal ME/kg $BW^{0.65}$, RER did not statistically differ between the obese and lean state, with a mean value of 58 kcal ME/kg $BW^{0.65}$ **(Table 7)**.

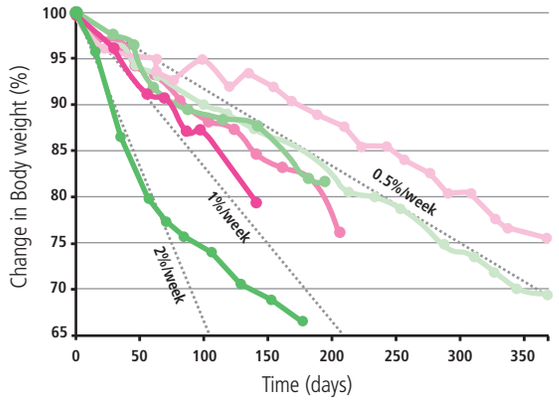
For weight loss, the level of daily energy intake must be adequate to cover the basal metabolic energy expenditure but not the total daily energy expenditure. In practice, the level of energy restriction should not be lower than BMR, e.g. 21 kcal ME/kg BW or 39 kcal ME/kg $BW^{0.65}$ as measured in experimental conditions. The initial energy allowance is estimated at about 60% of calculated energy requirement for the ideal body weight of the cat.

In general, weight loss will be faster at the start of the treatment and will decrease thereafter, but the physiologic response is quite unpredictable **(Figure 19)**. Therefore, it may be necessary to adjust energy intake frequently during the weight loss period to achieve optimal body fat loss and to decrease the risk of hepatic lipidosis and insulin resistance.

The initial allocation is only a starting point; during the weight loss program, the level of allocation has to be adapted to the rate of weight loss. This means a small (e.g. ~5%) reduction of the amount of food fed if the rate is too slow. Measuring cups are an unreliable method of measuring out food; instead, owners should be instructed to weigh the food on kitchen electronic scales which therefore enables small changes to be accurately made.

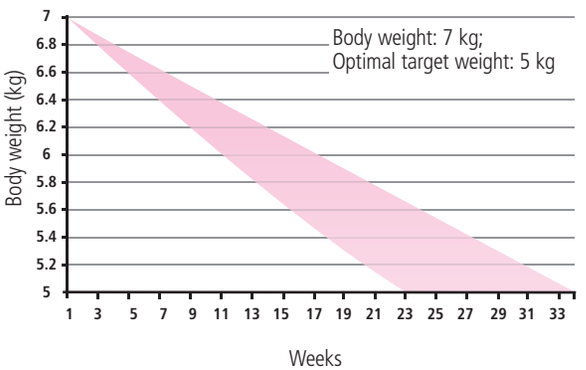
It is essential to ensure that, if possible, no additional food is given by the owner (or scavenged by the patient). Healthy treats may be allowed as this enables the owner to maintain their bond with the pet. This should, of course, be factored into the overall calorie provision and not on top of it. The caloric value of drinks (e.g. milk) must be also included as part of the overall plan.

FIGURE 19 - VARIOUS WEIGHT LOSS CURVES



In general, weight loss is faster at the start of the treatment decreases thereafter. It is necessary to adjust energy intake frequently during the weight loss period to achieve optimal body fat loss (adapted from German, et al, 2008, in press).

FIGURE 20 - DURATION OF THE WEIGHT LOSS PROGRAM FOR AN OBESE CAT



Slower weight loss is acceptable if the owners and clinicians agree with this approach.

TABLE 9 - DAILY AMOUNT OF FOOD ACCORDING TO THE TARGET BODY WEIGHT

Ideal body weight (kg)	Energy allocation (kcal ME/day)	Dry diet (g) (3000 kcal ME/kg)	Canned diet (g) (600 kcal ME/kg)	Dry + canned diets Dry (g)	Canned (g)
3	105	35	175	15	100
3.5	120	40	200	20	100
4	140	45	230	25	100
4.5	160	50	270	35	100
5	175	60	290	40	100
5.5	190	65	320	45	100
6	210	70	350	50	100

Energy allocation based on 35 kcal/kg of ideal body weight (body score ⩾ 4.5)

► How do I evaluate the duration of the weight loss?

Once the clinician knows the target body weight, an estimate of the likely duration of the regimen can be determined **(Figure 20)**. Such information has to be clearly explained to the owners, so that they are aware of the time commitment required for success.

► How do I estimate the daily food intake?

Calculation of the starting daily energy allocation is shown in **Table 8**. To ensure compliance of the nutritional treatment, the presentation must look like the usual food: dry food, wet food or a home made diet. More than 2/3 of owners prefer to mix dry and wet foods. It is essential that the exact portion size is accurately measured at each meal time **(Table 9)**. Their accuracy can be verified by weighing the first portion of the food at the clinic, and giving it to the owner to weigh on their own scales.

► How do I monitor the weight loss program?

It is essential to follow the progress of patients frequently during any weight management program, particularly during the initial period, when owners need the most support and when problems are most likely to be encountered. It also provides an opportunity to verify compliance, deal with any issues or concerns (e.g. excess begging behavior, problems with implementing play sessions), and to provide feedback, encouragement and support.

> Regular veterinary checks

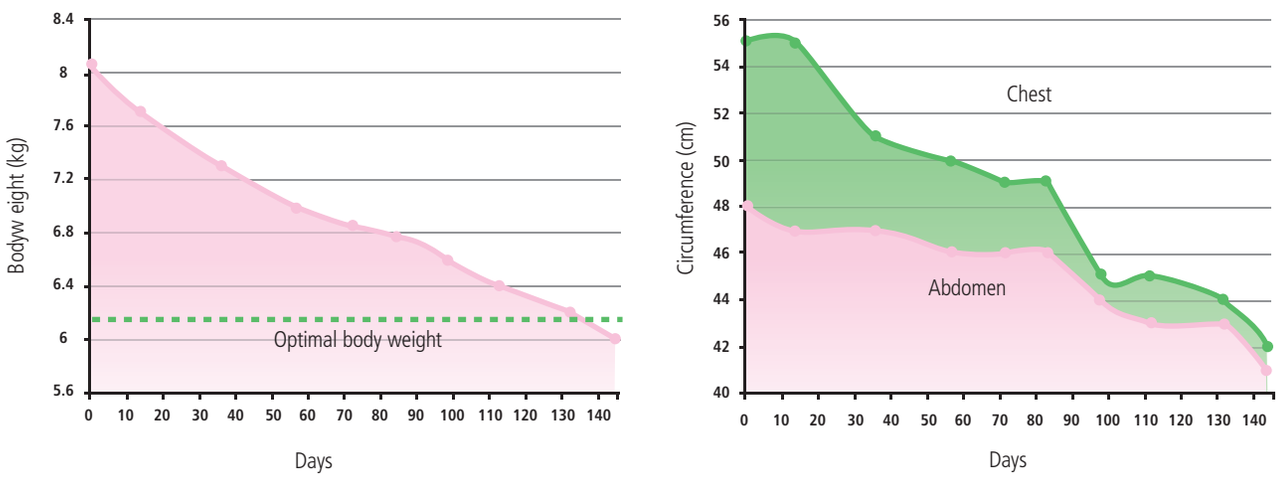
Owner motivation is the key to a successful outcome. Regular rechecks will help maintain compliance and owner motivation. A check every 2-4 weeks is recommended; if check-ups occur less frequently than every 4 weeks, compliance with the program will slip. It may also lead to a delay before a change is made, meaning that weight loss does not continue at an optimal rate.

> Measurement of the weight loss

At each check-up, the cat should be weighed and a physical examination performed. Owner perspective on progress should be gauged and any problems with the program discussed. If necessary, changes to the dietary plan can be made and any issues identified and resolved.

Body weight is the principal outcome measure of interest and used to decide upon whether changes to the plan are required (reduction in amount of food fed, increase in dose of medication). In order

FIGURE 21 - EVOLUTION OF BODY WEIGHT CHANGE VERSUS MORPHOMETRIC MEASUREMENTS
(Clinical Case n°1)



to minimize variability amongst measurement, the same set of electronic weigh scales should be used, and regularly validated. Owners must not be discouraged by the fact that 1% weight loss per week is not very much (e.g. 60g for a 6 kg cat).

The BCS chart can be used as a visual aid for leading discussion and providing owners with positive feedback. However, given that body condition is likely to change gradually, it is not essential to repeat the BCS at every visit.

Morphometric measurements are an additional means of monitoring outcome, and can be used to relay success in terms that the owner will understand (e.g. similar to a decrease in the size of the waist in people) **(Figure 21)**.

Periodic photographs provide an excellent visual demonstration of success, but should be taken in a standardized manner to enable comparison between time-points.

All measurements and comments should be recorded and used to provide positive feedback, wherever possible, for the owner. Veterinarians should also encourage owners to record daily food intake in a diary; this information can then be reviewed at each visit.

> Follow-up by phone

A first phone call within 48 hours after starting the regimen might be helpful to ensure the compliance of the owner. Then, regular calls from a technician responsible for overseeing the program, is an excellent means of checking on progress, enhancing compliance and addressing any problems as early as possible. The involvement of other members of the veterinary team is a good way to boost success and make owners appreciate the commitment of the practice.

► What should I do at the time of first reassessment?

Regular revisits are made to assess progress throughout the weight loss regimen. Having interim target weights (in addition to the final target) can help maintain the owner's motivation throughout the process. There are three possible scenarios at the time of the first weigh-in.

> Successful outcome

The cat loses weight at a normal rate and the owner is satisfied. One can then renew the regimen and fix the time of the next appointment.

> The cat did not lose weight or even worse, gained weight!

In this situation, it is necessary:
- to verify that the calculation of the daily amount of food is correct. If this is the case and there is no other possible explanation, a reduction (usually 5-10%) in food intake may be necessary.
- to re-evaluate family environment without making the owners feel guilty. How is the motivation of the owner? Are instructions clear enough? Are there any neighbors likely to feed the cat? Verify whether any non-compliance (e.g. feeding additional items) has occurred. If this is the case, it may not be necessary to alter the amount fed.
- to consider additional diagnostic investigations such as to examine for possible hormonal disorders. In cats, hyperprolactinemia and acromegaly are common and alter the ability of the cat to lose weight. Until recently, medical treatment has not been available to correct this situation.

9 - Composition of the diet

Reduction of energy intake is the cornerstone of any dietary intervention. There are many strategies to decrease the energy density of a diet:
- decrease the amount of fat
- increase the dietary fiber content
- increase the water content.

Figure 22 - From gross energy to net energy

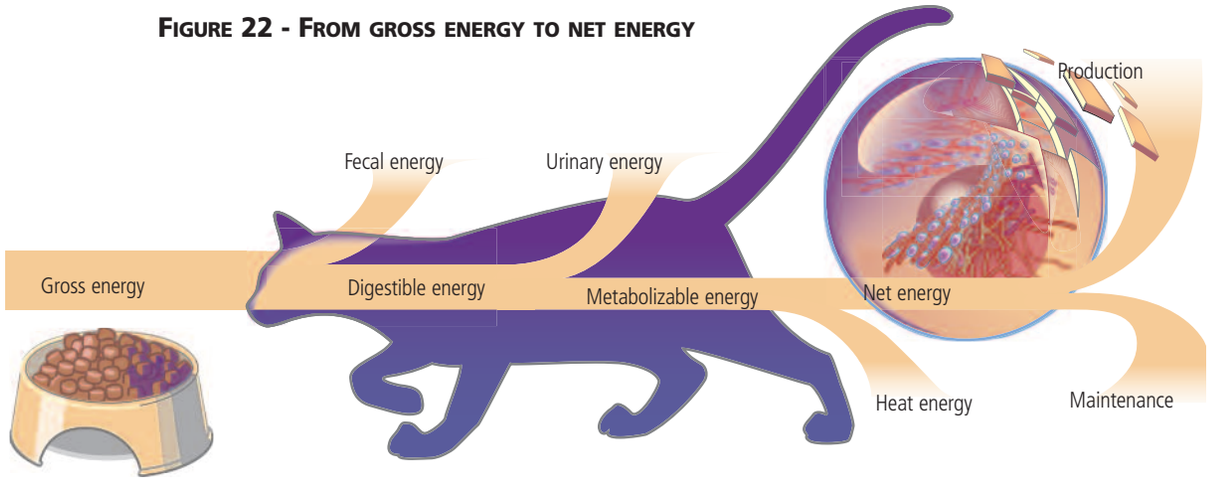
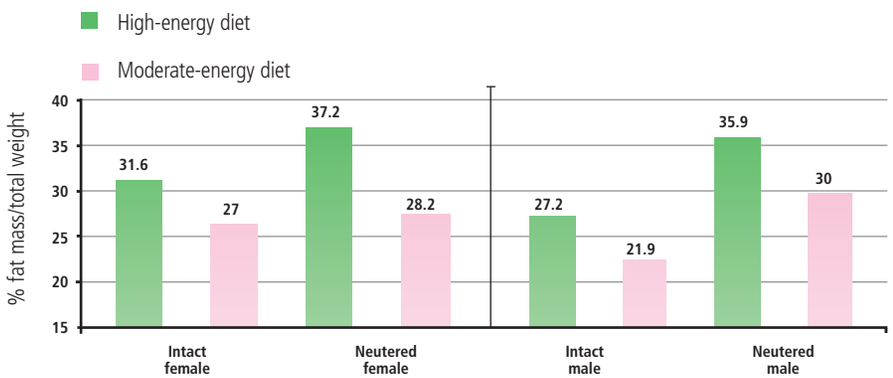


Figure 23 - Influence of sex and energy level of the diet on body fat mass of cats fed ad-libitum for one-year

(from Nguyen et al, 1999b)



The fat mass increases after neutering because the cat consumes more energy while expending less energy. The phenomenom is especially clear in males that consume a high-energy food. This type of food is not adapted to the needs of a neutered cat.

► Influence of energy density on energy consumption

Energy density refers to the amount of energy in a given amount of food. In practice, energy density is expressed as kcal of metabolizable energy per 100 g of food **(Figure 22)**. For the same amount of food, a lower quantity of energy is consumed when the diet has a low energy density.

In one study *(Lester et al, 1999)*, sedentary entire cats who had previously maintained body weight while consuming ad libitum moist meat-based diets with a constant fat content were able to adapt to a higher-fat meat-based diet by significantly increasing fat oxidation. In addition, along with the increased fat oxidation, the high fat diet did not show any hyperphagic effect. This study underlined the capacity of the cats to maintain their body weight on very high-fat diets in certain conditions. However, the situation is different in neutered animals living indoor and fed ad libitum with very palatable dry food **(Figure 23)**.

In these circumstances, feeding low fat dry foods lowers the risk of obesity. In cats, food consumption tends to remain constant and is independent of the calorie content of the food; thus the mass or volume of food consumed appears to be the main factor implicated in the regulation of

body weight *(Rolls et al, 2005)*. This suggests that gastric distension is one of the main factors driving satiety in this species. A recent study by one of the authors confirmed that cats tend to eat the same amount of food whatever the energy density of the diet *(Martin et al, 2008)*. Two commercial diets with different levels of energy (diet A: 360 kcal/100g; diet B 415 kcal/100g) were offered to two groups of cats for five weeks (cross-over study). Mean food intake did not differ on the two diets (58±2 g/d/cat with A and 56±2 g/d/cat with B) but the energy intake did vary (44±2 kcal/kg/d for A and 50±2 kcal/kg/d for B). These findings are confirmed by studies which have shown that cats fed high fat dry foods ad libitum are more likely to be obese *(Scarlett et al, 1994)*.

One advantage of feeding a hypoenergetic food to cats undergoing weight loss, is that the volume of food fed is closer to the volume of a maintenance diet fed at maintenance. This can help to improve owner compliance. For example **(Table 9)**, assuming that the same daily energy contribution is required (140 kcal ME); whilst on the weight loss diet the cat will consume 45 g of food per day, which is close to that of cat feed a standard ration at maintenance (50 g). In this example, the cat does not risk a deficiency and has an adequate amount of food per day.

► Diet formulation

The main factor that drives weight loss is the level of dietary energy fed, but it should be remembered that diet also provides many essential nutrients. Supplementation of such nutrients (relative to energy content) is usually recommended to prevent deficiency diseases from arising during weight loss. Whatever diet is chosen, the veterinarian has a duty to ensure that the diet is complete and well-balanced.

An additional characteristic of a weight loss diet is palatability since this will maximize compliance with treatment. Thus, there are many factors that must be taken into account when considering the most appropriate meal composition for a cat undergoing weight loss.

> Decreased amount of fat

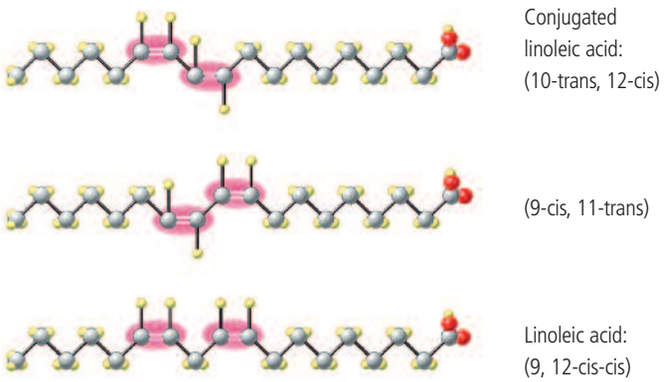
Fat has a high energy content (9 kcal ME/g) compared to protein and carbohydrates (4 kcal ME/g). Hence, low energy density diets tend to be low fat diets. *Bauer* (2006) has recommended a new classification for dietary lipids.

- A facilitative fat is a saturated fat that increases energy density of the food; it can be stored in adipose tissue for future use, improves palatability and acceptability of the food and promotes fat-soluble vitamins absorption. To decrease energy density, facilitative fats should be limited in the foods.
- Functional fats are usually polyunsaturated fatty acids. They are involved in many biological processes such as growth, reproduction, hormonal synthesis, inflammation and gastrointestinal, skin or brain health. Essential fatty acids must be obligatory found in foods but only small amounts are needed to meet the nutritional requirements.

Cats fed a low fat (9.2% DMB), high protein (33.5% DMB), low fiber diet lose weight safely *(Bouchard et al, 1998)* without signs of hepatic lipidosis or of any deterioration of skin and coat condition.

Minimum fat content of diets designed for obese cats should focus on essential fatty acids. A low fat diet should provide 0.14 g $BW^{0.67}$ linoleic acid (LA) and 0.0005 g $BW^{0.67}$ arachidonic acid (ARA) to meet the maintenance fatty acid requirement of cats *(NRC 2006)*. If we take the example of an obese cat (BW = 6.0 kg, target weight = 4.5 kg), the recommended allowance would be 0.46 g and 0.0016 g for LA and for ARA, respectively. This would correspond to a concentration of

FIGURE 24 - 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.

5.6 g LA/1000 kcal ME and 0.02 g ARA/1000 kcal ME (These values take into account the fact that the cat may be subjected to a 50% reduction of energy intake.)

Recently, many researchers have focused on the effect of conjugated linoleic acid (CLA) **(Figure 24)** in obesity *(Nagao and Yanagita, 2005)*, because some animal studies have shown promising effects on body weight and fat deposition. The theoretical benefits of CLA are said to include decreased energy and food intake, increased energy expenditure, decreased pre-adipocyte differentiation and proliferation, decreased lipogenesis, and increased lipolysis and fat oxidation. However, recent work in cats has suggested that incorporation of CLA in weight loss diets has no significant effect *(Leray et al, 2006)*.

Obese cats fed high fat diets may present with hyperlipidemia and moderate elevation in serum triglycerides and cholesterol concentrations *(Ginzinger et al, 1997)*. The use of fish oil in the treatment of hyperlipidemia has been extensively studied in a number of other species (see chapter 6). Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are long-chain omega-3 fatty acids found in fish oil and they are known to decrease the serum concentration of free fatty acids *(Singer et al, 1990)*. A diet high in long-chain omega-3 fatty acids was shown to improve the long-term control of glycemia and lower plasma insulin levels *(Wilkins et al, 2004)*.

> Increased dietary fiber

Fiber is defined as plant components that are resistant to degradation by mammalian digestive enzymes, especially amylase. Indigestible carbohydrates reach the colon and become an available substrate for bacterial fermentation. Substrates for bacterial fermentation mainly include structural polysaccharides (hemicellulose) and non-structural polysaccharides (gums, mucilages) but also resistant starch. Cellulose and pectins are not very good substrates for bacteria in the GIT of cats.

The current classification of dietary fiber is based on their physicochemical properties and their ability to undergo bacterial fermentation. Fermentable fibers yield increased hydrogen, carbon dioxide, ammonia and short chain fatty acids (SCFA). These final end products are of particular interest as they can interact with the host in a variety of ways and are involved in many metabolic processes when reaching the liver or the peripheral blood. Physiological properties include promotion of colonocyte differentiation and proliferation, stimulation of sodium and water reabsorption, inhibition of pathogenic bacterial growth, enhancement of colonic blood flow and colonic longitudinal smooth muscle contraction. As in other species, SCFA concentrations in the feline colon depend on the type of fiber found in the diet *(Sunvold et al, 1995a; 1955b; 1995c)*.

In vitro fermentation techniques using feline colonic bacteria have shown that the greatest total SCFA production occurs when fibers such as locust bean gum, guar gum, and citrus pectin are used, while fibers such as cellulose, gum karaya, or xanthan gum result in production of lower concentrations of SCFA. However, in cats, fibers yielding the largest amount of SCFA produced gastrointestinal side effects, such as increased fecal output and diarrhea *(Sunvold et al, 1995a)*. Beet pulp, which is a fiber source containing a mixture of soluble and insoluble fibers, has been suggested to be a source of choice for cats to optimize both SCFA production and fecal consistency *(Sunvold et al, 1995a)*. Nevertheless, studies on cats are scarce.

High dietary fiber (DF) content allows caloric dilution of the diet which helps to produce a satiety effect and to control body weight in obese cats. Nevertheless, high fiber diets may have unpleasant side effects for owners, such as excessive defecation and/or constipation *(Bouchard et al, 1998)*. When formulating a high fiber diet, the potential impact on nutrient digestibility has also to be considered. However, in practice, no negative impact has been reported with most of the hypoenergetic diets containing large amounts of DF. If high fiber diets present a poor apparent digestibility of the proteins *(Fekete et al, 2001)*, this effect is due to the nitrogen retention by the bacterial flora: excreted biomass increases with the fiber. Apparent and ileal protein digestibility must not be confused.

In deciding on a level of DF to include, it is also necessary to consider the taste preferences of cats. *Houpt & Smith* (1981) noted that cats disliked dilution of their food with a non-caloric solid such as kaolin or cellulose. In practice, according to our clinical experience, high-fiber veterinary foods for obese cats are well tolerated, and for the majority of the animals there is no problem with acceptance.

> Water content

The natural diet of a cat contains about 70-80% water. In addition, high dietary water content can decrease energy intake even on a high fat diet *(Rolls et al, 2005)*. Therefore, using an increased water content to reduce dietary energy density may be a particularly useful method for cats. The amount of food offered with a canned food (about 20% of dry matter) is about three to six times higher than the amount offered with a dry food (90% dry matter) for an equal daily energy allowance **(Table 10)**. It is of particular interest for cats that usually ingest large amount of dry food because the size of the meal could be the main regulator of food intake.

> Avoiding protein deficiency

Given that cats are obligate carnivores, a high level of dietary protein is essential; in wild cats, daily energy is supplied by protein and fat, whilst carbohydrates are not consumed. Nitrogen metabolism is very specific in cats, as hepatic enzymes involved in nitrogen catabolism are not adaptive. Dietary protein provides essential amino acids for protein synthesis and non-essential amino acids as energy substrates. If the amount of protein in the diet is insufficient, the result is loss of lean body mass which can then diminish the body's ability to respond to infectious agents and stress.

TABLE 10 - AMOUNT OF FOOD OFFERED WITH A COMMERCIAL OBESITY DRY FOOD AND A COMMERCIAL OBESITY CANNED FOOD

Commercial obesity dry food	Commercial obesity canned food
Energy density: 300 kcal/100 g	Energy density: 60 kcal/100 g
Obese cat: body score: 4; ideal body weight (IBW): 5 kg Energy allocation: 30 kcal/kg IBW: 30 x 5 = 150 kcal/day	
Amount 1 ≈ 50 g/d	Amount 2 ≈ 250 g/d

TABLE 11 - ESSENTIAL NUTRIENTS FOR CATS
(from NRC 2006)

	Minimum requirement (g/1000 kcal ME)	Adequate intake (g/1000 kcal ME)	Recommended allowance (g/1000 kcal ME)
Protein	40 (3.97 $BW^{0.67}$)	-	50 (4.96 $BW^{0.67}$)
Fat	-	22.5	22.5
Calcium	0.4	-	22.5
Phosphorus	0.35	-	0.64
Magnesium (mg)	50	-	-
Potassium	-	1.3	-
Taurine	0.08	-	0.1

According to the current NRC requirements (2006), the recommended allowance maintenance requirement of protein for an adult cat is 4.96g crude protein (CP)/ $BW^{0.67}$ **(Table 11)**. Since maintenance protein requirements are expected to be the same in obese adult cats, the protein level of the diet should be supplemented. For example, an obese cat (BW = 6.0kg, target weight = 4.5kg) has a recommended daily protein allowance of 16.5 g CP and should be fed approximately 162 kcal ME/day to achieve weight loss. For a hypoenergetic diet to provide enough protein, it should contain almost 100g CP/1000 kcal ME. Diets with CP concentration less than 85 g CP/1000 kcal ME are not adequate to satisfactorily cover the feline requirement. However, if severe energy restriction is required to induce and maintain weight loss (far lower than expected), even diets supplemented with protein to 100g CP/1000 ME may be deficient.

The reduced energy density of weight loss diets, related to reduced fat content and high fiber and/or water content, can have a negative impact on palatability. Animal proteins are generally considered as attractive for cats. Therefore, providing a diet which is rich in proteins of animal origin may help in maintaining palatability of low energy (low fat) diets.

One potential concern with feeding a high protein diet is that it may be deleterious for health, especially in older animals. In this respect, some clinicians are concerned with a possible negative impact on pre-existing chronic kidney disease (CKD). However, there is no evidence that supports a link between high protein intake and the development of CKD in dogs and cats. Further, the diets are only supplemented in protein relative to energy content, so that when feeding on a weight loss regime, total protein intake is not actually increased.

Two groups of 8 cats were fed two diets designed for weight loss (1% of initial BW per week) *(Laflamme & Hannah, 2005)*; one group received a diet where 46% calories were derived from protein (76 g CP/1000 kcal ME) and the second group received a diet where 36% calories were derived from protein (60 g CP/1000 kcal ME). During the study, mean energy intake did not differ between the two groups and, neither rate of weight loss or total weight loss differed. However, changes in body composition were observed. Loss of body fat was increased ($p<0.001$), and loss of lean tissue was reduced ($p<0.001$) in the high protein group.

In the context of weight loss "high protein diet" does not actually mean increased protein intake, but simply maintaining normal intake whilst energy content is reduced.

> Carbohydrates

Carbohydrates are not essential for cats since this species has specific metabolic adaptations for low carbohydrate intake. Moreover, high dietary carbohydrate content may decrease apparent protein digestibility *(Kienzle, 1994)*. Whilst a limited amount of carbohydrate has no detrimental effect on weight loss in cats, increasing carbohydrate content of a feline weight loss diet may not be beneficial. High carbohydrate diets (> 25% of calories) are not recommended in obese cats as they are commonly insulin-resistant (see chapter 5).

> L-Carnitine

Supplementing a weight loss diet with L-carnitine has been shown to be beneficial in a number of species, including cats. L-carnitine is synthesized in the liver and absorbed in the digestive tract, and is an essential co-factor for lipid oxidation *(Steiber et al, 2004)*. In brief, L-carnitine assists in the transportation of long-chain fatty acids into the mitochondria in various tissues including the liver, the heart and skeletal muscle. It also facilitates α-keto acid oxidation and influences urea cycle function. Stimulation of fatty acid oxidation is beneficial during weight loss, because fatty acid oxidation can affect feeding behavior *(Ronnett et al, 2005)*. In this respect, inhibition of fatty acid oxidation stimulates food intake in animals fed a high fat diet (40% of ME as fat), but is ineffective when fed a low fat diet (7% of ME as fat). Thus, maintaining fatty acid oxidation, by supplementation of L-carnitine, may contribute to the regulation of energy balance and metabolic

homeostasis and has an effect on appetite control. In cats, supplementation with L-carnitine has been shown to have a positive effect on weight loss and fatty acid oxidation *(Center et al, 2000; Ibrahim et al, 2003)*. L-carnitine administered at 250 mg PO q12h in cats is safe and has a significant effect on the rate of weight loss in some studies *(Center et al, 2000)*. As this dose is very high and out of economical consideration in petfood, further studies using L-carnitine at a more practical dose are required.

> Antioxidants

An increase in insulin secretion, plasma free fatty acids or plasma glucose leads to an increase in reactive oxygen species (ROS) production and oxidative stress. Moreover, many studies have demonstrated that oxidative stress is associated in both the etiology and complications of diabetes. Many studies conducted *in vitro* or in animal models have shown that antioxidants (mainly α-lipoic acid, vitamin C, vitamin E, glutathione, N-acetyl-L-cysteine, aminoguanine, zinc) improve insulin sensitivity *(Evans et al, 2003)*.

Recently, studies have focused on the benefit of α-lipoic acid on glucose uptake and this antioxidant shows promising results in the prevention and treatment of diabetes mellitus in humans *(Çakatay, 2006)*. Daily dosage ranges in humans were from 600 mg to 1800 mg IV or oral with few to no side effects (*Head, 2006)*. Alpha-lipoic acid is considered safe in humans. Nevertheless, a study in cats *(Hill et al, 2004)* described acute toxicity of α-lipoic acid at a dose of 30 mg/kg. Currently, the maximum tolerated dose (MTD) of LA in cats remains unknown. Additional studies are needed to evaluate the effectiveness of antioxidant treatment in obesity and related diseases and to determine MTD in cats.

Conclusion

It is relatively easy to diagnose obesity in a cat and to prescribe a diet. The challenge lies in convincing the owner to introduce the necessary changes in the feeding and lifestyle of the animal in order to induce and maintain significant weight loss. Every suggested change runs the risk of provoking resistance from the cat-owner system. In order for the weight reduction program to be effective, the owner has to have adequate motivation. To develop this motivation, it is certainly appropriate to use a stage by stage approach and remember that each stage is a stepping stone. Omitting one or more stages will be detrimental to the process.

At the time of every consultation, it is necessary for the veterinarian to recognize where the owner is in relation to these phases. By doing so, he can adjust the arguments used in conversation and can alter recommended treatment approaches in response to the attitude of the client. It is also important to be prepared for resistance on the part of the owner, which can be expressed as doubts and reluctance to comply with the proposed solutions, and to be able to respond appropriately. It may be beneficial to undergo some form of training in order to acquire the ability to motivate clients.

To avoid any nutritional deficit during a weight loss program, specific foods have been formulated. The composition of such diets takes into account the energy restriction such that the relative concentration of nutrients is increased. Therefore, despite the imposed energy restriction, cats on a weight loss program should eat a daily amount of all nutrients (other than fat) which is similar to that of cats fed at maintenance. Therefore, to make a food with a reduced energy value reduce the quantity of the total fat content, increase water and/or fiber and provide enough of the essential nutrients (amino-acids, essential fatty acids, minerals and vitamins) to prevent any deficiency.

Frequently asked questions on feline obesity

Q	A
How do I adapt the cat to the diet?	A weight loss program involves modifying the composition of food (hypoenergetic and high protein) and controlling the quantity of food offered on a daily basis. Since satiety depends primarily on the quantities consumed, many cats have difficulties in consuming a reduced amount of food. Therefore, for some cats it may be necessary to acclimatize them to the reduced intake and new food. In this respect, a ~7-day period of gradual change is usually successful. If a cat refuses a particular food, it may be possible to improve acceptance by temporarily adding a small amount of the previous diet. Alternatively, a different formulation (moist diet) of weight loss diet could be chosen or a home-made devised.
Are there any alternatives to commercial weight loss diets?	It is feasible to develop a home-prepared weight loss diet for cats which is balanced and meets NRC requirements. However, it is the veterinarians duty to advise on such rations and to ensure that the chosen recipe meets nutritional requirements.
Some owners would prefer not to change the food of their cat to avoid behavioral issues or because their cat is a very capricious eater: should this attitude be encouraged?	A maintenance diet meets all nutritional needs when energy requirement is "normal". In the case of a non obese cat weighing 3.5 kg at maintenance, the daily protein contribution will be 16.2 g, 0.4 g of phosphorus and calcium, and 26 mg of taurine. For an obese cat with a target weight of 3.5 kg, the energy restriction imposes an allowance of 126 (36 kcal/kg IBW x 3.5kg) kcal ME per day, instead of 210 kcal ME for maintenance (60 kcal/kg IBW x 3.5 kg). If the same food is fed, the cat will consume 9.4 g of protein per day, 0.2 g of phosphorus and calcium, 15 mg of taurine. Since these amounts are lower than the recommended daily allowance for a cat *(NRC, 2006)*, feeding such a diet over a prolonged period could lead to deficiencies, in particular with regard to nitrogen balance. Moreover, in order to enable such a low level of energy to be consumed, the daily allocation will need to be only 30 g! Most owners would struggle to accept such a proposal. Hence, using a standard maintenance diet is an inappropriate means of treating obesity during a weight loss program. Although concerns over diet palatability are a reason frequently cited by owners for not implementing a weight loss program, lack of diet palatability is rarely a problem for most of the commercial diets on the market if introduced gradually.
How do I manage obesity for a cat in a multi-pet household?  © Lucile Martin	Whilst it is difficult enough to instigate an effective weight reduction plan in a cat living alone, multi-cat households represent a particular challenge. One option would be to feed all cats the same (e.g. weight reduction) diet. However, it is likely that group-feeding was one of the factors that allowed the obese cat (s) to become overweight in the first place; in this respect, if food is left out for all cats to share, the tendency is that greedy cats over-eat at the expense of cats with better appetite control. Therefore, in order for an owner to guarantee that all cats maintain their body weight excess food must be left out allowing some of the cats to over-eat. Thus, the only solution is to instigate individual feeding plans for each cat. This can be done in the following ways: - feed the cats in separate rooms or locations - feed the cats in the same locality but supervise them at all times and pick up feed bowls as soon as each cat stops eating - feed cats at different times - put the food for the cat (s) in normal body condition is a location where the obese cat (s) cannot reach. For instance, food could be placed in an elevated position if the obese cat is unable to climb; alternatively, the food could be placed in a box with an opening that only the normal cats can fit through.

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Focus on:

L-carnitine

Obesity definition and origins

L-carnitine (sometimes know as vitamin B_T) is a water-soluble substance derived from two amino acids, lysine and methionine. It is synthesized in the liver in cats. L-carnitine has a role in energy production in cells.

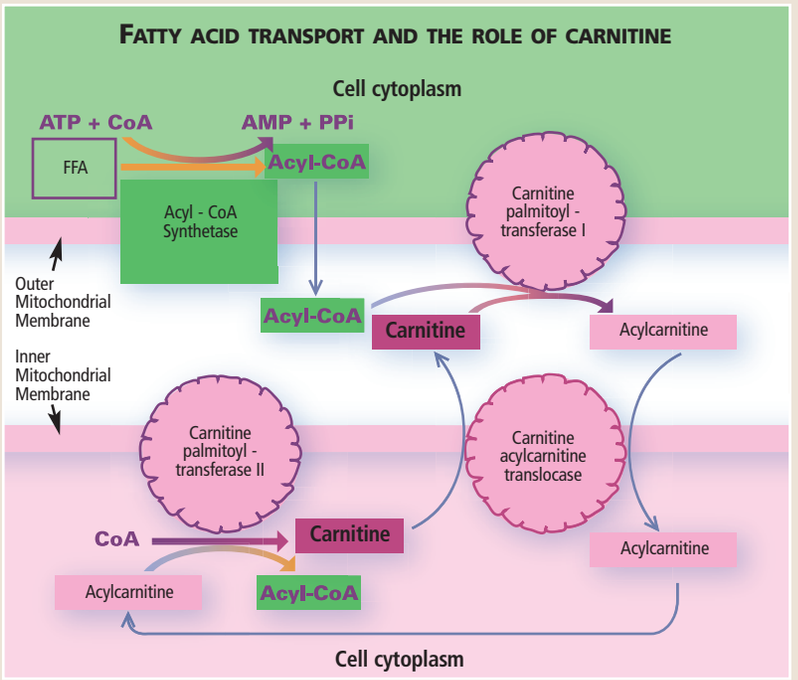
Dietary sources with the highest content include meat products (50 mg/100 g in beef and 200 mg/100 g in lamb).

Formula

Carnitine exists in two spatial forms – D and L, but only the L form is biologically active. The D form tends to inhibit the action of the L form.

Biological role

L-carnitine is essential to the molecular system that transports long-chain fatty acids inside the mitochondria, where they are oxidized to produce energy.



Benefits of L-carnitine in preventing and treating obesity in cats

In obese cats, supplementation of L-carnitine (250 mg PO/12h), combined with a restricted caloric intake (36 kcal/kg of target weight) helped to accelerate weight loss *(Center et al, 2000)*. Cats receiving L-carnitine lost weight faster than cats in the control group: 23.7% in 18 weeks (1.3% per week) compared with 19.6% in the control group (1.0%/week).

Another study examined the potential role of L-carnitine in fat metabolism during the induction of hepatic lipidosis *(Blanchard et al, 2002)*. Spayed female cats received 40 mg/kg of L-carnitine per kg of food (control group) or 1000 mg/kg (study group). The concentration of L-carnitine increased significantly in the plasma, muscles and liver of cats in the study group. In addition, these cats exhibited better protection against the risk of hepatic lipidosis during fasting following obesity. Therefore, L-carnitine has a favorable impact on hepatic metabolism of obese cats.

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© Yves Lanceau (British shorthair)

Obesity is not generally a reason for the consultation, but rather something that is found during the consultation. Many owners do not want to know that their animal is obese, especially when the owner is also overweight. It can be very difficult to convince owners to maintain the animal's diet if there are no clear visible signs that the cat is losing weight.

Success factors of a weight loss diet for cats

Owner motivation

This is essential. The veterinarian has a very important role to play in convincing owners of the validity of a weight loss diet for overweight cats.

Recommended methods for motivating owners include:
- Getting them to palpate the cat, so they are aware of the fat deposits
- Putting the cat's excess weight into human terms (in equivalent weight); e.g. a cat that is 40% overweight is the same as a 165-pound man actually weighing over 230 pounds!
- Providing information on the following:
  - the health problems caused by excess weight
  - the benefits of a diet in terms of mobility and coat, etc.
  - the importance of the owner's involvement in the success of the animal's diet

NUTRITIONAL PLAN FOR:		
Name of the cat:	Neutered: ☐	Intact: ☐
Age:	Male: ☐	Female: ☐
Date:	Current weight:	

It can be very difficult to convince owners to maintain the animal's diet if there are no clearly visible signs that it is losing weight.

Your cat is overweight
Target body weight:
New diet recommended:

The choice of food and how it is given

Caloric intake will have to be reduced, but there are rules that need to be followed.

- **USE ONLY low energy food in the diet**

Reducing the daily ration of the typical daily diet will lead to deficiency of essential nutrients such as proteins, vitamins and minerals. This will result in negative consequences: muscle atrophy, poor quality skin and coat, weakening of immune defenses etc.

Furthermore, the choice of a specific food makes it possible to provide adequate meal volume and prevent the cat from developing undesirable behavior, such as agitation, incessant meowing or stealing food.

- **DO NOT feed the cat leftovers**

- **WEIGH the daily ration precisely**

Regularly weighing the daily ration is recommended, always with the same scales. Relying on volume measurements (i.e. cups) can result in accuracies and predispose to overfeeding.

- **DIVIDE the daily ration**

Dividing the daily ration into several servings provided multiple time during the day increases the post-prandial thermogenesis and so increases energy expenditure. Furthermore, it also reduces the feeling of hunger provoked by once daily feeding.

Exercise

Everything that can stimulate the cat to move is potentially beneficial:

- look for games that the cat enjoys
- put the food bowl somewhere else or place the kibbles throughout the home to encourage the cat to move around

Monitoring

Poor follow-up is a major cause of failure. Regular clinical observation makes it very easy to adjust the daily intake to the physiology of the individual cat.

The ideal is to have the owner visit every two weeks to weigh the animal and check that weight loss is advancing at 1-2% per week. If the pace is too slow (< 1%) the results will not be seen and if it is too fast (> 3% per week) there will be a greater risk of relapse and more extensive muscle atrophy at the end of the diet.

It is highly unlikely that the cat will lose weight at the same pace throughout the duration of the diet. Visits every other week will provide an opportunity to adjust the diet and modify the ration based on how weight loss is progressing.

A summary of the results at the end of the consultation provides a convenient way to view how the situation is progressing and how much still has to be done. It is also important to encourage the owner to continue with the dietary therapy.

Initial body weight:			Target body weight:		
Date	**Actual body weight (kg)**	**Weight loss since the last visit (g)**	**Current diet**	**Daily food intake (g/day)**	**Exercise (0/+/++/+++)**

Practical pointers for implementing and monitoring a weight loss diet

Weight loss phase

1- Determine the target weight

The target weight is based on the body condition score (BCS) at the first visit.

The BCS enables the estimation of excess weight as a percentage of body weight (see table on the right).

For example a cat weighing 7.2 kg has a BCS of 5/5. Its excess weight is therefore 40% of its actual weight. The target weight is accordingly 7.2/1.4 = 5.14 kg.

Body condition score	Excess weight
3.0 (ideal body score)	0%
3.5	10%
4.0	20%
4.5	30%
5.0	40%

2- Calculate the caloric intake needed to produce weight loss

Based on the BCS and the ideal body weight, a number of kilocalories per kg of target weight is determined as follows.

Body condition score	Adviced caloric intake
3.5 or 4.0	30 kcal
4.5 or 5.0	35 kcal

This degree of caloric restriction is required to obtain a weight loss of 1-3% per week. For example, the energy needs of a cat with a target weight of 5.14 kg and a BCS 5/5 is 35 x 5.14 = 180 kcal/day.

3- Convert the calorie intake into a daily ration

The daily ration in grams corresponds to the calorie intake as calculated divided by the energy density of the food.

E.g. if the energy density of the diet is 3,500 kcal/kg, the daily ration is 180 kcal/3 500 = 0.051 kg or 51 g/day.

A mixture of dry and wet food is possible, provided precise quantities of each food are prescribed.

4 - Adjust the ration during subsequent visits

The ideal rate of weight loss is 1-2% per week. A diet is generally maintained for several months. Regular visits will provide opportunities to assess the suitability of the energy intake and adjust the pace of weight loss where necessary (if weight loss per week is > 3% or < 1%).

DIET TRANSITION PLAN

Previous diet
New diet

1st and 2nd days:

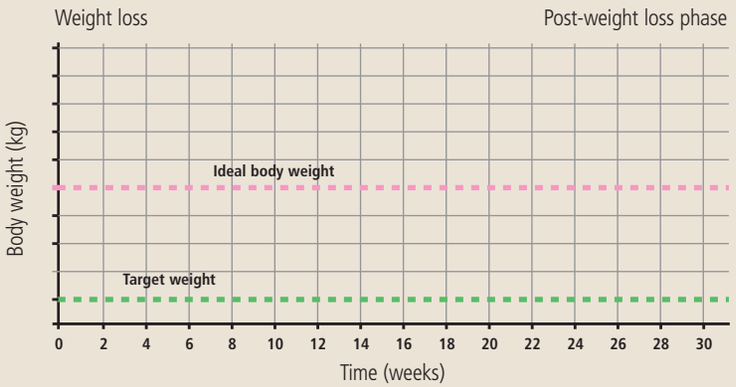
3rd and 4th days:

5th and 6th days:

Last day:

A food change is preferably made over a 10 day transition period.

BODY WEIGHT CURVE



Post-weight loss phase

Once the target weight is achieved, the cat enters the critical weight stabilization phase. Reverting to the cat's original diet without controlling its intake will lead to rapid weight gain (rebound effect), while the final objective of a weight loss diet must be to stabilize the cat's weight long-term.

Changing or keeping the food during the weight loss phase

Keeping the same food makes it easy to see the gradual increase in the ration.

Gradually increasing the daily energy intake

Daily caloric intake must be gradually increased to reach the level at which the optimal weight will be maintained. This is increased by 10% every two weeks.

The cat must be weighed regularly during this phase to verify that the new caloric intake is not causing the cat to gain weight.

Establishing the ultimate ration

Caloric intake should ideally correspond to the cat's maintenance energy requirement (MER), which is easy to find:

MER (kcal/day) = 55 x body weight (kg)

Most cats that are predisposed to obesity stabilize their weight at a level below the theoretical MER. Rather than reverting to the original food, the best option is to select a food that accounts for the animal's risk factors for obesity (e.g. especially, neutering).

Complete intake of all indispensable nutrients must be achieved when energy consumption is reduced.

Key points
to remember:

Formulating a food that facilitates weight loss in cats

A nutritional food formulated to produce weight loss must obviously be low in energy, but there are other imperatives that need to be addressed.

Nutritional balance adapted to reduced energy consumption

The concept of balance is key. All intake of indispensable nutrients must be envisaged with respect to low consumption. The concentrations of trace elements, vitamins, indispensable amino acids and essential fatty acids must be higher than those in a maintenance food.

When reduced fat intake is necessary, foods with the lowest fat content are not always most effective. More than the fat content, it is vital that the calorie intake is reduced. If the effect of reducing the fat content is also to reduce the energy density of the food, other means are possible to achieve this. These include increasing the fiber and/or the water content, and adapting the physical structure of the food to reduce its density.

Increasing the protein: calorie ratio compared with a maintenance food

During the restriction phase, any deficiency in essential amino acids must be avoided, while any loss of lean mass must be minimized. The protein level must therefore take account of the animal's lower food intake during the weight loss phase.

Conversely, too high a protein level is not advisable, as high-protein foods can easily induce overconsumption when rationing is not strictly observed.

L-carnitine supplementation

L-carnitine improves nitrogen retention and modifies the body mass in favor of lean mass. In obese animals, limiting the risk of the rebound effect is recommended after the weight loss diet.

Consideration for skin and joint diseases associated with obesity

A weight loss diet generally extends over many months, during which time it is important to consider the cat's general health. Diabetes, joint impairment and poor coat maintenance are the principal risks associated with obesity, so the nutritional approach must take them into account. The available responses include:

- reducing assimilable carbohydrate content and selecting a starch source with a low glycemic index (to reduce the development of insulin resistance)
- incorporating substances like glycosaminoglycans (chondroitin sulfate and glucosamine) to fight premature wear on joint cartilage in overweight animals
- strengthening nutritional intakes of key nutrients vital for optimal skin and hair coat (essential fatty acids, copper, zinc, vitamin A, etc.)

Dietary strategies to promote the sense of satiety in cats

Obesity introduction

Many low-calorie cat foods designed for weight loss diets are available in the veterinary market.

Unfortunately, these products are not always as successful as the manufacturers hope. The main problem is that the restricted intake changes the cat's behavior. Begging, constant meowing and even aggression may prompt owners to increase the ration, which compromises the success of the diet. The solution is to use a nutritional food that quickly provokes a feeling of satiety in the cat, thus reducing the chances that it will demand more food while keeping to the recommended ration. The aim of this study was to test different dietary strategies for promoting the sense of satiety in cats (reducing food volume and/or energy intake).

Materials and methods

The study was conducted on 16 adult cats of normal weight living in a cattery. These cats had always been fed with dry food. Four different dry foods were assessed in turn:

- a control food (protein: 41%; fat: 10%; TDF: 16%; metabolizable energy (ME): 3200 kcal/kg)

- a similar food but containing fiber with high water binding capacity (HWBC) (ME: 3115 kcal/kg)

- a high-protein food (HP) (protein: 46%; fat: 10%; TDF: 10%; ME: 3365 kcal/kg)

- a moderately high protein food (MHP) (protein: 36%, fat: 10%; TDF: 21%; ME: 3090 kcal/kg).

Four groups of 4 cats consumed these foods for 4 weeks, based on a Latin square protocol. After a 2-day transition, consumption was monitored for 5 days. The cats were fed ad libitum between 2 pm and 8 am next day (18 hours' food availability) with continuous access to water. Each cat was allocated its own bowl, access to which was controlled by means of an electronic collar. The criteria for assessing satiety were: total consumption (ingested energy: kcal/kg weight/day), satiety during feeding (size of meal: g/meal) and inter-meal satiety (time interval between two meals after consumption of at least 1 kcal during the preceding meal (min: sec/1 kcal). The data were expressed as mean ± standard deviation.

Results

The cats consumed all the food. The results are shown in the table below.

Conclusion

Very little information is available on cats (based on rigorously controlled studies). This study was able to demonstrate a "satiety effect" of different nutritional formulations based on the dietary behavior observed (energy consumed, meal size and interval between meals). Contrary to the findings in humans and dogs, high protein content is linked to increased consumption. Restricting protein content (by substituting protein for fiber) is therefore an original strategy for limiting spontaneous food ingestion. The nature of the fiber is important. Insoluble fiber with high water binding capacity has a satiety effect on the stomach.

These observations have been confirmed by recent clinical studies. In the future, they should serve as a basis in the formulation of foods for treating obesity in cats.

Reference

Servet E, Soulard Y, Venet C, et al. Evaluation of diets for their ability to generate "satiety" in cats. J Vet Intern Med *2008; 22: in press.*

Criteria	Control	HWBC	MHP	HP
Energy intake (kcal/kg weight/day)	43.8 ± 5.9^{ab}	41.9 ± 5.4^{a}	39.6 ± 6.3^{a}	48.9 ± 6.3^{b}
Size of meal (g/meal)	6.5 ± 1.5^{ab}	7.3 ± 1.8^{bc}	6.1 ± 1.3^{a}	7.7 ± 2.1^{c}
Interval between 2 meals (min: sec/1 kcal)	07'11" ^{ab}	10'08" ^{c}	09'32" ^{bc}	05'43" ^{a}

The different letters signify that the data are significantly different ($p<0.05$).

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Nutritional dermatoses and the contribution of dietetics in dermatology

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ABBREVIATIONS USED IN THIS CHAPTER

DGLA: dihomo-gamma-linolenic acid
DHA: docosahexaenoic acid
EPA: eicosapentaenoic acid
IgE: immunoglobulin E
ME: metabolizable energy
PUFA: polyunsaturated fatty acid
TEWL: transepidermal water loss

Nutritional dermatoses and the contribution of dietetics in dermatology

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The skin is a major organ with many different functions. Obviously, it is important for social interactions, giving each individual its characteristic appearance. It also serves as a barrier to maintain a stable internal environment. The skin plays a major role in the immune response to external factors, but also has a distinctive role in metabolism, sensory perception and temperature regulation amongst others. An imbalanced intake of nutrients such as amino acids, fatty acids, vitamins or trace elements disrupts the barrier function and the immune protection provided by the skin. The cat may become more sensitive to infection and may develop allergic reactions more easily. Skin and coat are a mirror of a cat's health and the quality of its food. Nutrition has a special place in feline dermatology, not only as an essential factor in the prevention of skin diseases, but also as a therapy for allergies and metabolic dermatopathies.

1 - Risk factors

► Breed specificities

In contrast to dogs where several skin conditions can be directly related to nutrition, there is little evidence of a link between a breed, nutrient and a specific disease in the feline literature. However, the Siamese seems to have an increased tendency to food allergy (see section on "Dietary hypersensitivities").

► Color of the coat

The color of a cat is a complex feature and influenced by genetics, environment (temperature, UV intensity and humidity all alter the coat's color by degrading the pigmentation) and nutrition (many nutrients play a role in pigment production).

The selection of colors in pure breed cats has become a specialist's hobby. Pigmentation is linked to the distribution of melanin in the hair shaft. Eumelanin (black to brown) and pheomelanin (red to yellow) combine to form the various shades of a cat's coat. The likelihood to produce eumelanin or pheomelanin is genetically determined but the enzyme which catalyzes the conversion from tyrosine can be a limiting factor. Pigment synthesis in the melanocytes depends on the supply of specific amino acids:
- phenylalanine and tyrosine are melanin precursors **(Figure 1)**
- cysteine is needed for the production of pheomelanin. It contains a high proportion of sulphur.

A dietary deficiency in tyrosine (or its precursor, phenylalanine) has been shown to induce a reddish change in the black hair of cats **(Figure 2)**. Similarly the deep orange colored cats turned pale orange when experimentally fed a diet lacking tyrosine *(Yu et al, 2001)*.

According to the *National Research Council (NRC)* 2006, the adequate intake for an adult cat corresponds to 0.38 g of phenylalanine and tyrosine per kg of metabolic weight i.e. a level of 3.83 g per 1000 kcal of metabolizable energy (ME). In a 4000 kcal ME/kg diet, it represents a minimum level of 15.3 g/kg of dry matter. To maximize black hair color, an equal quantity or greater of tyrosine to that of phenylalanine is required *(NRC, 2006)*.

FIGURE 1 - SYNTHESIS OF MELANIN FROM PHENYLALANINE

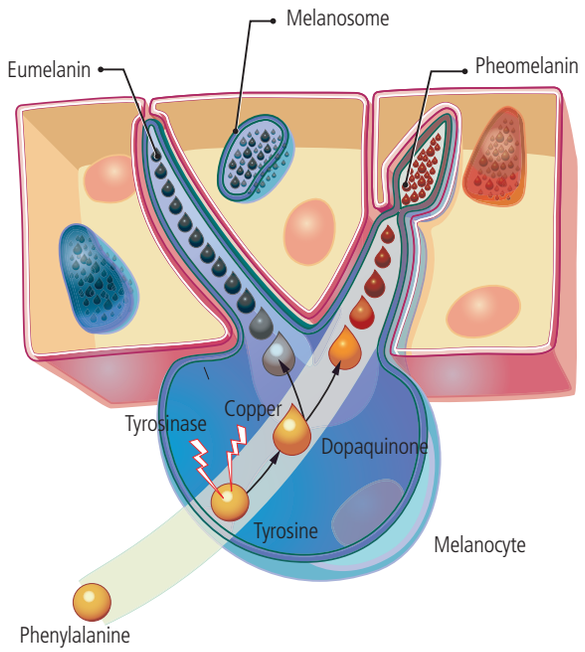

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Figure 2 - Influence of dietary tyrosine intake on color intensity in black cats. *Diets that cause the color of hair to change from black to reddish-brown are associated with a reduction in melanin in hair, a decreased total melanin concentration and low concentrations of tyrosine in plasma.*

► Environmental factors

White cats are prone to squamous cell carcinoma, especially on the ear pinna and nose. Neoplastic changes are often preceded by solar dermatitis (sun burn). Solar radiation is the most ubiquitous mutagen but except indoor confinement, very little can be done to prevent exposure to sun light and the related free radicals. Research has shown the benefits of antioxidants in preventing UV light induced skin tumors and supplementation of antioxidants in the food may thus be useful *(Liebler & Burr, 2000)*.

► Age and physiological states

In health and disease, age and physiological stage can greatly influence the quality of skin and coat. Growth, gestation, lactation, and old age will modify the nutritional requirements and are likely to interfere with the supply of nutrients to the cutaneous structures.

► Obesity

The physical constraints related to excessive weight reduce the ability of the cat to groom. This can lead to skin and/or coat conditions such as matted hair or anal sac impaction. Any other painful factor limiting the range of movement such as arthritis or idiopathic cystitis will have similar consequences.

► Concurrent diseases

The skin is a large organ requiring numerous macro and micro nutrients. Any condition interfering with the absorption of those nutrients will have consequences on the skin and coat **(Table 1)**.

► Nutritional balance

There is no published evidence of "generic food skin diseases" in the cat but, usually, when the diet is unbalanced, cutaneous signs often precede weight loss **(Table 2)**.

2 - Nutritional dermatosis

Nutritional dermatoses may affect cats in many different ways which are listed in **Table 2**.

► Specific nutritional imbalances

> Protein deficiency

Hair consists of 95% protein, and is rich in sulphur amino acids such as methionine and cystine. The growth of hair and renewal of the skin will absorb 30% of dietary protein *(Scott et al, 2001)*. Any situation where protein requirements are not fulfilled will lead to poor coat and skin with generalized scaling, loss of pigment, poor hair growth, easy shedding, thin, dull and brittle hair.

Protein deficiency can either be due to a lack of supply i.e. poor quality diet, unbalanced home prepared food, low protein diet or to protein loss related to a systemic illness such as protein losing gastro-enteropathy, nephropathy, hepatopathy, or chronic bleeding. The reason for the nutritional imbalance needs to be identified and corrected.

Table 1 - Various conditions interfering with the absorption of nutrients

Nutrients	Diseases or diets
Proteins	Any systemic disease inducing protein loss or impairing protein absorption (i.e: gastroenteropathy, hepatopathy, nephropathy, chronic bleeding)
Fats	Digestive disorders, neoplastic or inflammatory diseases leading to malabsorption or maldigestion Renal or liver diseases
Vitamins and minerals	Polyuria-polydipsia, large consumption of white raw eggs, unbalanced vegetarian diets

Table 2 - Cutaneous signs of an unbalanced diet

- Widespread scaling
- Crusting (non allergic miliary dermatitis)
- Patchy alopecia
- Lack of pigment
- Poor hair growth
- Thin, brittle, dull hair
- Seborrhea oleosa
- Recurring pyoderma
- Impaired wound healing
- Chronic or recurrent otitis

> Essential fatty acid deficiencies

Essential fatty acids are not synthesized by the organism, thus their supplementation in the diet is "essential". They are primarily the precursors of two families of polyunsaturated fatty acids (PUFA), omega-6 fatty acids and omega-3 fatty acids.

PUFA fulfill five main functions:
- incorporation in the structure of the cell membrane, which gives it its flexibility and permeability
- production of eicosanoids (leukotrienes, prostaglandins, etc.)
- maintenance of the skin barrier permeability (especially omega-6 fatty acids)
- cholesterol metabolism and transport
- immunomodulation through an influence on antigen presenting cells and T lymphocytes

PUFA deficiencies are observed 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 are xerosis, dull hair and a keratoseborrheic disorder. The response to PUFA supplementation is rapid.

- ***Linoleic acid***, a precursor of omega-6 fatty acids, 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, corn and soy oils.

DERMATOLOGICAL CONSEQUENCES OF SOME SPECIFIC DEFICIENCIES IN AMINO-ACIDS IN DOMESTIC SHORT HAIR CATS


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Dermatological consequences of isoleucine deficiency in a short hair cat. Note the crusty material around the eyes, nose pad and mouth. The hair coat is rough. In this kitten, bilateral conjunctivitis and bacterial infection with staphylococci suggest impaired resistance to common dermal bacteria.


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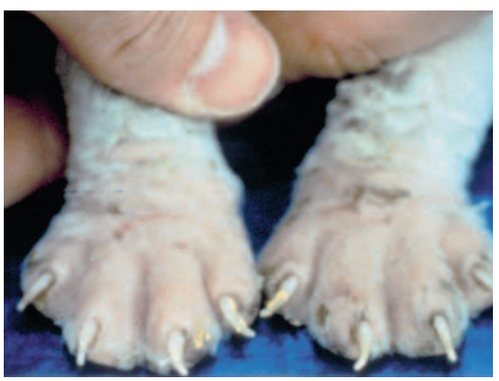
Isoleucine deficiency resulted in desquamation of the outer layer of the epidermis on the pads of the paws with cracking.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Dermatological consequences of a deficiency of sulphur containing amino-acids in a domestic short hair cat. Note the hyperkeratosis and swelling of the paws.


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Deficiency of sulphur containing amino-acids. Swelling, reddening and hyperkeratosis of the nail bed.

Cats are deficient in Δ-6 desaturase which is the enzyme needed for the first step of the transformation of linoleic acid into arachidonic acid. Thus linoleic acid and arachidonic acid are both essential nutrients for the cat **(Figure 3)**.

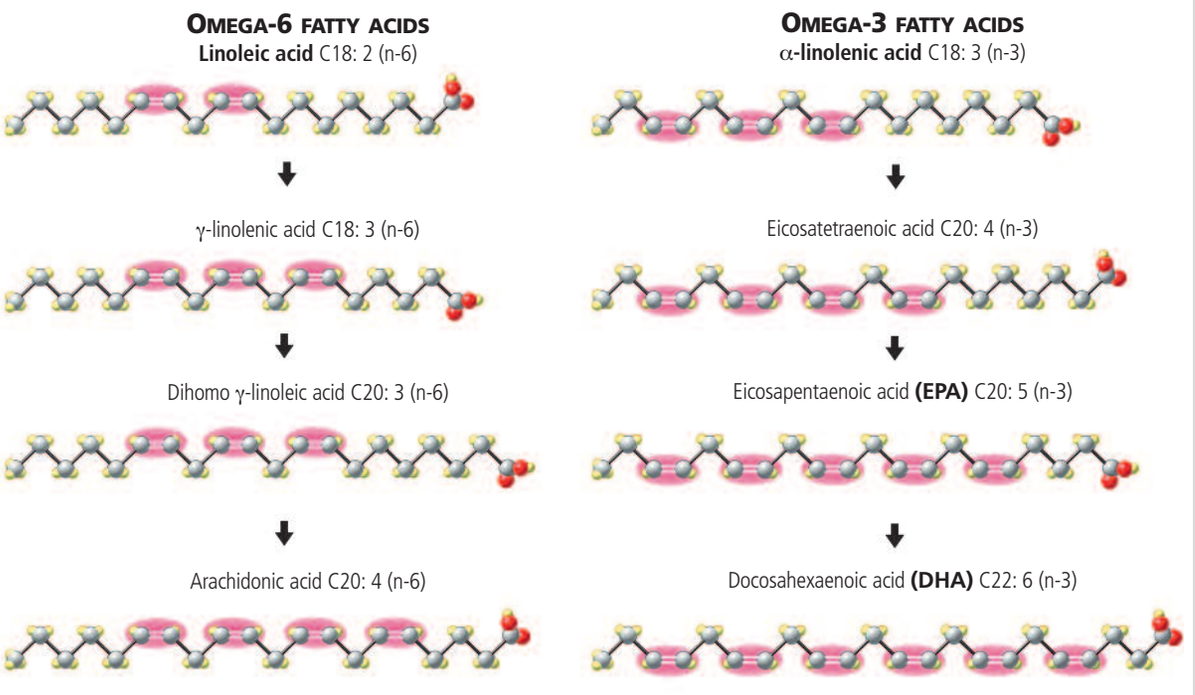
- ***Alpha linolenic acid***, a member of the omega-3 fatty acids, is found in green vegetables, fruits, grasses and plankton, and in concentrated form in the oil of plants like soy, flax, or linseed. The oils of fish from cold waters contain very high levels of two long-chain fatty acids derived from alpha linolenic acid: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) **(Figure 3)**. These two fatty acids participate in the fluidity of the cell membranes.

In addition to their anti-inflammatory, anti-neoplastic, immuno-stimulant, and cardio-protective properties, omega-3 fatty acids are also often used as anti-pruritic agents. Even in situations of an open wound or post-surgery, the benefit of supplementation still outclasses the mild reduction of perfusion which could potentially impede the healing process *(Scardino et al, 1999)*.

> Zinc deficiency

Zinc is a key element in many cellular mechanisms. Considering the fast turn over of epidermal cells, zinc is particularly necessary for a healthy skin and coat. Zinc is also needed for the biosynthesis of fatty acids, for the metabolism of vitamin A and for the inflammatory and immune response. Absolute dietary deficiency has not been reported in the cat but absorption of zinc can be inhibited by excessive levels of calcium, iron or copper due to competition for the absorption channels. Phytate present in cereals chelates zinc and will reduce its dietary availability. Other conditions preventing the absorption of zinc such as enteritis can also lead to depletion of the metal but usually the symptoms of the protein deficiency will be clinically apparent before signs of zinc deficiency occur.

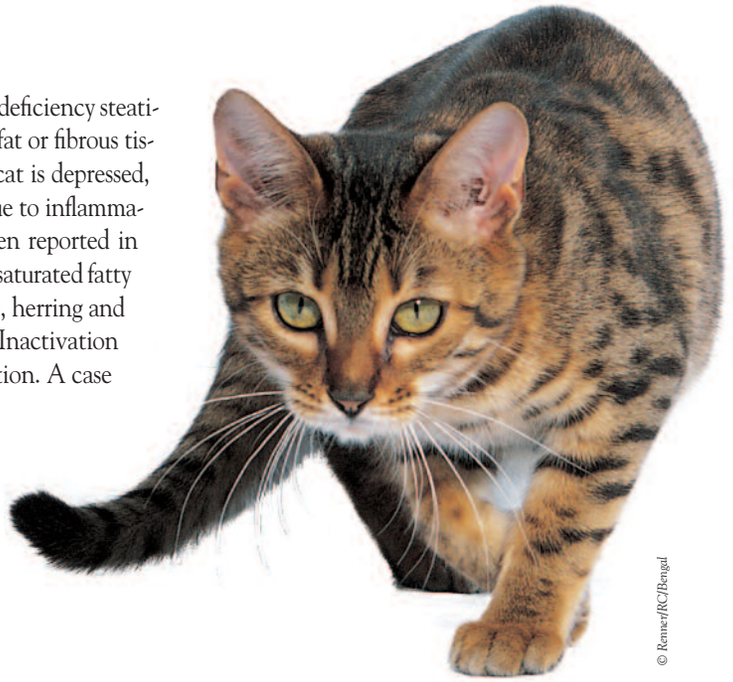
FIGURE 3 - HEPATIC SYNTHESIS OF LONG-CHAIN OMEGA-6 AND OMEGA-3 FATTY ACIDS FROM THEIR RESPECTIVE PRECURSORS



> Vitamin E deficiency

Pansteatitis (synonyms: feline vitamin E deficiency, vitamin E deficiency steatitis or yellow fat disease) is characterized by diffuse nodules of fat or fibrous tissue, especially in the groin or on the ventral abdomen. The cat is depressed, febrile, and reluctant to move or jump. Palpation is painful due to inflammation of the subcutaneous fat. Nutritional pansteatitis has been reported in young and obese cats fed a diet containing large amounts of unsaturated fatty acids and/or insufficient vitamin E. Canned red tuna, sardines, herring and cod but also diets based on pig brain have been incriminated. Inactivation of vitamin E can occur during food processing or by fat oxidation. A case of pansteatitis associated with a pancreatic tumor has been described *(Fabbrini et al, 2005)*.

Histologically, the subcutaneous fat will exhibit ceroid deposits which are pathognomonic of the condition. In lesions without ceroid, specific staining will have to be performed to differentiate pansteatitis from pancreatic or traumatic panniculitis *(Gross et al, 2005)*.



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Cats have high requirements in terms of water-soluble B vitamins and they are unable to convert β-carotene into retinol (active form of vitamin A). These characteristics show that cats are adapted to a carnivorous diet: under natural conditions, they do not lack these vitamins since they are present in large quantities in animal tissues.

> Vitamin A deficiency

Cats are unable to convert β-carotene from plants to vitamin A and thus need to receive preformed vitamin A. Among several functions, vitamin A is required for ocular function but also for skin turn over. With vitamin A deficiency, the cat will exhibit a poor coat, alopecia and generalized scaling. The supply of a balanced, meat containing diet is usually sufficient to cure the condition. Vitamin A supplements are not recommended in the cat when fed a complete food because of the risk of hypervitaminosis A.

> Hypervitaminosis A

This condition was rather common in the past when cats were fed raw liver. It is still seen occasionally when the owner gives large amounts of cod liver oil supplement. The signs are mainly osteo-articular due to the cat's inability to move. As a consequence, the cat will be unable to groom properly, resulting in an unkempt, matted coat.

> Vitamin B deficiency

B complex vitamins are treated as a group. They are water soluble vitamins that cannot be stored. Biotin, riboflavin, niacin, inositol, pantothenic acid and pyridoxine are important for the quality of the skin barrier and deficiencies will lead to dry flaky seborrhoea accompanied by alopecia, anorexia, weight loss and pruritus.

Biotin deficiency sometimes occurs with consumption of numerous uncooked eggs. The avidin in the egg white binds to biotin and blocks its absorption. This will lead to a papulocrustous dermatitis.

A deficiency in riboflavin will lead to head and neck alopecia in cats. Niacin deficiency has also been described in cats fed a low protein high corn diet. Niacin and pyridoxine deficiencies can be produced experimentally. However, appropriately formulated commercial pet food contains high quantities of these vitamins.

Supplementation of B vitamins might be necessary with anorexia or polyuria. Vitamin B complex can be found in brewer's yeast and in balanced commercial food. Certain B vitamins work in synergy with histidine to improve the barrier function of the epidermis and decrease the TEWL (transepidermal water loss) *(Watson et al, 2006)*.

TABLE 3 - VARIOUS CLINICAL EXPRESSIONS OF ADVERSE FOOD REACTIONS IN CATS

Cutaneous problems	Miliary dermatitis Self-induced alopecia Head & neck pruritus Eosinophilic granuloma
Gastrointestinal problems	Vomiting Diarrhea Flatulence Weight loss

> Dietary hypersensitivities

The term dietary hypersensitivity or food allergy is used by many veterinarians and owners as a broad term to describe any immunological and non-immunological reactions to ingredients of the diet that result in a clinical adverse reaction in an otherwise healthy cat. This adverse reaction may occur in the form of gastrointestinal problems and/or cutaneous abnormalities typically associated with self trauma due to pruritus **(Table 3)**.

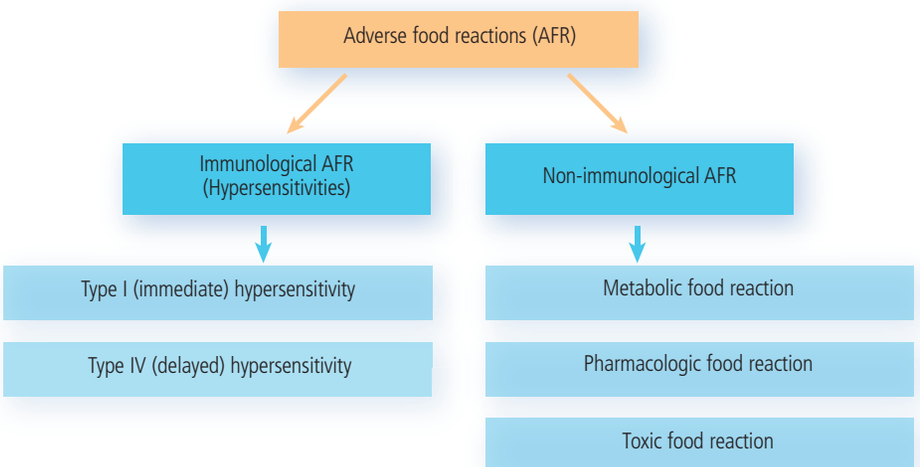
In the cat, adverse food reactions are considered to be relatively more common than in the dog *(Scott et al, 2001)*. In one search of feline records in a number of veterinary colleges, feline adverse food reaction occurred in 10% of the patients presented with allergic skin disease *(Chalmers & Medleau, 1989)*. It was the second most common disorder after flea bite hypersensitivity. However, another more recent report suggested atopic dermatitis to be much more common than adverse food reaction (73 versus 23% of 90 cats) *(Prost, 1998)*. This may reflect the different location, different setting of private dermatology referral practice versus veterinary teaching hospitals, the increased awareness of other hypersensitivities besides flea hypersensitivity in the cat, and/or owners increasingly willing to pursue involved diagnostic procedures for their pets. The prevalence of food hypersensitivity in humans is reported to be approximately 10% in infants *(Bock, 1987)* and 2% in adults *(Young et al, 1994)*. No such data is available for cats to the authors' knowledge.

> Etiology

In humans, non-immunological food reactions like toxic food reactions (e.g. toxins secreted by *Salmonella spp.*), pharmacologic reactions (e.g. caffeine) and metabolic reactions (e.g. lactase deficiency) comprise the majority of food-related problems *(Sampson, 2003)*. The term hypersensitivity is used more stringently only for immunologically mediated reactions to food ingredients. Type I hypersensitivities are most common, although type IV mediated food hypersensitivities and mixed forms have been described **(Figure 4)**.

In cats, type I hypersensitivity has been presumed as edema is the predominant clinical sign in some cats *(Walton, 1967)*. However, in most clinical cases, the pathophysiological mechanism is not determined and adverse food reaction is diagnosed exclusively by the association between diet and clinical signs.

FIGURE 4 - PATHOGENESIS OF ADVERSE FOOD REACTION



> Break in immune tolerance

In healthy humans, intact food antigens penetrate the gastrointestinal tract and enter the circulation without any clinical signs because most individuals develop tolerance to ingested antigens. This tolerance may be based on the induction of regulatory T cells *(Smith et al, 2000; Zivny et al, 2001)* or T cell anergy (where T cells are stimulated by antigen presenting cells via MHC class II molecules but without appropriate costimulatory signals) *(Chehade & Mayer, 2005)*. Maintenance of this immune tolerance depends on a variety of factors listed in **Table 4**.

TABLE 4 - FACTORS INFLUENCING THE MAINTENANCE OF IMMUNE TOLERANCE
(Chehade & Mayer, 2005)

Antigen dose High dose: T cell anergy Low dose: activation of regulatory T cells
Antigen form Soluble antigens are tolerated better than particulate antigens
Host genetics
Commensal flora
Host age
Gastrointestinal barrier function

In humans with a genetic predisposition for atopy, class switching of B cells leads to the production of antigen-specific IgE. A breakdown in oral tolerance and development of hypersensitivity may occur when food allergens penetrate the mucosal barrier and reach IgE antibodies bound to mast cells. Degranulation of these mast cells leads to mediator release, inflammatory cell influx and subsequent clinical signs. In the cat, little is known about the mechanisms underlying oral tolerance and hypersensitivity.

> Dietary allergens

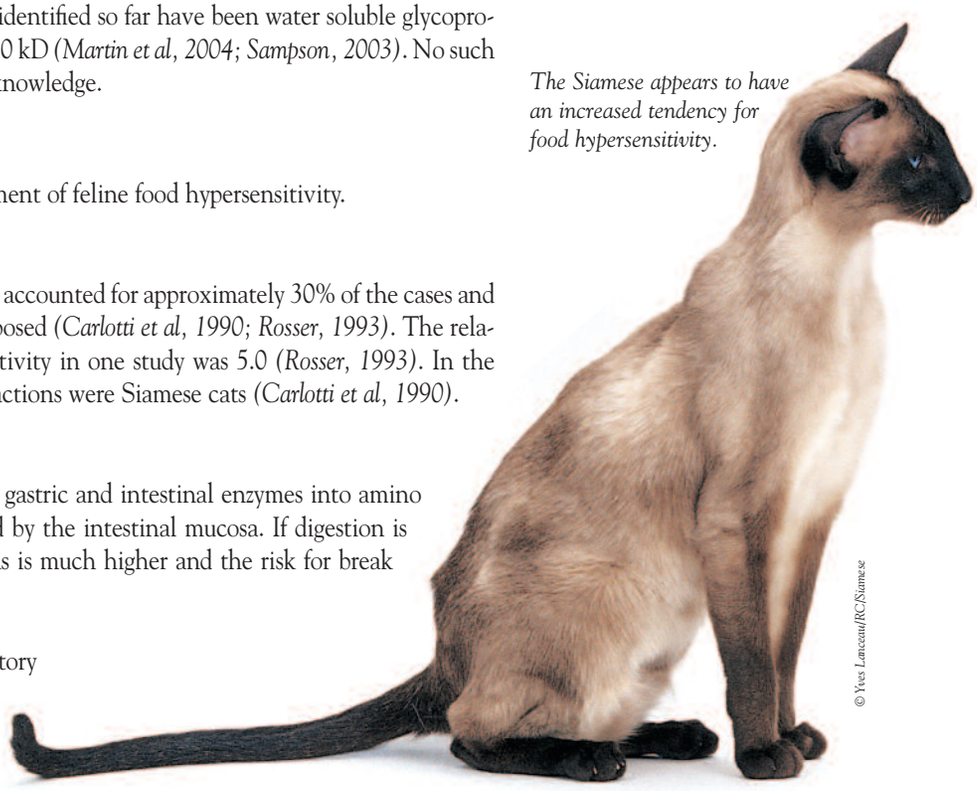
In three studies the most common allergens involved based on provocative challenge were fish, beef and dairy products *(Guaguere, 1993; Walton, 1967; White & Sequoia, 1989)*. One third of the cats could not tolerate any commercially prepared diet without recurrence of clinical signs. A list of reported offending allergens is given in **Table 5**.

TABLE 5 - ALLERGENS INVOLVED IN FELINE ADVERSE FOOD REACTIONS

Beef	Eggs
Chicken	Fish
Clam juice	Horse
Cod liver oil	Lamb/Mutton
Commercial foods	Pork
Dairy products	Rabbit

In one study, almost 30% of 55 cats with chronic gastrointestinal problems showed food hypersensitivity *(Guilford et al, 2001)*. Half of these cats reacted to more than one protein. The clinical feature identified to be most sensitive for the diagnosis of adverse food reaction was the concurrent occurrence of gastrointestinal and cutaneous signs.

In humans and dogs, the major food allergens identified so far have been water soluble glycoproteins with molecular weights ranging from 10-70 kD *(Martin et al, 2004; Sampson, 2003)*. No such data is available for the feline to the authors' knowledge.



The Siamese appears to have an increased tendency for food hypersensitivity.

Predisposing factors

Many factors may be involved in the development of feline food hypersensitivity.

Genetic predisposition

In two studies, Siamese or Siamese cross breeds accounted for approximately 30% of the cases and a genetic predisposition for those cats was proposed *(Carlotti et al, 1990; Rosser, 1993)*. The relative risk factor of Siamese for food hypersensitivity in one study was 5.0 *(Rosser, 1993)*. In the other report, 3 of 10 cats with adverse food reactions were Siamese cats *(Carlotti et al, 1990)*.

Maldigestion

Dietary proteins are typically broken down by gastric and intestinal enzymes into amino acids and small peptides which are assimilated by the intestinal mucosa. If digestion is defective, the molecular weight of the proteins is much higher and the risk for break down of tolerance increased.

This explains why chronic intestinal inflammatory disease may be conducive to the development of dietary hypersensitivity. However, if


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Figure 5 - Consequences of pruritus in a domestic short hair cat. *Face, head, pinnae and neck can all be affected in various combinations.*

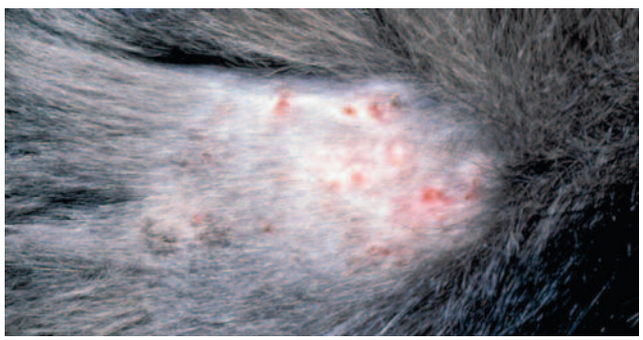
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Figure 6 - Characteristic lesion of miliary dermatitis in a domestic short hair cat. *Small papules and crusts on the trunk characteristic of military dermatitis.*

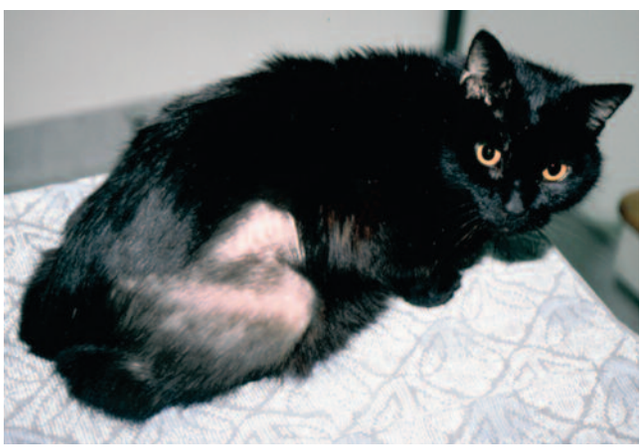
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Figure 7 - Consequences of an allergic pruritus in a domestic short hair cat. *Noninflammatory alopecia on the flanks and lateral thighs.*

the gastrointestinal inflammation seen in cats with chronic bowel problems was originally due to other causes and led to food hypersensitivity or if this hypersensitivity is solely responsible for the inflammatory changes is not known at this point.

Other hypersensitivities

Concurrent hypersensitivities such as flea bite hypersensitivity or atopic dermatitis are known in dogs with dietary intolerance and may also be a complicating factor in cats. In one of the first reports studying feline food hypersensitivity, 3 of 14 cats had concurrent hypersensitivities *(White & Sequoia, 1989)*. In a recent article, 6 of 16 cats with allergies were diagnosed with a combination of adverse food reaction and atopic dermatitis *(Waisglass et al, 2006)*. Another report described 90 allergic cats, 16 cats had an exclusive adverse food reaction, 4 cats had concurrent atopic dermatitis and adverse food reaction and one cat was additionally allergic to fleas *(Prost, 1998)*. Thus almost a quarter of cats with an adverse food reaction had concurrent hypersensitivities.

Clinical features

In the cat, clinical signs of adverse food reactions vary from pruritus with associated self trauma, eosinophilic granuloma, respiratory signs to gastrointestinal problems.

Head and neck pruritus

Head and neck pruritus was reported in cats with dietary hypersensitivity *(Guaguere, 1993; Medleau et al, 1986; Stogdale et al, 1982)*. Alopecia, crusting, erosions and ulcerations are seen in the affected area as a consequence of self trauma **(Figure 5)**. Pruritus is often severe and may be non-responsive to medical therapy. Secondary infections with bacteria or yeast are not uncommon. Pruritus and thus lesions can spread to other body sites and become generalized with time.

Miliary dermatitis

Small papules and crusts either localized (frequently on the head and neck) **(Figure 6)** or generalized are also seen with dietary hypersensitivities *(Mueller, 2000, Scott et al, 2001)*. In one study, 21% of the cats with adverse food reaction showed this reaction pattern *(White & Sequoia 1989)*. In another study, almost half of the cats with adverse food reactions had military dermatitis *(Carlotti et al, 1990)*.

Non-inflammatory alopecia

Self-induced, bilaterally symmetrical alopecia with no macroscopic lesions is also a common reaction pattern associated with feline adverse food reaction *(Mueller, 2000; Scott et al, 2001)*. Most commonly affected sites are the ventrum, inguinal area, thighs and flanks **(Figure 7)** Owners may or may not observe excessive grooming as a cause of the alopecia, as some cats do not exhibit that behavior in the presence of humans ("closet groomers"). In one report, 10% of all cats with adverse food reaction showed exclusively alopecia. In another report of 21 cats with presumptive psychogenic alopecia, adverse food reaction was diagnosed in more than half of the cats *(Waisglass et al, 2006)*.

Eosinophilic granuloma

Eosinophilic plaques are the most frequently reported lesion of the eosinophilic granuloma complex in cats with adverse food reactions, but other lesions such as linear granuloma have been reported *(Carlotti et al, 1990; White & Sequoia, 1989)*. Eosinophilic plaques are well circumscribed, erythematous, severely pruritic and often ulcerated plaques typically on the abdomen or medial thighs **(Figure 8)**. Linear granulomas are non pruritic, raised, firm, yellowish plaques, most commonly on the caudal thighs **(Figure 9)**.

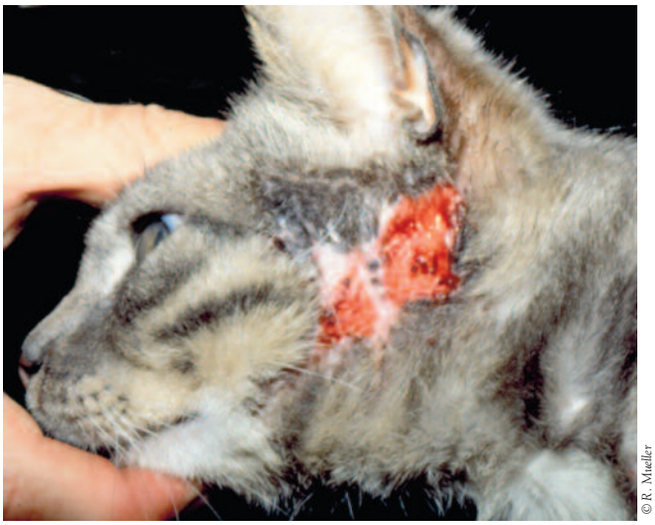


Figure 8 - Facial eosinophilic plaque in a domestic short hair cat.

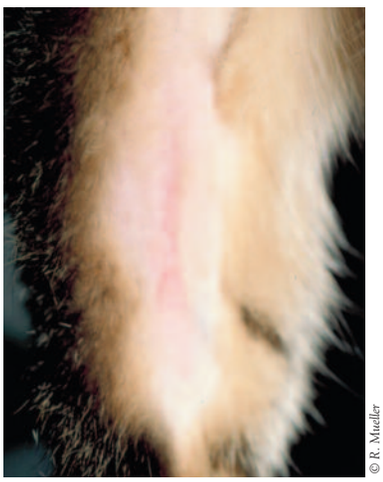


Figure 9 - Linear granuloma on the caudal thigh of a domestic short hair cat.

Gastrointestinal problems

Vomiting, diarrhea and/or flatulence may be clinical signs of feline adverse food reaction *(Guilford et al, 2001; Stogdale et al, 1982)*. Vomition may occur within minutes after eating or hours after the meal and often occurs infrequently. In many cats, diarrhea is due to large bowel dysfunction and thus excessive straining to defecate, mucus and/or blood in the feces may be seen. In one study of 55 cats with chronic gastrointestinal problems, almost one third were diagnosed as food sensitive based on resolution of clinical signs with an elimination diet and recurrence of those signs, when challenged with the previous diet. Most of these cats had a history of vomiting (56%) and a quarter of the cats exhibited chronic diarrhea. The remaining 3 cats had both clinical signs *(Guilford et al, 2001)*.

Diagnosis

Cutaneous signs of feline adverse food reactions usually present themselves as reaction patterns with a number of possible underlying causes, thus a thorough diagnostic work-up is essential in these patients. The list of differential diagnoses depends on the presenting cutaneous reaction pattern and is shown in **Table 6**. Diagnostic tests or trial therapies to rule out differential diagnoses depend on the presenting signs and may include evaluation of cutaneous cytology, superficial and deep skin scrapings, fungal cultures, ectoparasite treatment trials and skin biopsies.

TABLE 6 - IMPORTANT DIFFERENTIAL DIAGNOSES OF CUTANEOUS REACTION PATTERNS ASSOCIATED WITH FELINE ADVERSE FOOD REACTIONS

Reaction pattern	Differential diagnoses
Miliary dermatitis	• Allergies (flea bite hypersensitivity, atopic dermatitis, adverse food reaction, mosquito-bite hypersensitivity) • Ectoparasites (scabies, cheyletiellosis, ear mites) • Infections (dermatophytosis, bacterial infection) • Immune-mediated diseases (pemphigus foliaceus) • Neoplasia (mast cell tumor)
Self-induced alopecia	• Allergies (flea bite hypersensitivity, atopic dermatitis, adverse food reaction) • Psychogenic alopecia • Drug reaction
Head & neck pruritus	• Allergies (atopic dermatitis, adverse food reaction) • Ectoparasites (scabies, ear mites) • Otitis externa • Neoplasia (epitheliotrophic T cell lymphoma)
Eosinophilic granuloma	• Allergies (flea bite hypersensitivity, atopic dermatitis, adverse food reaction) • Idiopathic eosinophilic granuloma

TABLE 7 - EXAMPLES OF PROTEIN SOURCES FOR ELIMINATION DIETS IN CATS

- Duck
- Goat
- Horse
- Ostrich
- Pheasant
- Rabbit
- Venison

Intradermal testing/serum testing for food allergen-specific IgE

It is tempting to measure dietary allergen-specific IgE to identify the offending dietary allergen(s) and to use the results to choose a new diet. Although sometimes recommended by individuals and laboratories offering these tests, at this time there is no evidence available to the authors to justify such tests. In the dog, published data show that these tests are unreliable *(Jackson & Hammerberg, 2002; Jeffers et al, 1991; Kunkle & Horner, 1992; Mueller & Tsohalis, 1998; Wilhelm & Favrot, 2005)*. In the cat, only one report evaluated serum antigen-specific IgE in cats with adverse food reactions *(Guilford et al, 2001)*. Only half of the cats with confirmed adverse food reaction had a positive test result. The majority of cats either tolerated the food antigen that they had tested positive for or they had never been exposed to it and thus hypersensitivity seemed unlikely. Only 25% of the cats showed results that were consistent with the results of their elimination diet and re-exposures.

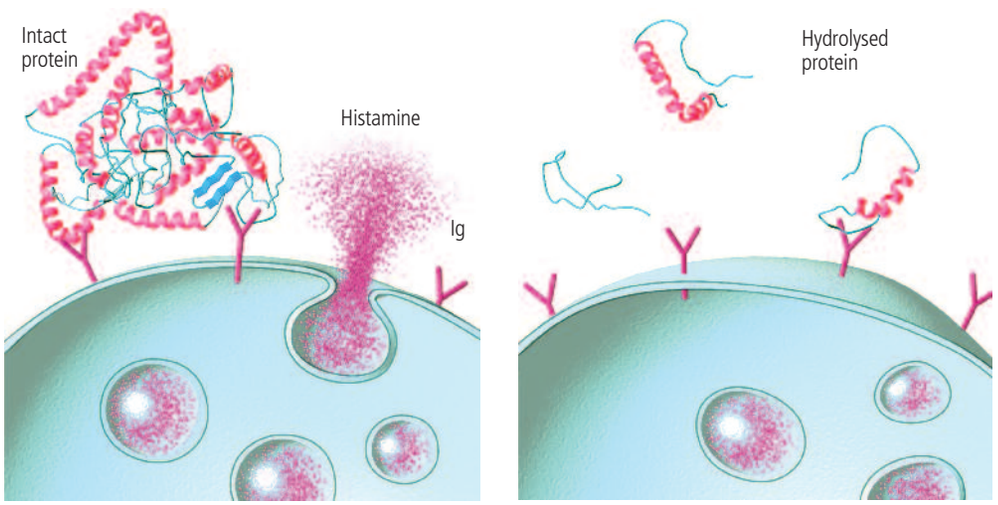
Home-prepared elimination diets

The only reliable means to diagnose adverse food reaction in the cat is currently a commercial or a home-prepared elimination diet with a protein source the cat has not been exposed to *(Mueller, 2000; Scott et al, 2001)*. Examples of possible protein sources are given in **Table 7**. Such a diet is typically not nutritionally balanced, but may be fed in adult animals for short periods of time (for the trial period, up to 12 weeks) without clinically apparent adverse effects. The protein source should be boiled, grilled or prepared in a microwave. The method of preparation depends on the individual circumstances, owner and cat. Some cats will accept a mixture of a protein and a carbohydrate source, in these cases a combination of both may be fed. However, most cats will prefer a diet based on protein sources only. Although taurine levels in meat are sufficient for cats *(Wills, 1991)*, particularly young animals on a home-prepared elimination diet may benefit from vitamin and mineral supplementation without flavors or additives *(Scott et al, 2001; Wills, 1991)*.

Commercial elimination diets

As alternative protein sources are sometimes difficult to obtain and require preparation, some owners may only be willing to use a commercial diet. Although numerous hypoallergenic diets are on the market, it is important to remember that the frequency of an adverse reaction to a protein is first and foremost related to the frequency this particular protein is fed to our feline companions. Lamb, fish and chicken, in the past considered first choices for elimination diets, are sometimes reported to be implicated in adverse food reactions of individual cats. These ingredients can still be effective in individual patients but only food with proteins that exclusively come from selected sources that the patient was not exposed to previously are acceptable.

FIGURE 10 – LOWER ALLERGENICITY OF HYDROLYSED PROTEINS VERSUS INTACT PROTEINS



Degranulation of mast cells (which leads to the release of histamine, responsible for inflammation), results from the binding of two amino acid sequences or epitopes on two immunoglobulins located on the mast cell surface. The lower the molecular weight of the protein, the lower the likelihood of containing these two amino-acid sequences.

Alternatively, hydrolysed diets may be fed. These foods are formulated on the basis of protein hydrolysates. The purpose of the hydrolysation is to fractionate the proteins into small peptides of low molecular weight **(Figure 10)**.

These peptides are less antigenic and more digestible and thus offer less stimulation to the gastrointestinal immune system. Thus, hydrolysed diets are theoretically the most suitable commercial elimination diets. In the dog, studies have documented clinical improvement of allergic patients on hydrolysed diets *(Biourge et al, 2004; Loeffler et al, 2004; Loeffler et al, 2006)*. No such studies have been conducted in cats to the authors' knowledge.

If there are several cats in the household, either the hypersensitive cat must be prevented from access to the other cats' food, or all the cats must be given the same elimination diet. © Yves Lanceau/RC/ European shorthair

Concomitant treatments

Antipruritic and/or antimicrobial treatment may be indicated during the elimination diet. The cat may also have concurrent disease that requires continuous administration of drugs. In these cases, the prescription of flavored medication must be avoided, as small amounts of offending allergens may lead to clinical signs and prevent remission with the diet. If medication is usually administered with food, any potential protein source previously fed must be avoided.

Special circumstances

Multi-pet households

If more than one animal lives in the same household, then the other animals must be fed separately. This is only possible, if the animals are housed completely separately or if the other animals feed rapidly and thus will empty their food bowl in a very short time when placed into a room without the patient with suspected adverse food reaction. Otherwise it is prudent to feed all the animals in the household the same elimination diet to avoid accidents, where the patient consumes additional food from other pets that will most likely prevent clinical improvement.

Outdoor cats

Many cats either live predominantly outdoors or at least have free and unlimited access to the outside. They may wander into other back yards or houses and help themselves to pet food available there. Thus, ideally these patients need to be kept indoors for the duration of the diet, which can be difficult for the cat and owner.

Cats that typically hunt mice or birds will continue that habit during the dietary trial. Ideally these patients should be kept indoors for the duration of the elimination and challenge dietary trials.

Fussy eaters

Some cats may not like the new food offered to them during the diet trial. Cats can be determined and few owners will tolerate refusal of any given diet for more than a couple of days. With a home-prepared diet, warming up the food, salting it very slightly or preparing it differently may entice the cat to accept it. With commercial diets, a gradual change from the original food to the diet over three or four days may increase the chance of acceptance. If neither of these measures is helpful, a new elimination diet may need to be formulated.

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Monitoring the diet

Compliance with the diet can be difficult not only considering the patient, but also the owner. A thorough client education supported by written instructions will increase the chances of success. Every family member and visiting friends must be informed of the need for strict adherence to the agreed diet trial.

A telephone call a few days after instituting the diet will be helpful in identifying possible problems. At that time, any

Table 8 - Example of pruritus scores

Note	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

questions the owners may have are answered. Regular appointments after three to four and six to eight weeks are needed to monitor compliance, motivate and emotionally support the owner. Depending on the food and the cat, weight gain or weight loss may ensue. The owner must be instructed to monitor the cat's weight and if there is weight gain, diet intake should be decreased. If the patient loses weight, more food should be offered.

Length of the diet and interpretation of results

A diet trial should be conducted for six to eight weeks. If remission is achieved faster, then of course the diet can be discontinued earlier. After the diet trial, the previous food is fed again and should lead to a recurrence of clinical signs within hours to at the most, two weeks. At this point reinstitution of the elimination diet with subsequent resolution of clinical signs confirms the diagnosis of adverse food reaction. If however after two weeks no deterioration has occurred, then improvement was due to other factors such as treating secondary infections, change of seasons or concurrent ectoparasite treatment trial.

If there is spectacular improvement and complete remission occurs, judgement of success is simple. However, if there is partial improvement, interpretation is more difficult. Scoring systems for pruritus **(Table 8)** and/or lesions or digital photographs may be helpful in these patients. A provocative test is as important in these patients as in the cats with complete remission on the diet to ascertain the diagnosis.

Sequential rechallenge with the introduction of one protein source every one or two weeks allows correct identification of the offending allergen(s). Although many owners are reluctant to perform such a sequential rechallenge due to the associated emotional and organizational efforts, knowledge of the type of allergens involved frequently permits a wider choice of diets likely to be tolerated long term. Alternatively, the elimination diet may be continued long term. With a home-prepared diet, a nutritionist should be consulted to balance the diet and avoid nutritional deficiencies.

3 - Metabolic diseases

► Metabolic epidermal necrosis/necrolytic migratory erythema

Necrolytic migratory erythema is a skin disease in humans, that most commonly occurs secondary to a glucagon-secreting pancreatic tumor *(Tierney & Badger, 2004)*. However, liver disease, internal malignancies other than pancreatic tumors and even glucocorticoid administration have been reported as causes of this disease *(Mullans & Cohen, 1998; Tierney & Badger, 2004)*.

In the dog and cat, the terms diabetic dermatopathy, hepatocutaneous syndrome, metabolic epidermal necrosis or superficial necrolytic dermatitis have all been used, but a standard nomenclature has not been accepted *(Scott et al, 2001)*. In the dog, the most common causes are liver disease, hyperadrenocorticism, diabetes mellitus, pancreatic tumors and phenobarbital administration *(Gross et al, 1993; March et al, 2004; Torres et al, 1997; Yoshida et al, 1996)*. Two of the four cats reported in the literature had hepatopathies and the remaining two had pancreatic tumors *(Beardi, 2003; Godfrey & Rest, 2000; Kimmel et al, 2003; Patel et al, 1996)*. The exact pathogenesis of metabolic epidermal necrosis has not been elucidated, but a deficiency of amino acids, fatty acids and/or zinc is discussed in the dog *(Outerbridge et al, 2002; Tierney & Badger, 2004)*.

Clinical signs in the cat include stomatitis, gingivitis, alopecia, scaling and mild crusting. The skin lesions are bilaterally symmetrical and affect the axillae, ventrum, and inguinal area as well as the tail. Foot pads and mucocutaneous junctions were affected in one cat. Skin biopsies show diagnostic features of severe parakeratosis with underlying severe edema of the upper epidermis, and irregular epidermal hyperplasia with mild to moderate inflammation of the underlying dermis and

appendages. Ultrasonography of the liver may reveal a diffusely coarse echotexture with a reticular pattern or a pancreatic mass.

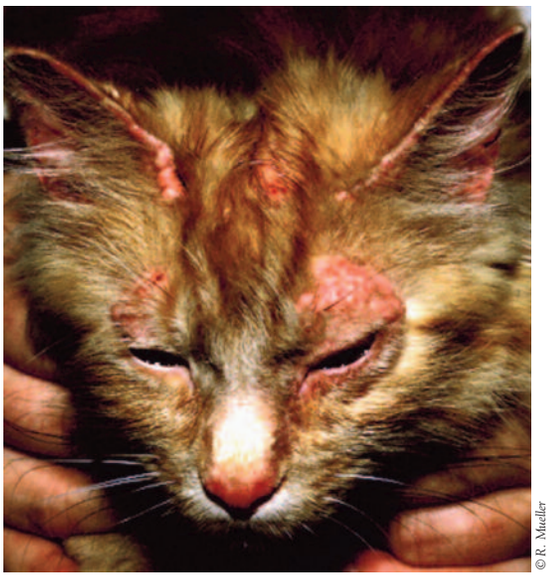
Treatment of human necrolytic migratory erythema involves removal of the pancreatic tumor, skin lesions subsequently resolve without further therapy *(Chastain, 2001; Zhang et al, 2004)*. In dogs, removal of a pancreatic tumor has also resulted in complete clinical remission *(Torres et al, 1997)*. However, in most patients, advanced liver disease is the cause. In these patients, high quality proteins such as eggs in association with zinc and fatty acid supplementation may be helpful. In severe cases, intravenous amino acid infusion may lead to temporary remission *(Gross et al, 1993, Outerbridge et al, 2002)*. However, if the underlying disease cannot be treated successfully, the prognosis is poor. To date, successful treatment of this disease in the cat has not been reported.

TABLE 9 - CAUSES OF FELINE XANTHOMAS

- Diabetes mellitus
- Chronic administration of megestrol acetate
- Congenital lipoprotein lipase deficiency
- High dietary fat intake
- Idiopathic

► Xanthoma

Feline xanthomas are benign granulomatous lesions with several possible causes **(Table 9)**. Hereditary hyperlipoproteinemia is one possible etiology *(Grieshaber, 1991; Johnstone et al, 1990; Jones et al, 1986)*. It may be due to congenital deficiency of lipoprotein lipase, an enzyme responsible for hydrolysis of the lipids in the chylomicrons and the release of free fatty acids in the peripheral tissues *(Bauer & Verlander, 1984)*. Xanthomas have also been reported in cats with diabetes mellitus *(Jones et al, 1986; Kwochka & Short, 1984)*. A case series of 5 cats described frequent high fat treats such as cream, butter and ice cream as possible causes, all of these cats responded to a low fat diet *(Vitale et al, 1998)*. Leakage with extra- and intracellular deposition of lipoproteins from the capillaries into the tissue is suspected to occur in humans and may also occur in cats. Idiopathic feline xanthoma may also exist *(Denerolle, 1992)*.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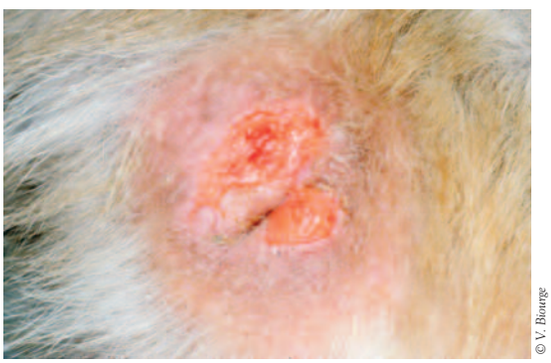
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Figure 11 - A DSH cat with facial alopecia, erythema, and papules due to xanthoma. *Clinical signs of xanthomas in cats include white to yellowish papules, plaques and nodules that may or may not be ulcerated.*

Lesions most commonly develop on the head, particularly the preauricular area and pinnae **(Figure 11)**. Bony prominences may also be affected.

The diagnosis is confirmed histologically. A nodular to diffuse granulomatous inflammation with foamy macrophages and multinucleated giant cells is characteristic. Diabetes mellitus or excess dietary fat intake should be ruled out as underlying causes.

Treatment consists of addressing the underlying disease and feeding a low fat diet (< 25 % of calories of the diet provided by fat). If diabetes mellitus is treated successfully, the diet may be changed back to normal. In patients with idiopathic or congenital xanthomas, it may be prudent to continue the low-fat diet for the remainder of the pets life.

Lesions due to a specific underlying cause resolve spontaneously once the underlying cause is addressed successfully. A low-fat diet is recommended and will be particularly useful in cats with the idiopathic form of xanthoma.

4 - Nutritional therapy in dermatology

► Dull coat, xerosis

The coat's sheen is connected to the composition of sebum secreted by sebaceous gland secretions and stored in the hair follicles. The lipids in the composition of sebum are species and in the dog breed specific *(Dunstan et al, 2000)*, but the production and the quality of the sebum is also influenced by food *(Macdonald et al, 1983)*. Dryness of the skin (xerosis) is caused by decreased water

content. The increased water loss through evaporation may be due to low humidity conditions of the environment or an increased transepidermal water loss. In cats, linoleic acid deficiency has been shown to be a possible cause for the latter *(Macdonald et al, 1983)*.

► Color change of black coats to reddish brown

In some black cats, the coat color changes to a reddish brown. This color change is associated with low tyrosine plasma concentrations, has been induced in cats given a tyrosine-deficient diet, and is reversed by diets containing a high concentration of tyrosine or phenylalanine. Current dietary recommendations for dietary tyrosine and phenylalanine for kittens are below those required to support maximal melanin synthesis in black adult cats. The requirement appears to be greater than a combination of 4.5 g tyrosine plus 12 g phenylalanine/kg diet but less than 24 g phenylalanine alone/kg diet *(Yu et al, 2001)*.

► Skin wound healing

To maximize wound healing and to be able to formulate appropriate nutritional supplements in the pre- and post-surgery period in humans, nutritionists have studied the stimulation of re-epithelialization and of the immune system to decrease the chance of secondary wound infections. A number of oral preparations are available in human medicine, but similar products for cats are not available to the authors' knowledge.

Protein and zinc deficiencies are associated with delayed wound healing and care should be taken to optimize protein and zinc intake in wounded animals *(Robben et al, 1999)*.

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 wound healing in dogs *(Scardino et al, 1999)*. A vitamin E supplement helps protect PUFA's from oxidation. Similarly, the positive role of curcumin, aloe vera and bromelaine has been shown in the canine wound healing process *(Fray et al, 2004)*. To the authors's knowledge, no such data exists for cats.

► Feline allergic skin disease

Feline atopic dermatitis is a multifactorial disease. However, in contrast to human or canine atopic dermatitis, the cat presents with a number of clinical reaction patterns *(Bettenay, 2000; Rees, 2001)* **(Table 4)**. Additional common causes for these reaction patterns are flea bite hypersensitivity and adverse food reactions (see above). Nutrition may be used in several ways in these feline patients.

A diet that does not contain adequate levels of tyrosine and/or phenylalanine to permit the complete synthesis of melanin induces a coat color change in black cats. The color becomes reddish brown.

> Reduction in inflammation with polyunsaturated fatty acids

Long chain polyunsaturated fatty acids have been shown to alleviate the symptoms of miliary dermatitis *(Harvey, 1993; Harvey, 1991; Lechowski et al, 1998)*. The fatty acid profile in plasma of affected cats was different than that of normal cats and omega-3 supplementation increased plasma concentrations of EPA and DHA and decreased dihomo-gamma-linolenic acid (DGLA), corresponding to clinical improvement. A combination of fish oil (omega-3) and evening primrose oil (omega-6) had a higher response rate than fish oil alone *(Harvey, 1993)*. Some cats with eosinophilic granuloma, another reaction pattern frequently associated with feline allergies, also respond to fatty acid supplementation *(Scott et al, 2001)*.

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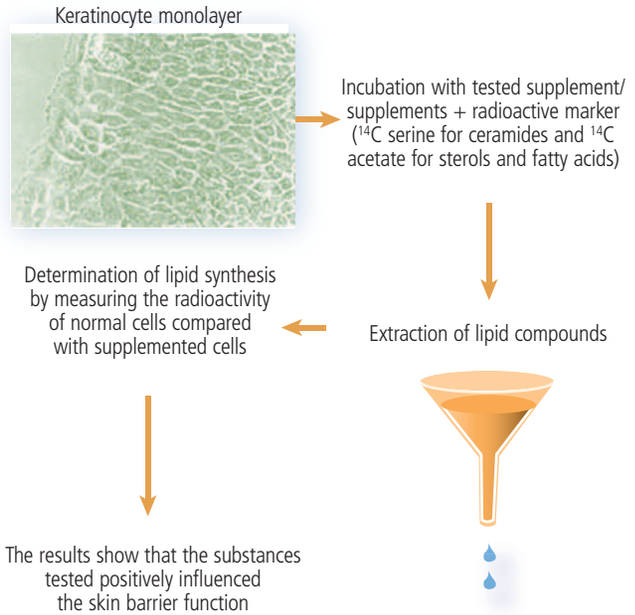
> Prevention or control of dietary hypersensitivities

Up to 40% of cats with atopic dermatitis have concurrent adverse food reactions *(Waisglass et al, 2006)*. Such possible dietary hypersensitivities may be addressed by either using food sources avoiding the offending protein allergens or by using a hydrolysed diet where the antigens are of such small size that an allergic reaction may be prevented in many patients.

> Re-establishment of the skin barrier

Defects in intercellular ceramides in canine atopic epidermis have been described and presumably allow increased transepidermal water loss, increased penetration by antigens and increased adherence of staphylococci similar to what is seen in human patients with atopic dermatitis. In vitro studies (keratinocytes cultures) conducted by the Waltham Centre for Pet Nutrition 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 *(Watson et al, 2006)* **(Figure 12)**.

FIGURE 12 – MEASURING THE SYNTHESIS OF SKIN LIPIDS
(From Watson, 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. Unfortunately, no such reports exist for the cat to the authors' knowledge.

► Miscellaneous skin diseases

> *Urticaria pigmentosa*

Essential fatty acids were reported to be helpful in the control of exacerbations of feline urticaria pigmentosa, a maculopapular eruption of the ventral trunk with a perivascular to diffuse mastocytic and eosinophilic infiltrate in the dermis *(Noli et al, 2004)*.

> Dermatosparaxis/cutaneous asthenia

Dermatosparaxis is an inherited connective tissue disease characterized by excessive fragility and hyperextensibility of the skin. Because vitamin C is necessary in collagen synthesis, it may be useful in the treatment of feline patients with this disease. Although in contrast to dogs, two cats with dermatosparaxis treated with vitamin C did not improve *(Scott et al, 2001)*, one of the authors has seen improvement in two cats with this syndrome treated with vitamin C.

> Feline acne

Feline acne is a disorder characterized by comedones and crusts on the chin and lips **(Figure 13)** and the idiopathic form is considered a disorder of follicular keratinization *(Scott et al, 2001)*. It responds to a number of topical antimicrobial agents, but cats with recurrent feline acne have been reported to also benefit from fatty acid supplementation *(Rosenkrantz, 1991)*.

Figure 13 - Domestic short hair cat with acne. *Comedones and small crusts on the ventral chin.*

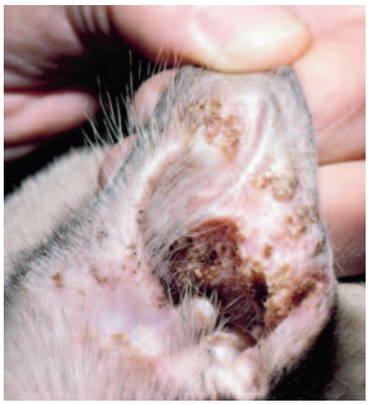

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Figure 14 - A cat with pemphigus foliaceus. *Crusts on the medial pinnae.*

TABLE 10 - 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

> Various immune-mediated diseases

Pemphigus foliaceus is a pustular and crusting skin disease **(Figure 14)** characterized by acantholysis of keratinocytes. Typically, immunosuppressive therapy with glucocorticoids or chlorambucil is recommended to treat feline pemphigus foliaceus. However, vitamin E and fatty acid supplementation have been reported to be useful in individual patients *(Scott et al, 2001)*. Similarly, vitamin E and essential fatty acids have been recommended as adjunctive treatment of feline discoid lupus erythematosus *(Scott et al, 2001)*.

► Prophylactic nutrition

In feline dermatology, nutritional interventions have been almost exclusively devoted to therapeutic functions. In human dermatology, nutrition is also used preventively. The problem with preventive nutritional intervention is the identification of the patient at risk. Although most cats kept as pets are domestic short hair cats and most diseases lack clear breed predispositions in the feline, some rare dermatoses show breed predisposition such as adverse food reactions in Siamese and thus may be suited to such interventions. Prospective controlled clinical studies are needed to evaluate the benefit of such an approach.

> Highly digestible foods

In human medicine, hydrolysates are mainly used in the prevention of adverse food reactions for high-risk children or their mothers to reduce the risk that clinical manifestations of atopy will develop **(Table 10)**. If such an approach is useful in feline medicine remains to be elucidated.

> Probiotics

In humans there is a significant difference between the intestinal flora of normal and that of atopic babies *(Bjorksten et al, 2001)*. Similarly, it has been shown, that supplementation of pregnant and breastfeeding mothers with *Lactobacillus rhamnosus* significantly decreases the clinical manifestations in their children *(Kalliomaki et al, 2003)*. In addition, supplementation with lactobacilli has improved the clinical signs of atopic children *(Rosenfeldt et al, 2003)*.

In the cat, the addition of probiotics in food or capsules presents technical problems. In a recent study, none of the probiotic supplements tested contained all the claimed bacteria *(Weese & Arroyo, 2003)*. However, it is possible to include probiotics in dry food and an effect on the feline immune response was observed after supplementation *(Marshall-Jones et al, 2006)*. If these probiotics could be used for the prevention or treatment of atopic disease awaits further study.

Conclusion

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

The treatment of many dermatoses involves the use of nutrients that reinforce the skin barrier function, or modulate the immune system, either as anti-inflammatory or as immunostimulatory agents. In the future, it is likely that more emphasis will be placed on the possible use of food for prophylactic purposes. Furthermore, the exact type and dose of optimal fatty acid supplementations and probiotics will need to be determined to greatly benefit our feline patients.

Frequently asked questions about the contribution of dietetics in dermatology

Q	A
Which nutritional deficiencies are most commonly implicated in feline dermatology?	Essential fatty acid and tyrosine deficiency are possible deficiencies leading to skin disease in cats.
Do cats get zinc deficiency?	In contrast to dogs, zinc deficiency has not been reported in cats.
Are adverse food reactions common?	In cats, adverse food reactions are more frequently seen than in the dog. An adverse food reaction should be considered particularly when head and neck pruritus are observed or there are concurrent gastrointestinal signs associated with the skin disease.
Which foods are the most likely to cause allergic reactions?	Fish, beef and dairy products are the most commonly reported food allergens in the cat. However, this may simply be due to the widespread use of these ingredients in cat food.
Is white meat less allergic than red meat?	This belief is incorrect. The color of the meat does not have any influence on its potential allergenic or hypoallergenic character. The risk increases with the quantity of meat ingested. Red meats such as venison are widely and successfully used as a basis for elimination diets, simply because these foods are not typically found in cat foods.
How do you diagnose atopic dermatitis in a cat?	Atopic dermatitis in the cat may present as a variety of cutaneous reaction patterns. These cutaneous reaction patterns in turn may be caused by many different diseases. Thus, the differential diagnoses for each patient with potential atopic dermatitis need to be ruled out prior to the diagnosis of atopic dermatitis. For example, all cats with potential atopy need to undergo strict flea control and an elimination diet to rule out flea bite hypersensitivity and adverse food reaction.
Can atopic dermatitis be controlled simply with PUFA supplementation?	Yes, but if the response is unsatisfactory after 6-12 weeks of treatment, other therapeutics should be used.
Can diet be the cause of non-inflammatory “endocrine” alopecia in the cat?	Years ago, non-inflammatory alopecia was considered a hormonal disease. However, true endocrine alopecia in cats is very rare. Subsequently, this disease was diagnosed as psychogenic alopecia. Some patients indeed develop psychogenic alopecia and responded to behavioral therapy. However, many of these cats are actually allergic cats; the overgrooming and alopecia is a response to pruritus. An elimination diet to rule out adverse food reaction is an essential diagnostic tool in every cat with non-inflammatory alopecia.

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Focus on:

Borage oil

Borage *(Borago officinalis)* is a plant originally from Syria. It is now grown in North Africa and various countries of Europe, including France, Britain, Germany and the Netherlands. The first traces of its use are from the first century AD. Traditionally, the young leaves were consumed in salads or soups and the flowers gave a refreshing flavor to wine.

Borage seeds

Borage blooms over two months, which means that not all the seeds become mature at the same time. It is important to only harvest the mature seeds, which look like grains of pepper, as they have twice the oil content of green seeds (30% vs. 15%).

Harvesting may be done naturally – recovering the seeds as they fall by rolling out a tarp between the rows – or mechanically, using small carts to catch the seeds, which are loosened by vibration.

Borage oil

The seeds dry out naturally somewhere cool in the shade. To avoid mold, they must be used shortly after harvesting. The oil is obtained by grinding and pressing the seeds. The procedure is performed in a cold environment. Above 50 °C (122°F), the fatty acids risk being denatured.

Unparalleled gamma-linolenic acid (GLA) content

The oil is obtained by pressing the borage seeds. Their unsaturated fatty acid content is 80% and they have a large content of a particular fatty acid of the omega-6 family, known as gamma-linolenic acid (GLA). GLA is normally synthesized from linoleic acid.

Most vegetable oils have a very high linoleic acid content, but the only oils that contain a beneficial quantity of GLA are borage oil, the oil of blackcurrant seeds and evening primrose oil.

Linoleic acid undergoes successive transformations to produce all the fatty acids of the omega-6 family. Each step is triggered by a particular enzyme. The metabolism of unsaturated fatty acids in cats remains a controversial subject. Some authors feel that Δ6 desaturase is ineffective in cats *(Sinclair et al., 1979)*. More recent studies *(Pawlosky et al., 1994)* show that the conversion of linoleic acid to GLA is possible, with increased efficacy when the animal is deficient. This process however remains limited in the cat. In this study, the authors reported that only 0.06% of the ingested linoleic acid was converted to GLA.

Nutritional benefit of GLA


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Borage oil is widely used in nutrition and cosmetology. It is used in products designed to rejuvenate the skin. It is especially indicated for the dry skin of cats that tend towards seborrhea. Cats respond very well to the addition of GLA to the diet.


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The supplementation of GLA promotes the increased production of type 1 prostaglandins over the production of type 2 prostaglandins, which are much more pro-inflammatory. Borage oil is accordingly potentially beneficial in all situations demanding an anti-inflammatory effect.


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Comparison of the GLA content of different vegetable oils

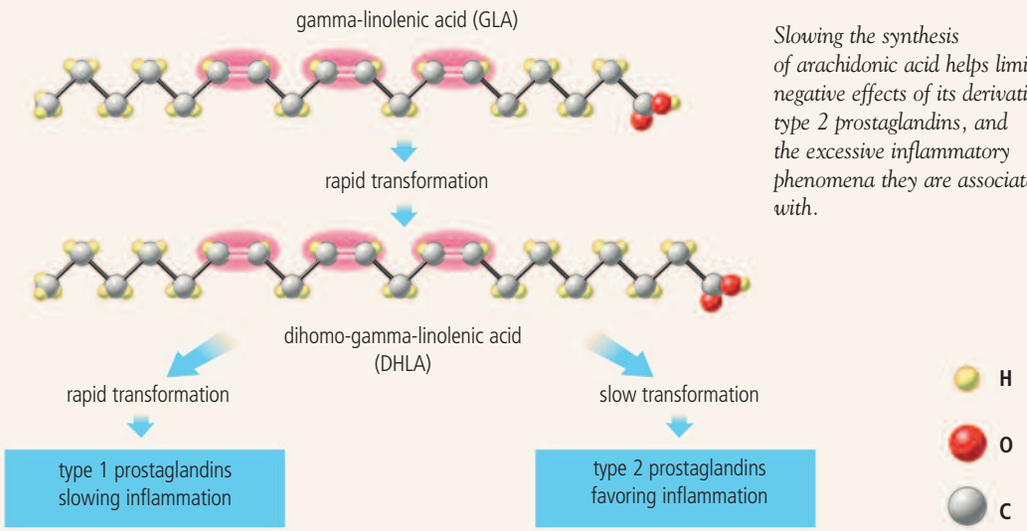
Vegetable sources	Linoleic acid%	Gamma-linolenic acid (GLA)%
Borage	35 to 40	20 to 25
Blackcurrant seeds	45 to 50	15 to 20
Evening primrose	70 to 80	8 to 12
Soy	50 to 55	-
Olive	8 to 10	-

Borage oil has the highest GLA concentration.

The beneficial effects of GLA have been studied most in dermatology. Major alterations to the condition of the skin (dull hair, scaling and skin ulcers that do not heal easily) are observed in cats fed for 18 months with a food containing sunflower seed oil, which is rich in linoleic acid, as the sole source of fat *(Frankel & Rivers, 1978)*. Substituting half the sunflower seed oil with evening primrose oil, which is rich in GLA, helps obtain a fast improvement in the condition of the skin in these animals. Reversion to the original diet results in deterioration of the condition of the skin again. This study therefore confirms the benefit of high GLA oil supplementation to alter linoleic acid desaturation.

Other studies show the benefit of GLA intake in feline dermatology. In cats with papulo-squamous dermatitis, the dietary incorporation of evening primrose oil, helped to obtain better therapeutic results than sunflower oil, *(Harvey, 1993a)*. With feline miliary dermatitis, the efficacy of GLA administration was improved when it was combined with fish oil *(Harvey, 1993b)*.

ORIGIN OF THE BALANCE BETWEEN TYPE 1 AND 2 PROSTAGLANDINS



Slowing the synthesis of arachidonic acid helps limit the negative effects of its derivatives, type 2 prostaglandins, and the excessive inflammatory phenomena they are associated with.

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Protein composition of cat hair

The daily protein requirement to regenerate skin cells and stimulate hair growth is estimated at almost 30% of the daily protein intake (Scott et al, 2001).

There is little data on the amino acid composition of hair. It is determined through hydrolysis with hydrochloric acid for 24 hours. This method may however lead to the degradation of some amino acids or underestimate the content when hydrolysis is incomplete. Studies *(Robel & Crane, 1972; Darragh et al, 1996)* have reported alternative techniques to minimize these inaccuracies. *Hendriks et al* (1998) reported that the color or sex of the animal has no impact on the amino acid composition of the hair.

TABLE 1 - AMINO ACID COMPOSITION OF THE HAIRS OF CATS AND SOME OTHER MAMMALS
(From Hendriks et al, 1998)

Amino acid	Content (mol/100 mol of residue)				
	Cat	Dog	Horse	Sheep	Human
Cysteine	15.9	16.7	14.4	13.1	17.8
Methionine	0.9	0.9	0.2	0.5	0.6
Aspartate	5.6	5.3	6.0	5.9	4.9
Threonine	6.4	6.2	6.5	6.5	6.8
Serine	10.6	10.5	9.6	10.8	11.7
Glutamate	11.4	11.1	11.3	11.1	11.4
Glycine	9.5	7.8	6.4	8.6	6.4
Alanine	5.1	5.1	5.5	5.2	4.6
Valine	4.9	4.9	5.9	5.7	5.8
Isoleucine	2.5	2.5	3.6	3.0	2.6
Leucine	6.7	6.1	7.5	7.2	5.8
Tyrosine	3.0	2.7	1.9	3.8	2.0
Phenylalanine	2.3	1.7	2.5	2.5	1.6
Histidine	1.2	0.9	1.1	0.8	0.9
Lysine	2.9	3.9	2.9	2.7	2.7
Arginine	6.1	6.3	7.9	6.2	5.8
Proline	4.9	7.3	7.8	6.6	8.4

The total nitrogen content of cat hair is said to be 15.1% *(Hendriks et al, 1998)*. This author also reported that amino acids represent 86% of the hair mass in this species. The remainder is divided between non-nitrogen compounds: minerals, sterols and complex lipids.

The amino acid composition of cat hair is similar to that of dogs, sheep, horses and humans, although the proline content in cats is lower than in the other species. The most abundant amino acids in cat hair protein are cysteine, serine, glutamic acid and glycine **(Table 1)**. Sulphur containing amino acids can account for up to 37% of the total amino acids *(Swift & Smith, 2000)*. They build cysteine bridges, which are essential to hair construction. Cysteine is also involved in the enzymatic production of pheomelanin *(Granholm, 1996)*.

Animal color or sex has no impact on the amino acid composition of the hair.

Key points

for covering protein requirement with respect to hair growth

The quantity of amino acids required for hair growth in a given period of the year can be estimated by multiplying the amino acid concentration in each cat hair by the hair growth rate during that period of the year *(Hendriks et al, 1998)*. The daily protein requirement to regenerate skin cells and stimulate hair growth is estimated at almost 30% of daily protein intake *(Scott et al, 2001)*.

The effects of general protein deficiency:

- Initially, a drop in the diameter of the hair and reduction in the size of the hair bulb
- Subsequently, the hair becomes dull and fragile, growing more slowly and falling out faster.

Isolated deficiency of sulfur amino acids (cysteine, methionine) may lead to the same clinical signs.

Studies show the impact of a deficiency of tyrosine and phenylalanine, a melanin precursor. After a few weeks red hairs begin to appear, especially in black cats. Supplementation reverses this phenomenon. The hairs of reddish cats (which have pheomelanin pigments) also take on a lighter color in response to deficiency *(Morris et al, 2002; Anderson et al, 2002; Yu et al, 2001)*. *Morris et al* (2002) show that around three times as much phenylalanine and tyrosine is needed to obtain optimal coloration of a black coat than is needed for the normal growth of a kitten. These authors recommend a minimum intake of 18 g/kg of dry dietary matter.

Around three times as much phenylalanine and tyrosine is needed to obtain optimal coloration of a black coat than is needed for the normal growth of a kitten.

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Digestive diseases in cats: the role of nutrition

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ABBREVIATIONS USED IN THIS CHAPTER

BIPS: barium-impregnated polyethylene spheres
IBD: inflammatory bowel disease
Ig (A, G or M): immunoglobulin
IL (6, 10, 12): interleukin
MHC: major histocompatability complex
NSAID: non-steroidal anti-inflammatory drug
PCR: polymerase chain reaction
PEG: percutaneous endoscopic gastrostomy
PLE: protein-losing enteropathy
PPN: partial parenteral nutrition
SCFA: short chain fatty acid
TDF: total dietary fiber
TGF β: transforming growth factor beta
TNF α: tumor necrosis factor alpha
TPN: total parenteral nutrition

Digestive diseases in cats: the role of nutrition

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Jürgen Zentek graduated from the Faculty of Veterinary Medicine (Tierärzliche Hochschule) in Hanover, Germany in 1985. After employment in a veterinary practice, in 1987 he led a research project at the Department of Animal Nutrition, studying the energy intake and skeletal development in growing Great Danes. He obtained his degree as a specialist in animal nutrition and dietetics in 1993. After a year in Bristol, UK, at the School of Veterinary Science, he took the Chair of Clinical Nutrition at the Veterinary University of Vienna in 2000, becoming the Head of the Institute of Nutrition. Since 2005 he has been a Professor of the University of Berlin. His ongoing research is on clinical dietetics of domesticated animals, the relationship between nutrition, intestinal microflora and immunity of the GI tract.

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Nutrition is the cornerstone of the treatment of digestive diseases. However, considering actual pathophysiological knowledge about gastroenterology, it seems obvious that there is no diet adapted to all kinds of digestive cases. The general objectives of the diet are: stimulating dietary consumption, improving digestion and nutrient absorption, maintaining normal digestive motility and intestinal transit, and decrease inflammation when it exists. In addition, the dietetic strategy must plan to provide the right nutrients to optimize the bacterial flora and to protect the mucosal barrier.

1 - Physiology of the gastrointestinal tract

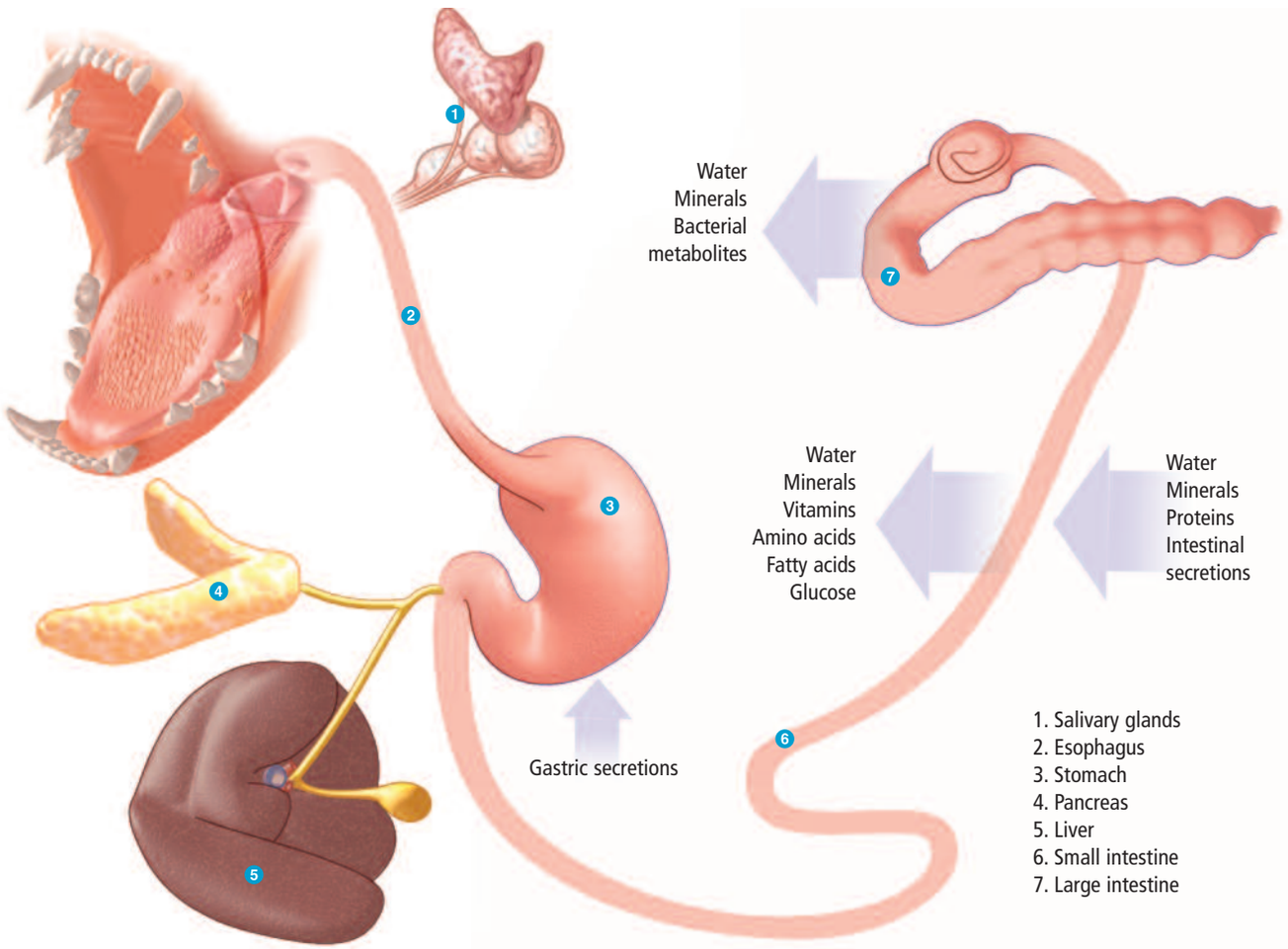
► Oral cavity (Figure 1)

Morphologically and physiologically, domestic cats are highly specialized carnivores, as shown by their dentition, nutritional requirements and sense of taste *(Bradshaw, 2006)*. The tongue is rough and has multiple hooklike appendages. These filiform or fungiform papillae enable the cat to lick up liquids and to scrape flesh off bones *(Ojima et al, 1997)*. There are approximately 250 fungiform papillae on the tongue of an adult cat; they are most numerous on the tip. Their size – and the mean number of taste buds – increases from the tip to the back of the tongue *(Robinson & Winkles, 1990)*. A cat's sense of taste – except sweetness – is mediated via taste buds mainly located in the tongue. The cat has specific and unique feeding preferences linked to its ability to smell amino acids and peptides *(Zaghini & Biagi, 2005)*. The dentition of cats is typical of carnivores. Cats have 26 milk teeth that are replaced at age five to seven months by 30 permanent teeth. The permanent dentition is made up of 12 incisors, 4 canines, 10 premolars and 4 molars **(see chapter 11)**.

► Esophagus (Figure 1)

The esophagus is a tube that transports food from the mouth to the stomach. At body weights of 4-5 kg, the average length is 22-23 cm. The cervical segment of the esophagus accounts for about one third of the whole length and the thoracic segment about two thirds (the abdominal segment is very short in the cat) *(Hegner & Vollmerhaus, 1997)*. Coordinated contraction of the longitudinal and circular esophageal musculature is important for the peristaltic transport of a

FIGURE 1 - GENERAL DIGESTIVE TRACT ANATOMY IN THE CAT



food bolus through the esophagus (*Dodds et al, 1973*). Motility is subject to a myogenic control system and additional nerve control mechanisms (*Preiksaitis & Diamant, 1999*). The esophageal glands produce a mucinous secretion that helps lubricate the food bolus. Although cats are able to swallow large pieces of food or prey, the esophageal passage of capsules or tablets may be prolonged or tablets may become trapped due to their diameter or surface structure (*Graham et al, 2000*). The possibility of medication-induced esophagitis should be considered when administering ulcerogenic drugs to cats.

► Stomach (Figure 1)

The stomach has a comparatively large capacity for prey or food storage. The stomach may be subdivided into several anatomical and functional regions. The cardia is the site of entry, the fundus, body and antrum are the middle parts and the pylorus is the transitional zone to the duodenum. Normally, gastric emptying delivers food to the small intestine at a rate that allows optimal intestinal absorption of nutrients (*Wyse et al, 2003*). The pylorus is surrounded by muscle tissue and regulates food transport into the duodenum. The pyloric muscle prevents the reflux of duodenal contents and bile into the stomach lumen.

Endocrine G-cells are scattered diffusely in the basal part of the mucosa and produce gastrin, a major stimulus of gastric secretory response to meal intake (*Cerny et al, 1991*). In the stomach, hydrochloric acid secretion by the oxytic cells and pepsin, secreted as pepsinogen by the chief cells, initiate protein digestion.

Lipase activity occurs in the surface mucous cells in newborn cats after ingestion of milk (*Knospe & Plendl, 1997*). Lipase is localized as pepsin in the chief cells but is also present in pepsin-free cells, the mucus surface cells of the fundus and the antrum (*Descroix-Vagne et al, 1993*).

Gastric motility and emptying is subject to various regulatory mechanisms, including reflectory, neural and endocrine factors. Diet composition may affect gastric emptying, with fat and large particle size having a delaying effect (*Strombeck, & Guilford 1996a; Hall & Washabau, 1999*). The stomach can retain ingesta for up to 15 hours before it passes to the intestine (*Brugère, 1996*). The gastric transit time, determined from the first exit of barium-impregnated polyethylene spheres (BIPS) from the stomach had a median of 6 h (range 3 to 8) in sedated and a median of 2.5 (range 2 to 6) in unsedated cats. The median of 50% gastric emptying time was 6.4 h (range 2.5 to 10.9), and complete gastric emptying was seen after 12 h with a range 6 to 27 h. The orocecal transit time of BIPS was 6.5 h and the 50% orocecal transit time was 8.8 h (range 4.6 to 12.8) (*Sparkes et al, 1997*).

► Small intestine (Figure 1)

The duodenum, jejunum and ileum are the three histologically defined parts of the small intestine. Bile and the pancreatic secretions enter into the duodenum via the common bile duct and are necessary for the solubilization of fat and the enzymatic digestion of the intestinal content.

The small intestinal mucosa has a specific structure with crypts and microvilli covered by a single epithelial layer. The crypts are the location for cell proliferation. The absorptive enterocytes bear a high density of microvilli, which increases the surface area substantially. The paracellular space is closed by different proteins with specific functions that prevent uncontrolled permeation of bacteria or macromolecules through the intestinal wall. A mucous layer, the glycocalix, consisting of carbohydrates and proteins, covers the brush border. The glycocalix has a high enzymatic activity for the breakdown of macromolecules to absorbable units and provides a specific microenvironment for bacteria associated with the gut wall.

Besides its absorptive capacity, the small intestine has a considerable secretory capacity via the crypts and the goblet cells. Endocrine cells contribute to the regulation of the digestive processes.

The duodenal glands are located caudally to the pylorus and produce mucous secretion with neutral, sulphated and carboxylated acid mucosaccharides *(Takehana & Abe, 1983)*. The compounds in food that have passed through the small intestine undigested or unabsorbed enter the large intestine and are fermented by microbial enzymes. A sphincter terminates the small intestine and prevents reflux of chyme and bacteria.

TABLE 1 - RESPECTIVE PROPORTIONS OF THE INTESTINE IN SELECT SPECIES
*From: *Barone, 1984; **Meyer et al, 1993; ***Dukes, 1984*

	Dogs	Cats	Humans
Small intestine*	1.7 - 6 m	1.0 - 1.7 m	6 - 6.5 m
Large intestine*	0.3 - 1 m	0.3 - 0.4 m	1.5 m
Relative weight of the digestive tract/body weight**	2.7% (giant dogs) to 7% (small dogs)	7%	10%
Body length/ intestinal length***	1/6	1/4	1/5

► Large intestine (Figure 1)

The cecum, colon and rectum are the three parts of the large intestine where undigested organic matter is fermented and fluid, minerals and bacterial metabolites are absorbed. Due to the carnivorous character of the cat, the size of the large intestine is small **(Table 1)**, probably because there was no evolutionary need for a large fermentation chamber *(Chivers & Hladik, 1980)*. The large intestine has no microvilli and its surface morphology differs considerably from the small intestine. The crypts of Lieberkuhn contain absorptive and secretory cells. The large intestine of cats is characterized by a dense microbial community with high metabolic activity.

2 - Physiology of nutrient digestion

► Protein digestion (Figure 2)

Protein digestion is located in the upper gastrointestinal tract. Cats are normally very efficient in protein digestion and the apparent digestibility of proteins is similar to dogs *(Zentek et al, 1998; Funaba et al, 2005)*. The digestive capacity of the younger cat may be lower than that of adult animals, due either to the physiological development of the gut or diet-induced enzyme modulation *(Harper & Turner, 2000)*.

Protein digestion is initiated in the stomach. A sequence of proteolytic enzymes is required to split the dietary proteins. Most important are endopeptidases such as pepsin or trypsin. Proteins are initially digested by pepsins *(Shaw & Wright, 1976)*. Pepsins require an acidic environment for their activation: cats produce a highly acidic gastric secretion, the pH in the feline stomach varies from 2-3 *(Hall, 2000)*. Pepsin is deactivated as soon as it enters the alkaline milieu of the duodenum and jejunum.

The small intestine has a slightly alkaline pH due to the secretions of the epithelial glands and the bicarbonate-rich pancreatic juice *(Williams, 1996)*. This is necessary for the continuation of protein digestion by the proteolytic enzymes of the pancreas and the small intestinal mucosa. Feline trypsin seems to occur in one isoform only and trypsinogen, which is activated to trypsin by the activity of intestinal enterokinase, is closely related to the trypsinogen in other mammalian species *(Steiner et al, 1997)*. Luminal protein digestion releases small peptides and amino acids that are transported through the brush border and absorbed by specific active carrier-mediated transport mechanisms through the gut wall.

FIGURE 2 - DIGESTION AND ABSORPTION OF PROTEINS

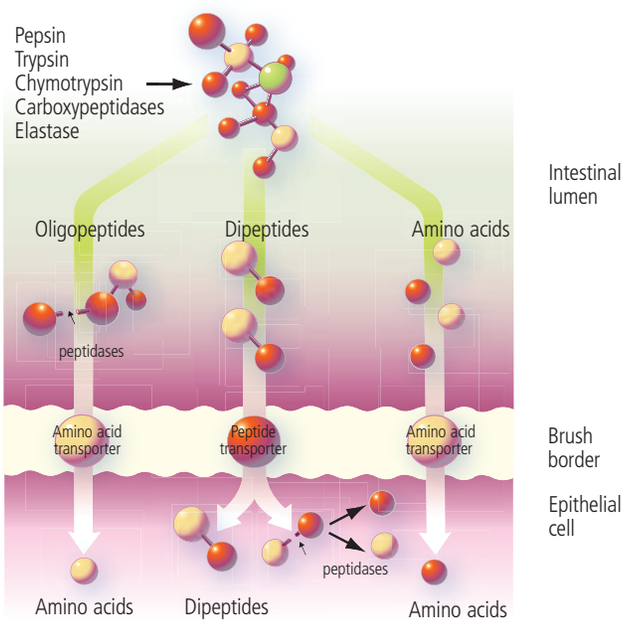


Figure 3 - Digestion and absorption of carbohydrates

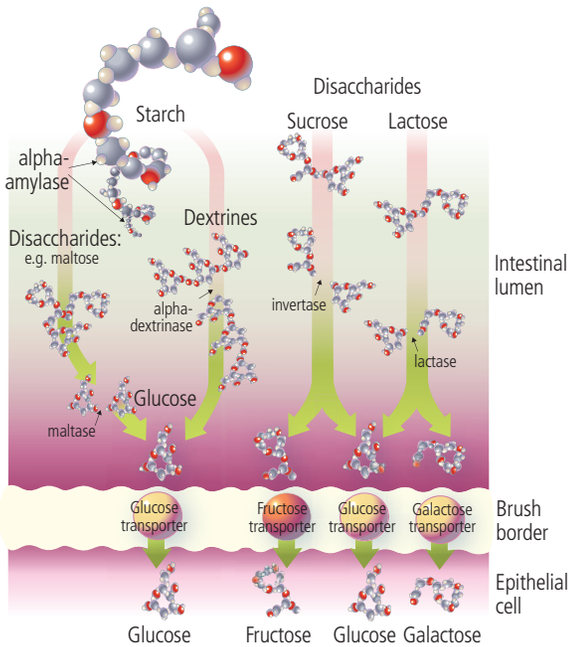
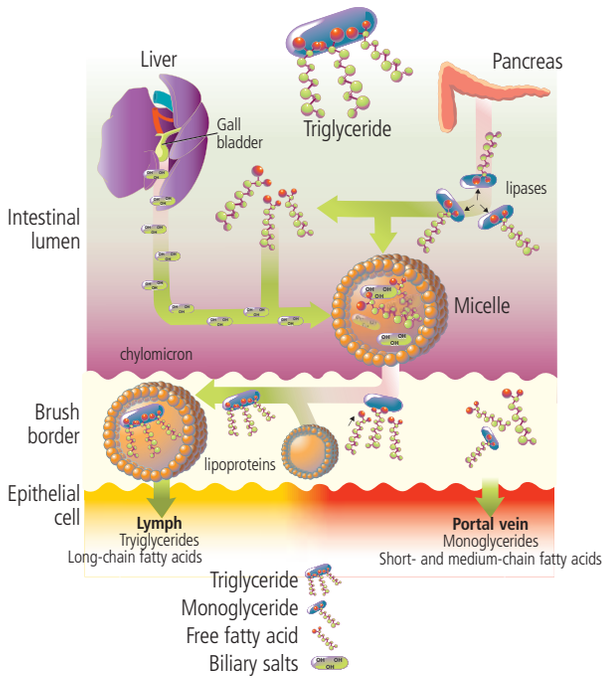


Figure 4 - Digestion and absorption of fats



Uptakes of arginine and lysine were high throughout the suckling period and the perinatal intestinal hyperplasia observed in many other mammalian species seems to be absent in cats *(Buddington & Diamond, 1992)*.

► Carbohydrate digestion (Figure 3)

The cat's ability to digest and tolerate such complex carbohydrates as starch is very high, although amylase activity in pancreatic tissue and small intestinal content is low compared to most other species *(Kienzle, 1993)*. It decreases in the lower gut, probably due to intensive microbial degradation. Dietary carbohydrate levels had no obvious inductive effect on disaccharidase activities.

Maltase, isomaltase and sucrase activity did not depend on age. In contrast, lactase activity decreased from newborn kittens to adult cats and only few adult cats can have significant lactase activity in the jejunum *(Kienzle, 1993)*. The tolerance for simple sugars is much more limited due to a limited intermediary capacity for sugar metabolism compared to most other species *(Morris et al, 1977; Kienzle, 1994; Appleton et al, 2004)*. Apparent total digestibility of sugars was determined in adult cats and reached almost 100%. However, the prececal digestibility may be considerably lower depending on the sugar source and the degree that the starch is cooked *(Kienzle, 1993)*.

► Fat digestion (Figure 4)

Cats are well adapted to fat digestion. Fats are not only important energy sources but also have additional functional properties *(Bauer, 2006)*. Obviously, healthy cats can tolerate high dietary fat levels without a negative impact on digestive function. An age-related reduction in apparent fat digestibility was observed in cats fed on different fat sources with different degrees of saturation. Saturated fatty acids had a slightly lower apparent digestibility in young and senior cats *(Peachey et al, 1999)*.

Fat digestion may be severely impaired in cats with exocrine pancreatic insufficiency *(Nicholson et al, 1989)* or in animals with impaired bile secretion. Bile acids are not only important for the solubilization of fatty acids but also for the activation of pancreatic lipase *(Strombeck, 1996b)*. Bile acids are reabsorbed in the ileum and re-circulated to the liver. The absorbed long chain fatty acids are re-esterified in the intestinal epithelium and incorporated into chylomicrons before the release into lymphatics. Medium chain fatty acids can be absorbed directly into the blood, but palatability of medium chain fatty acids is usually low in this species *(MacDonald et al, 1985)*.

3 - Microbiology of the gastrointestinal tract

Microbial colonization of the gastrointestinal tract starts directly after birth, and the composition of the intestinal microflora approaches the spectrum of adult cats during the first weeks of life *(Osbaldiston & Stowe, 1971)*. The development of the microflora in kittens is comparable to other species: *Clostridium perfringens*, *Escherichia coli* and *Streptococci* are among the first organisms to colonize the alimentary tract of kittens. The gut flora of cats is characterized by relatively high numbers of *Clostridium perfringens* and lecithinase negative clostridia, probably reflecting the carnivorous type of diet. Normally, the intestinal microflora maintains a self stabilizing symbiotic balance with the host organism *(Strombeck, 1996a)*. The bacterial concentration in all parts of the gastrointestinal tract of healthy cats is high and bacterial densities of 10^{12}/g feces, mainly anerobic bacteria, are normal.

The intestinal microflora may contribute to the health and well-being of the host, supporting the digestive process, but it may also be a significant factor in the pathogenesis of intestinal diseases. Its composition and metabolic activity is subjected to influences by the individual and interfering diseases. Diet composition, protein quantity and quality, feed processing *(Backus et al, 1994)*, dietary fiber and digestible carbohydrates *(Fahey, 2003)* and feed additives such as probiotics *(Rastall, 2004; Marshall Jones et al, 2006)* also affect the composition of the microbiota.

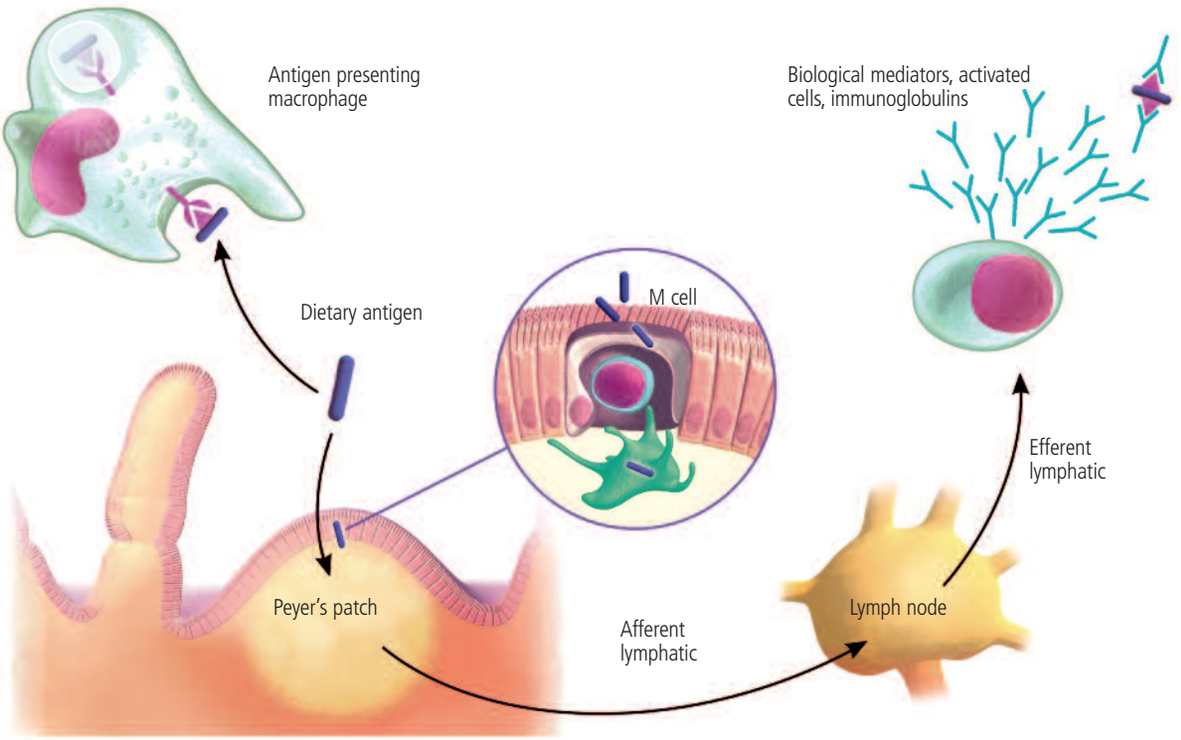
4 - Gastrointestinal mucosal immune system **(Figure 5)**

The gastrointestinal tract contains a dense population of immune cells with multiple characteristics and functions. Its main task in healthy animals is to achieve tolerance against dietary and endogenous bacterial antigens. On the other hand, the gastrointestinal immune system must be conditionally reactive against pathogenic bacteria or harmful environmental antigens.

The gut-associated immune system has anatomically defined and diffuse structures. These may act specifically as inductive or effective sites, providing the ability for an adequate immune response. The intestinal mucosa harbors a high density of immune cells that are often organized in cell clusters, either visible as lymph follicles or more prominently as Peyer's patches. Given the antibody secreting cells, IgA+ plasma cells predominate in the small intestine, and IgM+ plasma cells are found in higher concentrations than IgG+ plasma cells *(Waly et al, 2001)*. Plasma cells are found in all regions of the small intestine with greater numbers in the lamina propria and Peyer's patches compared to the epithelium *(Howard et al, 2005)*.

Cats have elevated numbers of intraepithelial lymphocytes a proportion of which express surface IgM, but the significance of this finding is still uncertain. T-cells (CD3+) and T-cell subsets (CD4+ and CD8+) follow a specific distribution pattern with greater numbers in the villous lamina propria than in the lamina adjacent to the crypts. Intra-epithelial lymphocytes are mainly CD8+ T lymphocytes; CD4+ T-cells dominate in the lamina propria. Antigen presenting macrophages and

FIGURE 5 - THE INTESTINAL IMMUNE SYSTEM



The gastrointestinal immune system of recognition of dietary antigens is mainly due to Peyer's patches and antigen presenting macrophages. The effective mechanisms are dispatched in diffuse intestinal structures.

dendritic cells in the lamina propria express L1 and major histocompatibility complex (MHC) class II. B-cells predominate in Peyer's patches with 40% B-cells, 28% CD4+ T-cells and 20% CD8+ T-cells.

Diseases that are associated with infections or allergic reactions in the gastrointestinal tract involve the local or general immune system *(Day, 2005; Stokes & Waly, 2006)*. IgA is the dominant immunoglobulin in intestinal secretions of cats, as in other species. Normally, oral tolerance is induced for short periods after introduction of novel antigens into the diet. In cases of dysregulated immune response, cats may become hypersensitive to the newly introduced dietary antigen prior to the establishment of tolerance.

MHC class II expression by leukocytes with dendritic cell or macrophage morphology in the lamina propria was significantly greater in cats with inflammatory bowel disease compared to healthy cats. MHC class II expression by enterocytes was also more pronounced in diseased cats *(Waly et al, 2004)*.

Cytokine expression seems to be important in determining the reaction of the gastrointestinal immune system to antigen challenges. Cats with intestinal inflammation had significantly more transcription of pro-inflammatory and immunoregulatory genes encoding IL-6, IL-10, IL-12, p40, TNF-α and TGF-β than cats with normal histology *(Cave, 2003; Nguyen Van et al, 2006)*.

5 - Common gastrointestinal syndromes in cats

► Dysphagia

Dysphagia is a difficulty in swallowing. It may be due to an obstruction, a painful oropharyngeal or esophageal disorder, or it may be a motility problem *(Washabau, 2005)*. The main sign is regurgitation.

Regurgitation is defined as the passive expulsion of saliva or non-digested food. It often occurs very soon after the ingestion of food, although in the event of saliva regurgitation it may occur less rapidly. Contrary to vomiting, regurgitation occurs suddenly, without prodromal signs or abdominal contractions *(Guilford & Strombeck, 1996b)*.

An esophageal disorder produces other clinical signs:
- ptyalism
- halitosis
- dysorexia or anorexia
- odynophagia (painful swallowing)
- polypnea
- coughing and/or discharge in the event of secondary pneumonia.

> Complementary tests

Plain radiography

Physiologically, the esophagus cannot be visualized by radiography. Its appearance on a plain radiograph may be due to localized or generalized dilatation, or to the retention of liquids or solids. These images enable the identification of a radiodense foreign body or suggest the presence of a foreign body based on indirect signs (localized dilatation, localized air densification, pneumomediastinum) *(Konde & Pugh, 2003)*.

Radiography with contrast medium

This confirms any dilatation if the plain radiographs are insufficient. The use of barium is contraindicated if parietal perforation is suspected due to the risk of mediastinitis. The presence of image subtraction suggests a foreign body or an endoluminal mass.

Fluoroscopy

This dynamic test is worthwhile when a functional problem is suspected. It may be beneficial when evaluating the extent of stenosis **(Figure 6)**.

Esophagoscopy

The endoscopic examination **(Figure 7)**, which is conducted under general anesthesia, is the examination of choice to explore all esophageal disorders of anatomical, inflammatory or neoplastic origin. It enables immediate macroscopic evaluation of the surface of the mucosa, biopsies, extraction of foreign bodies or enables dilatation of post-inflammatory or post-traumatic stenosis.

► Vomiting

Vomiting is defined as the active reflexive rejection of the stomach content preceded by prodromal signs (nausea, ptyalism, abdominal contractions). The dietary behavior and lifestyle of carnivores mean that occasional vomiting is not considered alarming. In its more acute and more frequent form however, it is one of the main reasons among cats for a visit to the veterinarian.

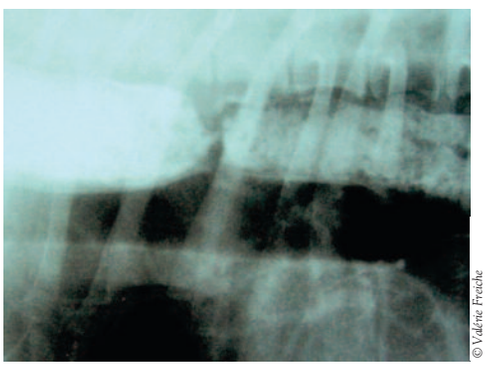


***Figure 6** - Radiograph with contrast medium that indicates esophageal stenosis.*

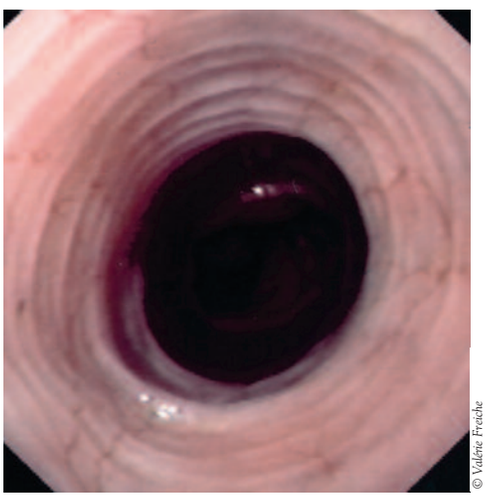


***Figure 7** - Esophagoscopy. Normal aspect of the distal esophagus of a cat showing characteristic rings*

There are a huge number of disorders that can cause vomiting. Therefore, the etiological diagnosis, when justified, is based on a number of tests, which must be conducted as part of a logical approach. The digestive causes of acute or chronic vomiting are considered after the exclusion of all other potential causes in cats: viral infections, hernias, neoplasia, metabolic diseases, kidney failure, neuroendocrine diseases, intoxication and others *(Moore, 1992; Gaschen & Neiger, 2004; Simpson, 2005)*.

Vomiting with a digestive origin may be due to stomach problems. The most common are: inflammatory diseases, neoplasia, the presence of hairballs, pyloric obstruction, ulceration or foreign bodies **(Figure 8)**. Primary gastric motility problems may be suspected with chronic vomiting, however, they are more common in dogs than in cats. In the absence of a specific disorder, there may be a problem with stomach emptying *(Hall & Washabau, 1999)*.

In cats, vomiting may also be a sign of a more distal disorder, even in the absence of any other sign. This is a peculiarity of the species. Major causes of vomiting not situated in the stomach include pancreatic diseases, inflammatory diseases or cholecystitis *(Strombeck & Guilford, 1996b)*.

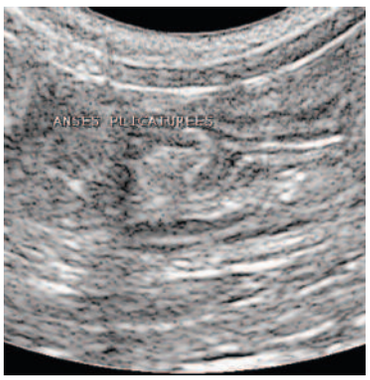


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Figure 8 - 5 year old female cat who presented with anorexia.
The abdominal ultrasound shows loops of the small intestine that are abnormally collapsed due to the presence of a linear foreign body.

> Signs of vomiting

The aspect or chronology of vomiting with respect to the ingestion of food sometimes provides some pointers. Some criteria are reliable:
- uncontrollable or unpredictable vomiting suggests an occlusive syndrome, peritonitis, pancreatitis, cholangiohepatitis, a metabolic, or a severe viral disorder;
- the presence of undigested food well after meal time suggests a gastric retention syndrome (functional or anatomical in origin) or pancreatitis;
- vomiting in the morning before eating is common with chronic gastritis (or reflux gastritis);
- a large volume is common with an occlusive syndrome or delayed gastric emptying.

However, the nature or time of vomiting with respect to meal time commonly provides no pointers as to the cause:
- the presence of blood may be evidence of an underlying disorder with a very poor prognosis (neoplasia) or conversely an entirely benign and reversible inflammatory state.
- some neoplastic diseases are expressed by crude, non-specific symptoms, that emerge slowly;
- chronic sub-occlusive states are difficult to characterize, especially if they are caused by the ingestion of a linear foreign body.

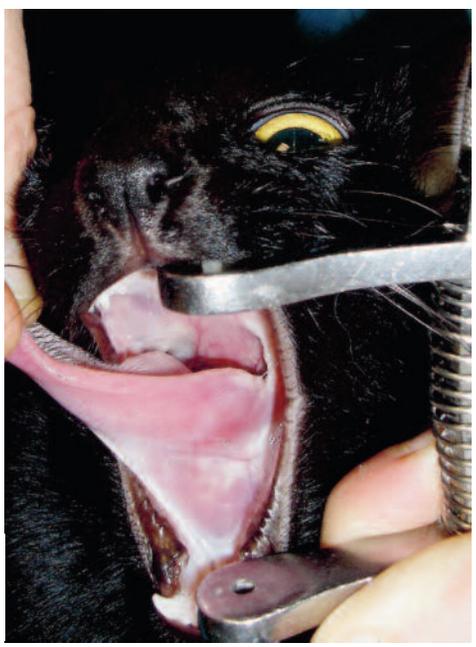

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Figure 9 - Foreign body in the oral cavity.
The inspection of the oral cavity is part of the clinical examination. A linear foreign body attached to the base of the tongue can be extracted.

> Clinical examination

There must be a precise and complete clinical examination as part of an internal medicine approach *(Tams, 1996)*. If the cat is not cooperative, moderate sedation will make the examination easier.
- An inspection of the oral cavity **(Figure 9)** must always be conducted. It may reveal the ingestion of a linear foreign body or ulcers caused by uremia.
- Abdominal palpation is likely to provide pointers, such as the identification of a compressive digestive or extra-digestive mass, or palpation of a foreign body. The pressure generated by palpation may reveal induration or the presence of isolated sources of pain. Indirect signs are also seen, such as the accumulation of gas or fluid in front of a digestive lesion.
- If the cat is not obese, the presence of hyperplastic lymph nodes must always be palpated.
- A rectal swab (which generally necessitates tranquilization) enables evaluation of the rectal mucosa and the acquisition of a fecal sample (traces of fresh or digested blood).
- The hydration state of the cat.

Table 2 - Benefits of complementary tests used in the diagnostic evaluation of vomiting

Complementary test	Diagnostic benefit: specific searches
Hematological analyses (blood count/CBC)	Anemia – Leucopenia or leucocytosis
Biochemical analyses; basal T_4	Metabolic diseases – Hyperthyroidism – Hypoproteinemia
Serum electrolytes	Dehydration – Addison's Disease (highly unlikely)
Urine analysis	Urine specific gravity – pH
Plain radiography	Radiodense foreign bodies – Digestive mass – Ascites – Ileus
Contrast radiography	Foreign bodies – Parietal modifications
Abdominal ultrasound	Digestive parietal lesions – Foreign bodies – Abdominal lymphadenopathy – Peristalsis – Other abdominal organs
Gastointestinal endoscopy	Gastro-duodenal, distal ileal and colonic parietal lesions – Gastric and duodenal foreign bodies (limits if linear foreign body)

> Diagnosis

Table 2 lists the benefits of complementary tests that may be conducted in the evaluation of a vomiting patient.

► Gastric retention syndrome

Gastric retention syndrome is defined as the stomach's incapacity to evacuate its content within the physiological time. This may be due to digestive lesions or functional disorders (primary or secondary digestive motor disturbances). Although more common in dogs, this syndrome has been reported in cats. The clinical signs include vomiting of partially digested food well after mealtime.

> Etiology of gastric retention syndrome

Obstructive digestive or extra-digestive compressive lesions

Some form of pyloric stenosis is the most common cause of gastric retention syndrome in domesticated carnivores. If they are intrinsic, they may be the result of several pathophysiological mechanisms.

- **Congenital pyloric stenosis (Figure 10)**: found in young animals, is due to hypertrophy of the smooth muscle fiber. In cats, it is described in Asiatic breeds, specifically the Siamese *(Strombeck, 1978)*

- **Secondary gastric retention syndrome with hairball (Figure 11)**, which can be lodged chronically and generate repetitive intermittent vomiting.

- **Post-inflammatory pyloric stenosis (Figure 12)**: healed pyloric lesions (old ulcerations, chronic inflammatory lesions causing major parietal fibrosis, foreign bodies trapped in the antral-pyloric mucosa) sometimes cause acquired stenosing lesions.

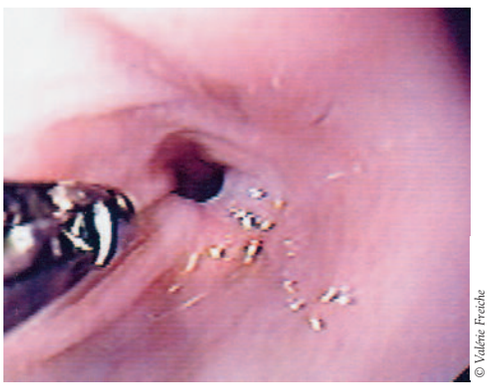
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Figure 10 - Pyloric stenosis in a young European cat a few months of age.
The pyloric diameter compared to biopsy forceps (2.8 mm).


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Figure 11 - Hairball secreted by a Japanese Bobtail (length: 5.5 cm).
Hairballs are the primary cause of gastric retention in cats.

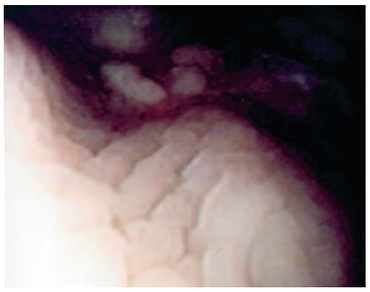
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Figure 12 - Post-inflammatory pyloric stenosis in a European cat who historically had gastritis. *Edema is visible in the mucosal antral area.*

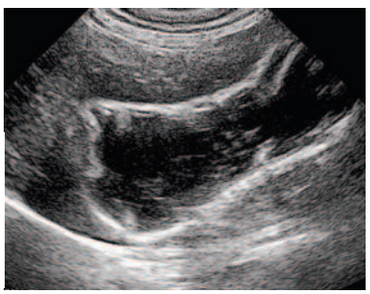
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Figure 13 - Male cat, 3 year old, presented for lethargy and vomiting. *The echocardiographic picture shows an abnormal gastric retention.*

- **Extrinsic digestive compression** (much less common): by adjacent abdominal organs (liver tumor, lymphadenopathy).

Digestive motor disturbances

Digestive motor disturbances leading to slower gastric emptying may be caused by hypomotility or dysregulation of the contraction rhythm. Either primary or secondary in origin, their pathogenesis is thought to be related to dysfunction of the gastric pacemakers. This leads to gastric "arrhythmia", as observed in the event of repetitive hairballs in cats *(Washabau, 2003)*. A gastric emptying disorder must be determined by studying the transit of solid food *(Wyse et al, 2003)*. This exclusion diagnosis is suspected when other examinations are within normal limits.

There are secondary motor disturbances:
- excessive sympathetic stimulation (stress, pain, deep abdominal lesions: peritonitis, pancreatitis, major parasitism): a very long gastric retention is observed with pancreatitis
- post-surgery iatrogenic trauma
- medical treatment: anticholinergic agents, opiates, non-steroidal anti-inflammatory drugs (NSAID)
- metabolic disorders: acidosis, uremia, hypokalemia, hypo- or hypercalcemia, endocrinopathies
- neoplastic process or ulceration (pain inhibiting transit by sympathetic stimulation).

> When should the gastric retention syndrome should be suspected?

The characteristic clinical sign of the gastric retention syndrome is vomiting of undigested food well after mealtime. However, owners also often describe vomiting of gastric juice. These signs are due to chronic gastric distension and inflammation of the mucosa, respectively.

Digestive motor disturbances associated with gastric retention syndrome may cause signs of dyspepsia, such as intermittent ptyalism, antalgic gait, gas bloat, very painful spastic crises and yawning. Abdominal palpation confirms the presence of gastric distension. The clinical signs are more alarming when motor disruptions are secondary to metabolic alterations or a septic state (peritonitis, pancreatitis).

TABLE 3 - BENEFITS OF COMPLEMENTARY TESTS USED IN THE DIAGNOSTIC EVALUATION OF THE GASTRIC RETENTION SYNDROME

Complementary test	Diagnostic benefits
Biochemical analyses	Metabolic diseases – Hyperthyroidism – Hypoproteinemia – Differential diagnosis of vomiting
Serum electrolytes	Rehydration – Differential diagnosis of vomiting
Plain radiography	Gastric dilatation – Radiodense foreign body – Digestive mass – Ileus
Contrast radiography	Gastric distension – Evaluation of gastric emptying time: *the ingestion of barium impregnated polyethylene spheres (BIPS) refines the actual emptying time and calculates the percentage of emptying correlated to time* – Thickening of the stomach wall – Foreign body
Abdominal ultrasound **(Figure 13)**	Measurement of the stomach wall – Identification of parietal layers – Appearance of the pylorus – Peristaltic waves
Gastrointestinal endoscopy	Stomach lesions – Extraction of foreign bodies – Pyloric lesions and parietal biopsies

> Diagnosis

Table 3 lists the benefits of the complementary tests that may be conducted to assist in the diagnosis of the gastric retention syndrome.

> Treatment

This ensues from the etiology when it can be identified, of the gastric retention syndrome.

Medical treatment

In the event of metabolic problems, treatment includes management of the underlying disorder and administration of prokinetic agents *(Hall & Washabau, 1999)* (metoclopramide, domperidone, ranitidine, etc). The administration of prokinetics entails a potential risk of occlusive syndromes.

Surgical treatment

Depending on the case, pyloroplasty, extraction of a foreign body, excision or the biopsy of polyps or neoplastic lesions may be indicated.

Dietary measures

Depending on the etiology, diet can be a significant adjunctive therapy *(Hall & Washabau, 1999)*. Dietary treatment can support gastric emptying. Small meals of a liquid or moist diet are the best recommendation for the initial therapy. If small foreign bodies or trichobezoars (hair balls) have been identified, lubricants such as paraffin that facilitate the propulsion through the gut, maybe beneficial. Bromelain, a cysteine protease contained in pineapple juice, has been suggested as a dietary treatment. In one study, bromelain was able to degrade trichobezoars to a variable extent *(Reed et al, 2004)*. However, more in vivo data are needed for the assessment of efficacy.

Dietary fiber plays an important role in preventing gastric retention. Dietary fiber significantly affects fecal hair excretion in cats and a high-fiber diet (12-15% total dietary fiber [TDF] as fed) is useful in the prevention of hairball formation *(Tournier et al, 2005)* (see Royal Canin Nutritional Information at the end of the chapter).

► Diarrhea

Diarrhea is characterized by the increased frequency of evacuation, moisture content and often volume of fecal matter. The owner will not always immediately identify diarrhea if the cat excretes outdoors.

In cats, the moisture content in a normal stool usually varies between 55% and 70%, depending on the food *(internal data from Royal Canin Research Center)*. It can go as low as 40% in constipation and as high as 90% with diarrhea *(Williams & Guilford, 1996)*.

Diarrhea is mainly caused by intestinal diseases, but other systemic diseases may affect intestinal function and can induce hypersecretion or malabsorption *(Battersby & Harvey, 2006)*. It can be due to diseases of the small or large intestine or it may affect both *(Tams, 2004)*. Acute cases can be caused by dietary indiscretion, infections with enteropathogenic viruses, bacteria or parasites. In chronic cases, lymphoplasmacytic or eosinophilic inflammatory bowel disease (IBD), bacterial dysbiosis or dietary allergy or sensitivity can often be the underlying problem. Exocrine pancreatic insufficiency is reported in the cat. It is certainly under-diagnosed in this species *(Williams, 2005)*. Drug intolerance and acute or chronic systemic diseases can induce diarrhea. Digestive tumors are also a common cause of chronic diarrhea in aging cats.

> Origin in the digestive system

There are far fewer clinical criteria to differentiate small intestinal diarrhea from large intestinal diarrhea in cats compared with dogs. This is due to the fact that disorders of the digestive walls are typically diffuse in cats.

Table 4 lists the criteria for differentiating small intestinal diarrhea and large intestinal diarrhea in domesticated carnivores.

> Pathophysiological reminders

Several mechanisms are involved in the increased water content of stools *(Freiche, 2000)*. When the small intestine is injured three types of physiological disturbance may occur separately or collectively to lead to the clinical expression of diarrhea:
- increased secretion of water and electrolytes
- decreased absorption of nutrients (mainly carbohydrates and lipids)
- decreased absorption of water and electrolytes **(Figure 14)**

FIGURE 14 - DIGESTIVE FACTORS THAT MAY AFFECT STOOL CONSISTENCY

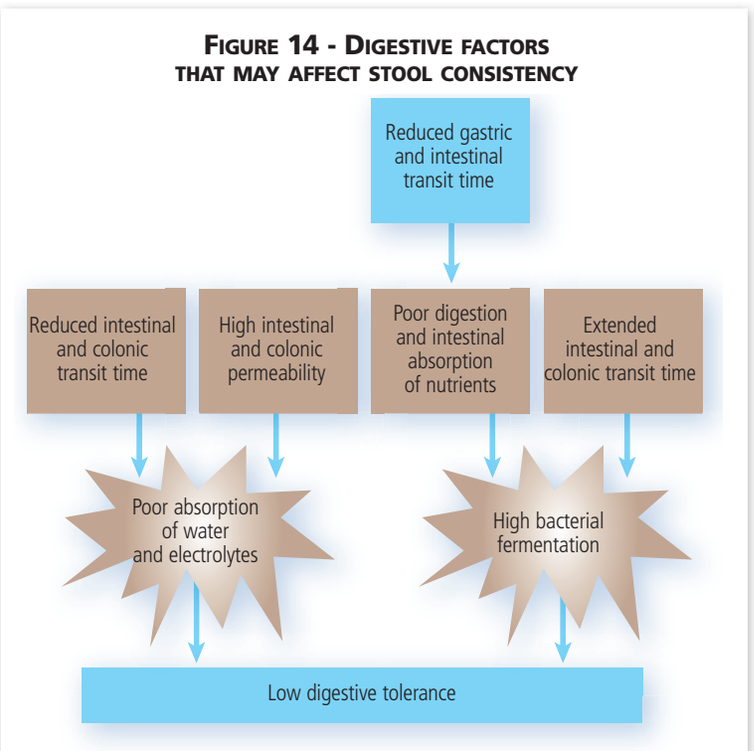


Table 4 - Differentiation of small intestinal and large intestinal diarrhea
(German & Zentek, 2006)

Sign	Small intestinal diarrhea	Large intestinal diarrhea
Feces		
- Volume	- Markedly increased	- Normal or decreased
- Mucus	- Rarely present	- Common
- Melena	- Rarely 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	- Usual 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	- Described in cats with colon disease
- Flatulence and borborygmi	- May occur	- Absent
- Halitosis in the absence of oral cavity disease	- May be present with malabsorption	- Absent unless perianal licking

When the colonic mucosa is responsible, failure of the reabsorption function of the colon and excessive secretory activity of the parietal mucus glands are observed.

> Coherence of diagnosis

Importance of the history and clinical examination

A very large number of diseases may cause chronic diarrhea. There is no general diagnostic plan that can be used in all cases, so the cat's history and a detailed clinical examination are essential.

At the end of these two steps the clinician must attempt to answer two questions that have a significant impact on the choice of treatment:
- does the diarrhea have a strictly digestive origin or could the cause be metabolic?
- is it small intestinal diarrhea or large intestinal diarrhea? **(Table 4)**

Sequence of complementary tests and differential diagnosis

In its specific context, each clinical case demands a logical sequence of complementary examinations. Various tests are possible:

- hemato-biochemical analyses, serological assays
- fecal examination
- biochemical exploration of malassimilation (folate and vitamin B_{12})
- digestive tract imaging: radiography, ultrasound, gastrointestinal endoscopy. These different techniques have radically transformed knowledge of gastroenterology over the past decade.

> Therapeutic consequences

Current therapies

Specific therapeutic plans are provided below for the most common diarrheal disorders in the cat:
- infectious gastroenteritis
- characteristics of diarrhea in kittens
- dietary intolerance
- chronic inflammatory bowel diseases (IBD)
- colonic diseases
- digestive neoplasia.

Dietary treatment

Dietary treatment is more of an adjunctive type of therapy in many cases of chronic small intestinal disease. As undigested food compounds are fermented by the colonic microflora and can have negative effects (such as gas formation and flatulence, and perhaps also promote further diarrhea), the diet should be highly digestible.

• Highly digestible diets

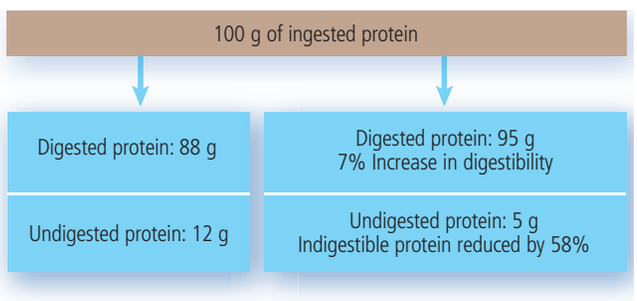
Diets for patients with suspected intestinal dysbiosis, to be characterized either as "small intestinal bacterial overgrowth" or as a disturbed micro-ecology in the upper or lower gastrointestinal tract, should be based on high quality ingredients. They support the patient by providing available carbohydrates and proteins that facilitate nutrient absorption in the small intestine. Highly digestible diets typically present dry matter digestibility values that exceed 85-88% and protein digestibility that exceeds 92%. These diets require less gastric, pancreatic, biliary and intestinal secretions for digestion. This results in almost complete digestion and absorption in the upper small intestine so that minimal residue is presented to the lower bowel **(Figure 15)**. Minimal residue reduces bacterial byproducts that may contribute to inflammation and osmotic diarrhea.

The passage of unabsorbed nutrients into the lower gut is reduced, as is the potential load of antigenic material. As long as dietary sensitivity or allergy cannot be excluded, an antigen-limited hypoallergenic diet is advantageous. These diets contain either highly digestible protein sources (e.g. protein hydrolyzates, low-ash poultry, fish) or other meats that are unusual in commercial diets (e.g. venison, duck, rabbit etc).

• Carbohydrates

Mucosal atrophy typically leads to a decreased availability of disaccharidases and carbohydrate malabsorption. Bacterial overgrowth and decreased transport of monosaccharides by malfunctioning enterocytes can also contribute to carbohydrate malabsorption, which in turn contributes to osmotic diarrhea. Therefore, diets formulated for cats with gastrointestinal disease should contain reduced quantities of highly digestible carbohydrate. Rice has long been considered the ideal carbohydrate for gastrointestinal disease. Rice is very highly digestible because it has a limited branched starch structure (amylopectin) and a very low dietary fiber content. Rice does not present any crossed antigenicity with wheat gluten and has rarely been implicated in adverse food reactions.

FIGURE 15 - IMPROVING DIGESTIBILITY TO LIMIT FERMENTATION IN THE COLON



A very low level of indigestible protein limits fermentation in the intestine and therefore the presence of substances that can promote inflammation and osmotic diarrhea.

TABLE 5 - INFLUENCE OF FERMENTABILITY AND FERMENTATION TIME IN VITRO OF DIFFERENT TYPES OF DIETARY FIBER ON THE DECOMPOSITION OF ORGANIC MATTER AND THE PRODUCTION OF SHORT CHAIN FATTY ACIDS (SCFA) IN CATS

From Sunvold et al (1995b)

Substrates	Soluble fibers	Insoluble fibers	Disappearance of organic matter (OM) (as)			Total production of SCFA (as mmol/g of OM)		
			6 h	12 h	24 h	6 h	12 h	24 h
Fructo-oligo-saccharides	++++		92.5	86.8	86.1	1.35	3.03	4.33
Citrus pectin	++++		49.6	76.6	85.5	2.02	4.2	4.71
Guar gum	+++	+	15.2	44.3	71.5	0.43	2.3	4.99
Beet pulp	+++	+	21.1	24.2	31.5	0.51	1.32	1.93
Cellulose		+++	0.7	0.4	0.6	-0.03	0.08	0.06

Dietary fiber rich in soluble fiber is heavily fermented by the fecal microflora, which leads to an increased production of SCFA.

Furthermore, rice improves the digestibility of dry diets, and contains soluble factors that inhibit secretory diarrhea.

Dietary fiber may benefit from an increased concentration or modified type of dietary fiber despite low-fiber diets (< 10% TDF) often being recommended. When indicated based on the clinical outcome, it can be worthwhile increasing fiber concentration by adding small amounts of insoluble or soluble fiber sources.

- On contact with water, soluble fiber such as pectin forms a gel (gelling capacity) or solution that can be more or less viscous (thickening capacity). Due to this viscosity, such fibers tends to slow down gastrointestinal transit by simply increasing resistance to the flow. Soluble fiber sources are also important regulators of the intestinal microbiota due to their high fermentability (**Table 5**).

- Insoluble fiber such as cellulose increases fecal bulk, fecal water content, absorbs toxins and normalizes both segmental and propulsive motility.

Both insoluble and soluble dietary fiber may be beneficial in the symptomatic treatment of certain large bowel diarrheas. In homemade diets, adequate supplements are 0.5 tablespoons of:
- cellulose or wheat bran when insoluble types of fiber are desired
- psyllium when soluble fiber sources are more promising. In commercial diets designed for intestinal disorders, various sources of fermentable fiber should already be included (e.g. beet pulp, fructo-oligosaccharides [FOS], mannan-oligosaccharides [MOS]).

• Energy density

Fat is often regarded critically as a compound in diets for patients with small intestinal disease: when fat digestion is impaired, the bacterial conversion of non-absorbed fatty acids and bile acids into hydroxylated fatty acids and deconjugated bile acids can increase fluid secretion and aggravate clinical signs of diarrhea.

On the other hand, weight loss and poor coat and skin quality can be major problems in cats with small intestinal problems. As high fat diets help provide energy and fat soluble vitamins to debilitated cats, the prescription of high fat diets is advocated. Fat digestibility is generally extremely high (up to 99%). In addition, a high-energy diet (> 20% on DMB) enables a reduction of the volume of the diet and decreases the intestinal load.

Therefore, the level of fat tolerated by cats with small intestinal disorders needs to be individually evaluated when increased dietary fat levels are warranted. It is justified to use increased fat intakes when weight loss is a prominent clinical sign and when a steatorrhea is not present.

• Probiotics and prebiotics

Probiotics and prebiotics have been suggested as treatment options for patients with intestinal problems.

Data on the efficacy and the presumed "stabilizing" effect of probiotics on digestive diseases are scarce. Often enough, products have not been evaluated with regards to efficacy or may not be suitable for cats and the specific conditions in the diseased intestinal tract. *L. acidophilus* (DSM 13241 strain) used as a probiotic increased the lactobacilli counts in feces and decreased numbers of *Clostridium spp.* and *Enterococcus faecalis (Marshall Jones et al, 2006)*.

Prebiotics are non-digestible carbohydrates that are fermented by gut bacteria in the small and large intestine. The basic idea is to offer a substrate to "beneficial" members of the gut flora and to promote a shift in the composition of the gut bacteria in favor of the "healthy" microbiota, such as *lactobacilli* and *bifidobacteria*. Through inhibitory process, these bacteria prevent the proliferation of potentially pathogenic bacteria *(i.e. Clostridium perfringens)*. These bacteria produce the short chain fatty acids (SCFA) butyrate, acetate and propionate, which provide fuel for the colonocytes. SCFA enhance sodium and water absorption, increase mucosal blood flow and increase gastrointestinal hormone release. These mechanisms contribute to the trophic effect that SCFA have on the intestinal mucosa, stimulating enterocyte and colonocyte proliferation.

Different prebiotic carbohydrates have been used, mainly inulin and various oligosaccharides (fructo-oligosaccharides, galacto-oligosaccharides, mannan-oligosaccharides). Some gastrointestinal changes can be expected, including pathogen control and reduced putrefactive compound production *(Hesta et al, 2001; Flickinger et al, 2003)*. The efficacy of these additives needs to be studied more in clinical patients to evaluate whether such feed additives and feed compounds are beneficial in cats with intestinal disease *(Sparkes et al, 1998)*.

> Protein-losing enteropathy

Protein-losing enteropathy (PLE) results from a range of gastrointestinal disorders that lead to non-selective protein loss. They are characterized by a total serum protein content less than 5 g/dL and an albumin concentration lower than 2 g/dL. These values must be interpreted on the basis of the normal reference ranges for the laboratory.

Although lymphangectasia remains the primary cause of PLE, many parietal disorders of the digestive tract are likely to be expressed as hypoproteinemia. Forms of PLE continue to be exceptional in cats, in the event of either IBD or digestive neoplasia. Identification of hypoproteinemia in cats always worsens the prognosis of the underlying disorder.

Disorders involved in PLE are listed in **Table 6.**

Dietary measures

Patients with PLE are often clinically fragile, and careful symptomatic therapy must be integrated with intensive dietary and medical management strategies in most cases *(Peterson & Willard, 2003)*. The nutritional management of cats with PLE is mainly based on diets with a low fat concentration. Low fat (≤ 10%, as fed) diets have been proven to be supportive because they counteract the pathophysiological events in PLE.

Long chain fatty acids are transported through the intestinal lymphatics. This may increase lymphatic vessel distension and increase intestinal protein loss and eventually lipid exudation. Linoleic acid and arachidonic acid have to be provided in sufficient amounts to fulfill the requirements. Medium chain triglycerides have some value because of their ability to be absorbed by bypassing the lymphatic system. A general limitation for using this type of fat is its negative effect on palatability and potential

TABLE 6 - ETIOLOGY OF PROTEIN-LOSING ENTEROPATHY IN CATS

Membrane permeability problems Alterations of the mucosa surface	Diseases of the lymphatic system
• Ulcerative stomach lesions • Lymphoplasmacytic enteritis (IBD) • Eosinophilic enteritis • Hemorrhagic gastroenteritis • Small intestinal bacterial overgrowth (SIBO) • Gluten intolerance • Massive digestive parasitism • Chronic intussusception • Chronic sub-occlusion (foreign body or tumor) • Iatrogenic (drugs, toxins)	• Focal or diffuse congenital lymphangectasia • Acquired lymphangectasis: - Inflammatory or neoplastic obstruction in the intestine - Obstruction of the peripheral lymphatic vessels (lymphangitis lipogranulomatous – neoplasia) - Lymphatic hypertension (pericarditis, right heart failure, neoplasia)

for inducing vomiting and diarrhea in cats. Higher supplementation with fat-soluble vitamins would be required and there are anecdotal reports of improvement with glutamine supplementation.

► Melena

Melena occurs when blood from the stomach or small intestine is passed in the feces. The color is black due to the degradation of hemoglobin. It occurs frequently in combination with coagulation disorders or in those cases when the structure of the gastrointestinal epithelium is severely compromised and if erosions or ulcerations have developed *(Kohn et al, 2003; Dennis et al, 2006)*.

► Fecal incontinence

Anal, gastrointestinal, neural or muscular disorders can cause fecal incontinence in cats *(Guilford, 1990)*. Intervertebral disc disease or tumors can also be associated with the condition *(Munana et al, 2001)*.

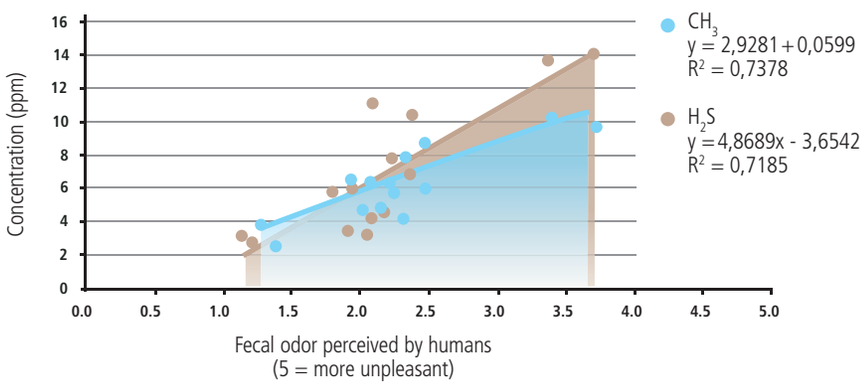
► Flatulence

Gas formation in the intestinal tract is a normal process related to the activity of the intestinal microflora. Around 200 volatile compounds are formed as the bacteria break down the digestive content in the large intestine. The main compounds are alcohols (such as methanol, ethanol etc), sulfur compounds (hydrogen sulfide, methyl/ethyl mercaptans etc), nitrogen compounds (ammonia, indole, phenol, skatole etc), volatile fatty acids (acetic/propionic/butyric/valeric acids etc) and other organic compounds.

Some of the substances produced in the intestinal tract are highly unpleasant **(Figure 16)**, such as sulfur compounds, ammonia, biogenic amines, indoles and phenols *(Lowe & Kershaw, 1997)*.
- Ammonia is formed mainly from the deamination of amino acids.
- Biogenic amines (cadaverin, histamine, putrescine, tyramine etc) are produced essentially by the decarboxylation of amino acids

FIGURE 16 - CORRELATIONS BETWEEN FECAL ODOR AND THE EMISSION OF HYDROGEN SULFIDE (H_2S) AND METHYL MERCAPTAN (CH_3SH) BY FECAL MATTER

(Source: Royal Canin data)



The hydrogen sulfide (H_2S) content is a good indicator of olfactory emissions, because its concentration is very well correlated with the perception of the human nose. There is also a good correlation between the odor perceived by humans and the methyl mercaptan (CH_3SH) concentration in air.

- Indole and phenolic compounds result from the decomposition of aromatic amino acids (tyrosine and phenylalanine)
- Sulfur compounds (hydrogen sulfide, mercaptans) from that of methionine and cystine.

The different components of an odor can be identified by gas chromatography together with mass spectrometry. It is also possible to judge the intensity of the odor by comparing it with increasing concentrations of 1-butanol *(Sorel et al, 1983)*.

Avoidance of dietary ingredients that favor intestinal gaseousness is of primary importance. Many legumes and other vegetable ingredients contain more or less non-digestible and microbially fermentable fractions. Some flatulence cases may be proof either of the poor quality of the food (generally mediocre protein quality) or the existence of a digestive function disorder *(Williams & Guilford, 1996)*. Flatulence is common in cases of dietary hypersensitivity. However, the problem is not well understood: some cases respond to dietary changes, and hence dietary treatment has to be adjusted according to the individual case. An eviction diet or an hydrolysed diet can help to manage dietary hypersensitivity cases.

6 - Enteral and parenteral nutrition

(See chapter 12 for more detail)

► Assisted feeding and enteral nutrition

For many gastrointestinal diseases, a period of assisted feeding is required. The rapid and thorough attention to the nutritional management of inappetent patients can decrease morbidity and mortality. Diets may be applied either by syringe or as small solid boli depending on the underlying disease or the preference of the patient or owner. Feeding tubes are an accepted way of providing nutritional support to animals unable or unwilling to consume adequate calories on their own *(Wortinger, 2006)*.

Enteral feeding is preferred and can be achieved by nasal, pharyngeal, esophageal, gastric or jejunal feeding tubes *(Ireland et al, 2003)*. The diameter of the tube should be large enough to permit feeding of the chosen diet, either specific enteral products or blended canned food that may be additionally diluted with water. Percutaneous endoscopic gastrostomy tubes have traditionally been considered to be the best-tolerated feeding device, but they are not without complications (vomiting and stomal site infection) and they require specific equipment and training. Esophagostomy tubes are an alternative and are simpler to place and have lower complication rates. For esophagostomy tubes, vomiting, scratching at the tube and bandage, removal of the tube and mechanical difficulties have been described *(Ireland et al, 2003)*.

► Parenteral nutrition

Total parenteral nutrition (TPN) is used to fulfill the total nutrient requirements in cats that are anorectic for longer periods and that cannot be maintained on an enteral feeding regime. Although the technique of parenteral nutrition is well established in many veterinary hospitals, it requires some training and equipment to avoid complications. Metabolic (hyperglycemia, hypokalemia), mechanical (catheter dislodgement, cellulitis), or septic problems may be related to the improper installment of parenteral nutrition in cats *(Crabb et al, 2006)*. Often these complications are mild and can be managed without discontinuation of TPN or adjustment of the infusion protocol. A more conservative estimate of energy requirements appears to be associated with a lower risk of hyperglycemia.

Using partial parenteral nutrition (PPN) delivers only a certain part of the required nutrients and energy. The risk of metabolic problems in cats is considerably reduced by this approach, although septic and mechanical complications may also occur *(Chan et al, 2002)*. Animals on combined enteral and parenteral nutrition can have a better clinical outcome than those receiving parenteral nutrition exclusively.

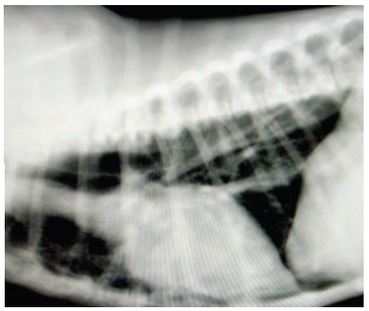

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Figure 17 - Thoracic radiograph of a cat consistent with megaesophagus. The esophageal wall, normally not seen, is visible here (two radiodense lines).

7 - Diseases of the esophagus and nutritional approach

► Conformation abnormalities of the esophagus

> Vascular abnormalities

The persistence of some vascular arches in the course of embryogenesis may cause extrinsic compression of the esophagus, leading to the formation of a crop above the stenosis. The most commonly described abnormality is the persistence of the fourth arch of the right aorta *(Twedt, 1994)*. The esophagus is clasped in an adhesion formed by the aorta, the non-vascularized residual arterial ligament and the pulmonary artery. The diagnosis is based on radiography (localized proximal esophageal dilatation) and endoscopy, and the treatment is surgical. Other abnormalities have been reported in carnivores (double aortic arch, persistence of subclavian arteries), but these conformation faults remain exceptionally rare in cats.

> Esophageal fistulas

Esophageal fistulas are rare in carnivores. They extend from the esophageal wall to the mediastinum or even the chest cavity. They are congenital, although they can result from trauma. Signs are mostly of a respiratory nature (dyspnea, coughing, fever). The diagnosis is based on radiography with contrast medium or esophagoscopy.

> Megaesophagus: medical aspects

Megaesophagus is a generalized dilation of the esophagus with partial or total loss of peristalsis and motility **(Figure 17)**. The congenital form is distinguished from the acquired form, the origin of which is sometimes identified or remains undetermined (idiopathic megaesophagus) *(Strombeck, 1978)*.

Epidemiology and pathophysiology

• Congenital megaesophagus

The congenital form is described in Asiatic breeds, specifically the Siamese *(Tams, 1996)*. While it has not been possible to show vagal innervation deficits, modification of the conduction of the afferent reflex arches that generate peristalsis can be suspected. Motility problems are implicated in the pathogenesis of congenital megaesophagus (contractions of ineffective amplitude, alteration of parietal elasticity).

• Acquired megaesophagus

No epidemiological studies have established any breed or sex predisposition for the acquired forms, and no hereditary transmission mechanism is suspected. All disorders entailing parietal lesions of the esophagus or an innervation fault are likely to cause the appearance of megaesophagus.

In the absence of clinical factors suggesting another etiology, acquired megaesophagus in cats should give rise to the hypothesis of dysautonomia. The involved pathogenic mechanisms have not been clearly described. This general disorder of the neurovegative nervous system means that colonic atony is often associated and the clinical signs are much more complex. The appearance of esophageal motility problems – even isolated – may also suggest severe myasthenia *(Moses et al, 2000)*.

Clinical signs

In the congenital forms the clinical expression often manifests itself during weaning: ever more frequent regurgitations, stunted growth compared with other kittens in the same litter. In some cases the regurgitations occur well after mealtimes, and owners may interpret them as vomiting, which may cause the clinician to orient towards an incorrect diagnosis.

Other clinical signs described are halitosis, abnormal sounds from the esophagus, coughing secondary to aspiration pneumonia (*Jenkins, 2000*). However, not all cats with megaesophagus present with respiratory signs. Conversely, respiratory disease is sometimes very important.

Palpation of the esophagus may reveal a perceptible dilatation of the ventral part of the neck. A muco-purulent discharge and audible rales are noted in the event of infectious pulmonary complications. The impairment of the general condition is inconsistent.

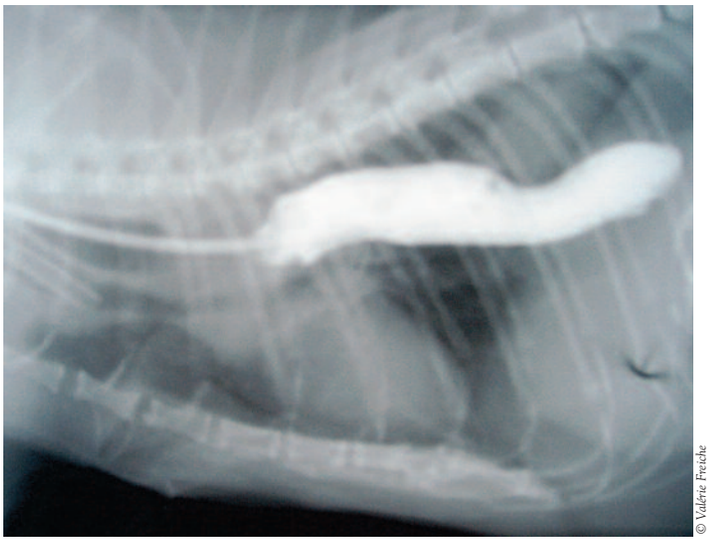
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Figure 18 - Extensive esophageal dilatation in a cat who presented for both dysphagia and severe respiratory difficulties.
Thoracic contrast radiography with barium.

Diagnosis

Radiographs of the thorax are used for the diagnosis. In case of doubt radiographs taken after the administration of contrast medium can confirm the esophageal dilatation. Digestive endoscopy is not among the complementary tests that help confirm the diagnosis.

• Plain radiography

The esophagus cannot usually be seen on a plain radiograph. Increased esophageal radio transparency is therefore abnormal. The size of the dilatation is variable. It may affect the whole organ or only the thoracic part of it. A radiodense line emphasizes the dorsal wall. These modifications are identifiable on the lateral and ventro-dorsal views. It is important that good quality radiographs are obtained to enable evaluation of the pulmonary tissue for characteristic densities and alveolar infiltrates, which are characteristic of aspiration pneumonia.

• Radiography with contrast medium

The administration of a contrast medium **(Figure 18)** will be necessary if the animal experiences deglutition problems or regurgitations if the plain radiographs are normal or insufficient to establish a definite diagnosis. The contrast medium may be a barium sulfate paste, but this is contraindicated in the event of dysphagia due to the risk of aspiration. Barium is very irritating for the bronchi. In this situation, an iodized product is recommended for contrast enhancement.

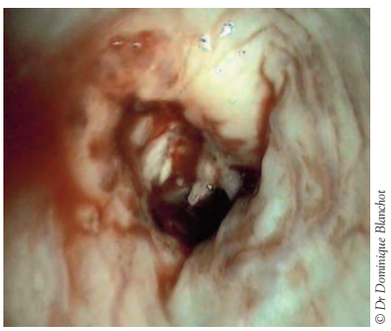
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Figure 19 - Esophageal tumor in a 14-year-old European cat.
Histological examination indicated an undifferentiated carcinoma.

• Endoscopy

In the event of megaesophagus, endoscopy can evaluate the integrity of the surface of the mucosa, but it is not the most reliable test for assessing the size of the esophageal lumen. However, in case of doubt in the differential diagnosis, it does help refine the diagnosis and exclude the presence of associated esophagitis.

Differential diagnosis

Owners are often imprecise in describing clinical signs. It is not uncommon for tardy regurgitations to be confused with very early vomiting. The differential diagnosis should include all other disorders that may cause dysphagia or ptyalism:

- pharyngeal disorders: foreign body, laryngeal paralysis (achalasia: very rare in cats)
- other esophageal lesions: foreign body, vascular abnormalities (crop), neoplasia (rare) **(Figure 19)**.

Treatment

The treatment of congenital megaesophagus or idiopathic acquired megaesophagus is based on hygienic and palliative measures. It makes great demands on the owner: feeding the animal in a raised position improves the assimilation of the food due to gravity. The consistency of the diet

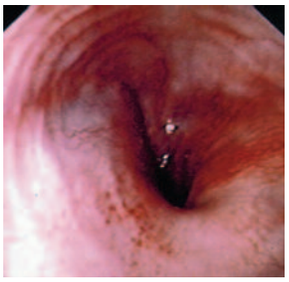

Figure 20 - Endoscopy of the distal esophagus of a cat. *Note the presence of erythematous punctures consistent with an acute inflammatory state.*

is an important but inconsistent factor: some cats regurgitate less with a liquid food, others have more success with solids.

In the event of bronchopulmonary complications, complementary symptomatic medical treatment can be commenced.
- Prokinetic substances (e.g. cisapride) may enable better esophageal clearance in cats as the distal section of the esophagus is comprised of smooth muscles. Unfortunately, cisapride is no longer readily available in every country.
- Antibiotic therapy is indispensable in the event of secondary bronchopulmonary lesions.
- Mucosal protective agents are indicated if erosive parietal lesions are identified.

However, the prognosis is sometimes so poor (especially in kittens) that euthanasia is ultimately chosen.

► Esophagitis

Inflammation of the esophageal mucosa **(Figure 20)** may be secondary to local trauma (ingestion of toxins, prolonged presence of a foreign body) or to repetitive gastroesophageal reflux (lower esophageal sphincter incompetence, degenerative disorders) *(Lobetti & Leisewitz, 1996; Han et al, 2003)*. General anesthetics (barbiturates) reduce the pressure of the caudal esophageal sphincter, favoring peri-operative reflux *(Freiche, 2006a)*. In rare cases, stenosing parietal lesions appear. The composition and acid pH of the gastric fluid makes it highly irritating for the esophageal mucosa.

> Clinical manifestations and diagnosis

These are not very specific and include pain during deglutition, hypersalivation, and dysphagia. Sometimes, the clinical signs are simply prostration associated with dysorexia.

All inflammatory disorders of the esophagus are likely to be secondary to functional problems due to alteration of motility. These peristaltic problems are very difficult to document in domesticated carnivores. The examinations of choice are fluoroscopy and endoscopy.

> Medical treatment

Nil per os is required to manage highly erosive or diffuse esophageal lesions (see the section on esophageal foreign bodies).

Antacids

The administration of antisecretors and antacids help increase the gastric pH and reduce the risks of parietal erosion in the event of reflux. The most commonly used substances are anti-histamine – 2 agents (cimetidine, ranitidine, famotadine etc) and proton pump inhibitors (omeprazole and derived substances). They must be administered for at least fifteen days. Cimetidine favors augmentation of the caudal esophagus sphincter tone, which is often deficient in esophagitis.

Local topical agents including aluminum-based cytoprotectives, sucralfate, or an association of alginic acid and sodium bicarbonate, are beneficial adjuvant treatments. Administered at the end of the meal, they constitute a protective film on the surface of the mucosa and protect the mucosa from reflux.

Antibiotic therapy

Antibiotic therapy is indispensable in combating local bacterial translocation. It helps prevent more serious lesions. When there are too many lesions on the mucosa or perforation is suspected, the administration of ampicillin is recommended. The association of cephalosporin and metronidazole may be proposed.

Corticosteroids

Their use in the prevention of stenosis is highly controversial. Experimentally, their preventive activity has not been proven. Conversely, they are implicated in the mechanism of perforation during preexisting parietal necrosis. Administered over short periods, they limit pain and present local anti-inflammatory properties.

Inserting a gastrostomy tube

With severe esophagitis, local mechanical trauma in the mucosa can be reduced if no solid or liquid passes through the esophagus for several days. Another advantage of fasting is the reduction in the local fibroblastic reaction, which favors the appearance of a healing stenosis. A gastrostomy tube must be placed at the end of esophagoscopy. An anastomosis is created within a few days between the stomach wall and the abdominal wall. The administration of an energy dense diet and medical treatment is achieved several times a day using syringes connected to a three-way valve attached to the tube. This care can even be provided by the owner following simple instruction. Local tolerance is good *(Ireland et al, 2003)*. Energy density of the enteral diets should be high and fat as energy source is best suited for that purpose. In many cases, blended canned diets can be used. Bolus-feeding techniques can maintain a normal nutritional status in cats.

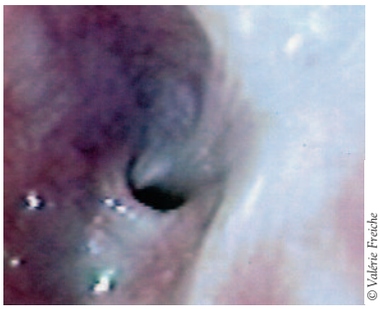
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Figure 21 *- Post-operative peptic esophageal stenosis in a 4-year-old female cat*

► Esophageal stenosis

The appearance of isolated stenosing lesions of the esophageal wall most commonly follows the ingestion of caustic products or the onset of postoperative gastroesophageal reflux *(Sellon & Willard, 2003; Freiche, 2006a)*. In cats, the oral administration of tetracycline has been implicated in the genesis of severe stenosing esophageal lesions *(McGrotty & Knottenbelt, 2002; German et al, 2005)*. Less commonly, these lesions appear postoperatively **(Figure 21)** or after the extraction of a foreign body.

Esophageal stenosis is predominantly benign in cats. The mucosa loses its elasticity and the affected section becomes fibrotic (simultaneous disorder of the lamina propria and the muscle wall). There does not appear to be any preferred location in the esophagus; lesions can be proximal or distal, or even in multiple locations in the same animal.

> Clinical manifestations

The two clinical signs of stenosis are regurgitation and esophageal dysphagia, the latter of which is a deglutition problem. It may be the consequence of pain or even alteration of the motility inherent to the lesion.

The clinical signs may manifest acutely (dyspnea, often pronounced dysphagia after ingestion of solids but also after ingestion of liquids if the stenosis is pronounced). They are correlated to the severity of the stenosis. The animal may lose weight rapidly. The lesions are incompatible with medium-term survival if the residual diameter of the esophageal lumen is less than 8 mm.

> Diagnosis

Thoracic radiography with or without contrast medium and esophageal endoscopy confirm the diagnosis. The differential diagnosis must exclude other causes of chronic vomiting or regurgitation:
- megaesophagus (rare in cats)
- esophageal crop due to vascular abnormality (rare in cats)
- diverticulum (rare in cats)
- hiatal hernia in the strict sense/gastroesophageal invagination (rare in cats)
- esophageal foreign body (less common in cats than in dogs in this location)

Thoracic radiography

When stenosis is the consequence of parietal fibrosis the plain radiographs do not reveal any abnormalities. Air dilatation may be suspected in front of the lesion, as the esophagus is normally radio-

transparent. Food residues may persist and create local contrast that permits diagnostic suspicion. Abnormal images may be seen if there is extrinsic or intrinsic compression by an endoluminal mass.

Radiographs after the ingestion of a contrast medium are often necessary to confirm the diagnosis (introduction of barium under anesthesia using a tube or fluoroscopy): this also helps provide an initial assessment of the scope of the stenosis.

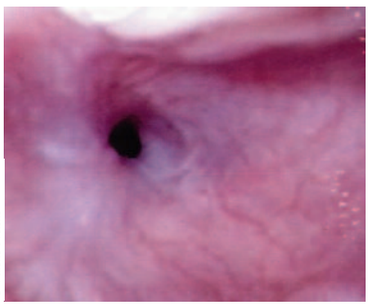

Figure 22a - Esophageal stenosis in a 8-year-old DSH cat.
This serious lesion has a peptic origin and has appeared after a general anesthesia realized for a convenience surgery.

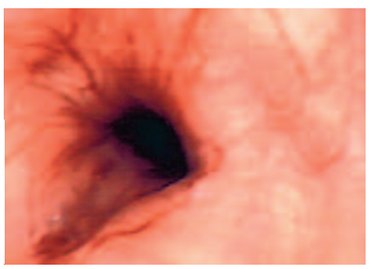

Figure 22b - Esophageal stenosis in a cat, secondary to a thoracic tumor.
In this particular case, due to the origin of the stenosis, endoscopic dilatation is not a therapeutic option.

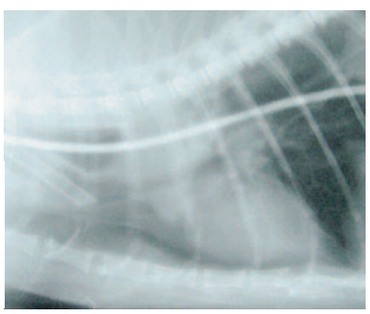

Figure 23 - Insertion of a thoracic labeling tube to measure the extent of esophageal stenosis. *The cat was presented for dysphagia. The esophageal compression was extrinsic.*

Indications and limitation of esophagoscopy

Endoscopy is the diagnostic test of choice in the exploration of this type of lesion **(Figure 22)**. The limit of the examination is the diameter of the lesion, which sometimes limits the passage of the endoscope towards the distal part of the esophagus. Esophagoscopy is complementary to radiography: it can be used to assess the residual diameter of the esophagus. The images obtained in the event of (post-reflux) peptic esophagitis are very characteristic.

The endoscope examination provides an assessment of the residual diameter of the esophagus **(Figure 23)**. It is conducted at the end of the diagnostic radiograph with contrast medium to evaluate the scope of the stenosis. The benefits of endoscopic treatment can also be assessed. If the stenosis is unique and short in length, endoscopic dilatation is indicated. The results are less certain if the stenosis extends for several centimeters or if there are multiple areas of stenosis.

> Treatment of the stenosis: practicalities

The treatment consists of several dilatation appointments using a balloon tube, which can be inflated under manometric control *(Haraï et al, 1995; Adama-Moraitou et al, 2002)*. The balloon catheter is introduced in the operator channel of the endoscopy. There is a tube sized to suit every case. The aim is to achieve repetitive parietal dilaceration in the cicatricial zones *(Freiche, 1999; Leib et al, 2001)*. However, in the case of annular stenosis with little fibrosis, the mucosa retains sufficient elasticity locally to enable perendoscopic dilatation without local dilaceration being visible at the end of the dilatation maneuvers: in this particular case, a surgical approach must be considered. The aim is to achieve a residual diameter of at least 10 mm at the end of treatment.

> Results and complications

The results are generally good when the indication has been properly determined. Endoscopic dilatations do not involve much pain, so they are well tolerated by the animal and lead to general recovery in a few weeks. Extended stenosis may however have a very poor prognosis. The same is true of multiple forms of stenosis or when the stenosis is the consequence of a neoplastic lesion.

Three to five successive appointments every couple of days are suggested for this type of treatment. A reduction in the diameter of the esophagus is systematic between two appointments due to the inevitable partial parietal cicatrisation. The in situ injection of local corticosteroids using an endoscopic catheter helps to limit this complication. This technique should be attempted initially. If such lesions are initially treated surgically, a new stenosis is likely to appear at the surgical site.

Immediate complications

The major risk is parietal rupture during the examination, which is rare. A surgical team must be ready to intervene in the event of complications.

Medium-term complications

Esophageal motility is always altered when a lesion is identified in this organ, regardless of the origin. The treatment of stenosis does not guarantee a return to the normal motility activity of the esophagus. For this reason, some cats are euthanized due to the persistence of dysphagia or the appearance of pulmonary complications related to aspiration.

► Esophageal foreign bodies

The rather unselective dietary behavior of carnivores means that the ingestion of foreign bodies is a relatively common reason for consultation. Cats are more "delicate" than dogs, so the incidence of foreign bodies in the esophagus and stomach is much less important in the former.

In cats, linear foreign bodies in the esophagus are often due to a twine or thread becoming trapped under the tongue **(Figure 24)** and lodging in the digestive tract. In this situation, it cannot be extracted by endoscopy. A wide array of objects is ingested, including needles and hooks.

According to studies, foreign bodies tend to lodge where the esophagus contracts, especially at the diaphragmatic hiatus or the entrance to the thorax, although the base of the heart is also possible.

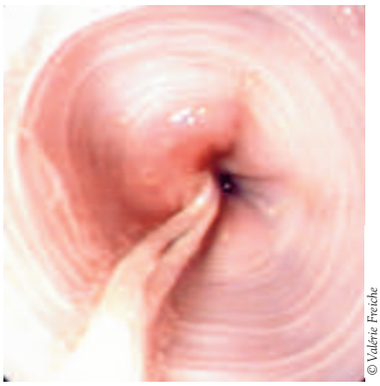

Figure 24 - Twine visible in the esophagus of a one-year-old male Exotic Shorthair. *The twine is lodged in the digestive tract.*

> Clinical diagnosis

The presence of a foreign body in the esophagus can produce alarming clinical signs and demands urgent intervention. Information from the owner is vital as it may provide pointers as to the type of foreign body ingested and especially when it was ingested. These factors impact the choice of the extraction method. On average, the duration between ingestion of the foreign body and presentation to the veterinarian varies from a few hours to a few days.

The severity of the clinical signs depends on the degree of esophageal obstruction and damage to the esophageal wall. If the lumen is only partially obstructed and the esophagus is not perforated, the animal may present in a subnormal clinical state allowing the absorption of liquids without difficulty. This explains why some foreign bodies are not discovered for some time. The differential diagnosis involves all the other causes of esophageal obstruction (neoplasia, congenital anomalies, extrinsic compressions).

When a foreign body is lodged in the esophagus, the animal often presents characteristic clinical signs:

- dysphagia
- anorexia
- fever (more inconsistent)
- ptyalism
- lethargy or agitation
- halitosis
- pain
- regurgitation
- breathing difficulties
- weight loss

Cervical palpation is abnormal when the foreign body is lodged in this area (needle).

> Complementary tests

Plain radiography

This simple and fast procedure will help confirm the diagnosis in more than 85% of cases according to the statistical data described in the literature *(Durand-Viel & Hesse, 2005)*. The radiological signs may be:
- direct, when the foreign body is radiodense (bone, metallic)
- indirect, in the event of partial esophageal dilatation or the presence of an abnormal quantity of air or liquid

Radiography with contrast medium

If the images are unable to help confirm the clinical suspicion, radiographs with contrast medium are required. If there is a strong suspicion of a perforated esophagus, an iodized labeling product is preferred over the administration of barium sulfate. Persistence of the contrast agent in front of the lesion or the presence of an image by subtraction, indentified in several consecutive images, is suggestive.

Esophagoscopy

This step is therapeutic. It confirms the nature of the foreign body – after other causes of obstruction or esophageal compression have been excluded – and it helps in the choice of therapy: attempted removal of the foreign body or surgery.

• Practical procedure

The endoscope is used to assess the shape of the foreign body, how tightly it is lodged between the mucosa and how much it can be moved. A foreign body that is initially difficult to move (like a hook) is often more difficult to extract **(Figure 25)**.

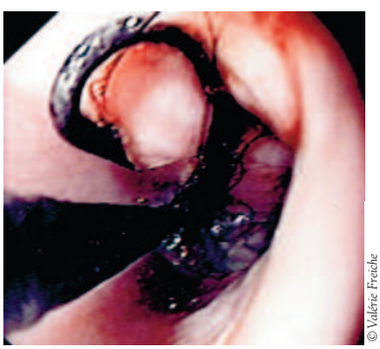

Figure 25 - Close-up of the end of a hook lodged in the esophageal mucosa of a cat. *An ulcerative lesion is probably present under the lodgement area.*

There are limits to endoscopic extraction:
- suspicion of esophageal perforation,
- highly ulcerated mucosa (risk of esophageal rupture),
- local superinfection in the event of delayed intervention.

Local evaluation of the condition of the mucosa is an important criterion in the decision-making process. If the foreign body has been lodged for more than 72 hours, the risk of perforation is much higher. Generally speaking, it is accepted that all extraction techniques using an endoscope must be attempted before the surgical option is used.

• **Results and complications**
According to the literature, the success rate of this type of intervention varies between 60% and more than 90% *(Durand-Viel & Hesse, 2005)*. The latter figure is correlated to the speed of intervention after ingestion of the foreign body, as the condition of the esophageal mucosa deteriorates rapidly when in permanent contact with a foreign body, especially a bone.

If there are clear indications, this procedure has a number of undeniable advantages:
- limits tissue trauma
- speed of functional recovery
- reduces post-surgery care
- timesaving.

The following complications are described:
- massive local hemorrhage (close to the large vessels in the periesophageal area) *(Cohn et al, 2003)*
- tears, perforations of the esophageal mucosa, deep ulcerations produced during the movement of the foreign body.

While the post-intervention lesions in the esophagus or stomach may be large, a tailored medical treatment produces active and rapid healing of the esophageal mucosa **(see Esophagitis)**.

Repeat esophagoscopy is recommended in the event of ulcerative lesions. It must be conducted within four or five hours of extraction. If these lesions are too large, provision of food or water is contraindicated. An enteral feeding tube (PEG) is inserted endoscopically at the end of the examination *(Mark, 2005; Wortinger, 2006)*.

► Esophageal neoplasia

> Different histological types encountered

Esophageal tumors are very uncommon in cats, contrary to humans. Esophageal tumors account for less than 0.5% of all cancer cases in domesticated carnivores *(Ettinger & Feldman, 2000)*. They usually affect aging animals. The most common histology types are undifferentiated carcinomas, osteosarcomas and fibrosarcomas *(Tams, 1996; Gualtieri et al, 1999; Shinozuka et al, 2001)*. In cats, the carcinoma is the most commonly described tumor, although it is much less common than it is in dogs. Benign tumors are rare and often asymptomatic (leiomyomas, papillomas).

In the event of helminthiasis caused by *Spirocerca Lupi* described in Africa, in Réunion and some parts of the United States and Guyana, the migration of larva from the stomach to the thoracic aorta ends in the implantation of an adult parasite in the esophageal wall. This causes the appearance of local nodules, which are likely to undergo neoplastic transformation. The infestation of carnivores mostly occurs after the ingestion of small reptiles or rodents (early treatment of these nodular lesions is with ivermectin). These tumors of parasitic origin generally have a poor prognosis when the diagnosis is established and their metastatic potential is high *(Guilford & Strombeck, 1996c; Freiche, 2005a)*. While this larval migration is well described in dogs, its appearance is more anecdotal in cats.

> Clinical signs

The clinical signs are non-specific to the primary lesion, dominated by dysphagia, the intensity of which is related to the degree of esophageal obstruction. The regurgitations are associated with other clinical signs: ptyalism, dysorexia, odynophagia and alteration of general condition. Hematemesis is reported when there is local ulceration. Signs of pneumonia may be secondary to aspiration.

The esophageal wall may also be the site of compressive phenomena of extrinsic origin with thoracic lymphoma, lymphadenopathy, pulmonary neoplasia or thymoma, but they are not primary esophageal tumors.

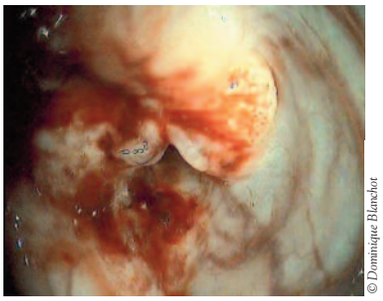
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Figure 26 - Malignant esophageal tumor in a 14-year-old European cat.

> Diagnosis

The diagnosis of esophageal tumors is sometimes delayed as the clinical signs manifest themselves at an advanced stage of development. Suspicion is supported by radiographic examination (with or without contrast medium) or ultrasound if the mass is distal. However, the examination of choice to establish a precise diagnosis is esophagoscopy **(Figure 26)**, which enables biopsy, a reliable evaluation of the extent of the lesion, and the surgical options. If the mass is under the mucosa, a tomodensitometric examination is complementary.

Disease staging is based on thoracic radiography. Malignant lesions are aggressive and can metastasize rapidly. In cats, the preferred sites of metastasis of esophageal carcinomas are the lymph nodes in the thorax, the lungs, the kidneys and the spleen.

> Treatment and prognosis

The surgical approach to esophageal tumors is complex because of the risk of local dehiscence of the sutures and the impossibility of wide resection. The prognosis of malignant lesions is often very low in the short term. The chemotherapeutic protocols proposed on the basis of the histological origin of the lesion therefore have only a palliative benefit.

► Nutritional approach to esophageal diseases

If enteral feeding is not contraindicated and the patient accepts it, food and water bowls should be raised. Cats can be fed "over-the shoulder". Patients can also be held vertical for a short while after feeding. This procedure facilitates the passage of food to stomach. If the patient needs assisted feeding for a longer period, energy and nutrient intakes and fluid volume have to be carefully balanced. The diet should deliver the complete nutrient spectrum in a reasonable volume.

High fat diets are preferred because of their higher energy density. The optimum type of food varies between cases. For some, high-quality liquid diets are best, for others, wet food or moisturized dry food is suitable. Diet viscosity should also be considered.

8 - Diseases of the stomach and nutritional approach

► Gastritis

Chronic gastritis is common in cats of all breeds, ages and sexes. When they are associated with lesions further down the digestive tract, they are considered to be a form of IBD.

> Etiology

The etiology is poorly understood. The inflow of inflammatory cells identified in gastric biopsies – lymphocytes, plasma cells, neutrophilic leukocytes, eosinophilic leukocytes – suggests local

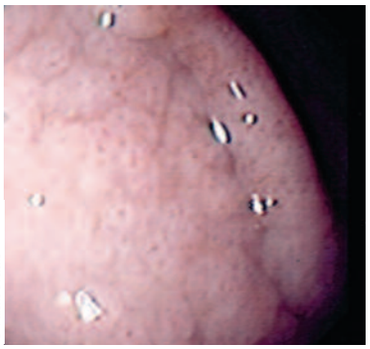
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Figure 27 - Severe gastritis caused by helicobacter identified in a 6-year-old female cat who presented with chronic digestive problems. *In low-angled light, compartmentation of the mucosa secondary to a mucosal edema is observable.*

immune disturbances in the maintenance of these lesions. Eosinophilic gastritis is often more complex to manage in medical terms. It may be associated with peripheral eosinophilia and the eosinophilic infiltration of other organs. Several publications describe cats infected with toxoplasmosis, presenting gastritis with an eosinophilic component *(McConnel et al, 2007)*. Intracellular parasites are not always found in histopathological analysis.

The incidence of spirochaete *(Helicobacter sp)* is high in domesticated carnivores, but contrary to findings in humans, their pathogenic role remains controversial **(Figure 27)**. However, severe gastritis is associated with high bacterial loads in cats. This is a reason for implementing eradication treatment in this species *(Hwang et al, 2002)*.

Gastritis associated with nematode infestation *(Ollulanus tricuspis)* has been described in the cat *(Cecchi et al, 2006)*. The parasites are identified in endoscopically obtained biopsies.

> Clinical expression

The clinical signs are not very specific dysorexia, intermittent vomiting, alteration of the general condition, developing through crises. The nature of vomiting or its occurrence with respect to meals is not reliable diagnostic information. The presence of blood is not necessarily a poor prognostic indicator, even if it expresses a more extensive alteration of the mucosal surface. This situation can be quickly reversed.

> Complementary tests

Endoscopy with phased biopsies is the examination of choice that produces a final diagnosis. The visual modifications accompanying these lesions include edema of the mucosa, heterogeneous coloration, thickening of some folds, the presence of erosions and multiple small ulcers.

Alterations identified by blood analyses (neutrophilic leukocytes, eosinophilic leukocytes) are not very specific. Radiography or ultrasound images are likely to exclude a number of diseases with similar symptoms. These imaging techniques do not provide an etiological diagnosis.

> Treatment

The medical treatment is specific if a cause can be identified. In most cases the use of corticosteroids is unavoidable. Each case demands individualized treatment based on the scale of the lesions as well as the clinical expression of the disease and the tolerance of the animal. Antacids (anti-H_2 and proton pump inhibitors) are typically indicated in the induction phase. Prokinetics (metoclopramide as cisapride is not available in every country) are beneficial in animals with altered motility. Immunosuppressive agents must be reserved for cases in which the usual treatment is not effective. These substances need a close clinical and hematological follow up and they may induce secondary effects in the cat.

> Specific nutritional approach

Nutritional measures are very important to stabilize the condition of these cats.

Acute gastritis

The patient should be fasted for a short period (less than 24 hours) and subsequently offered small amounts of food. The diet should constitute moist, low-fat food that can be administered in small boli by the owner. If the patient is dehydrated, the fluid, electrolyte and acid base equilibrium should be maintained by parenteral application of adequate solutions *(Remillard, 2000)* and at a later stage by parenteral application of enteral formulas *(Marks, 1998)*. The degree of dehydration determines the amount of fluid that has to be administered. The maintenance requirement for cats is determined by the balance between endogenous water production, water intake and water losses *(Paragon & Mahe, 1994)*. About 50 mL water/day/kg BW is considered as an adequate

maintenance requirement. Depending on the degree of dehydration the required amount may be almost doubled if no contraindication is identified.

Chronic gastritis

In chronic cases, it is helpful to feed the animal multiple small meals. The food should be warmed to body temperature and dilution with water often facilitates intake and improves tolerance. This may be explained by the lower osmolality and the faster passage of food through the stomach. Dietary fiber levels should be reduced because many fiber sources increase viscosity of the gastric contents. Diets with a novel protein might be selected if food allergy cannot be excluded. In all other cases highly digestible diets can be chosen.

There are no specific recommendations for the dietary treatment of cats with *Helicobacter* colonization of the gastric mucosa. If gastritis is present, the same dietary measures as given above in the relevant chapter may prove useful.

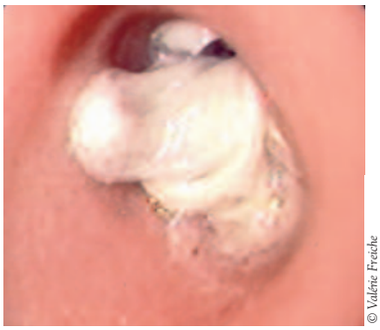

Figure 28 - Hairball identified during gastric endoscopy. *The foreign body caused a gastric retention syndrome.*

► Gastric foreign bodies

Foreign bodies in the stomach are less common in cats than dogs. Cats accounted for only 9.6% of cases in a study of 146 cases of foreign bodies in the esophagus and stomach *(Durand-Viel & Hesse, 2005)*. The varied nature of foreign bodies (needles, fishhooks, stones, plastic, electric wire) means the intensity of lesions of the mucosa vary also (chronic inflammation, ulceration, laceration if the foreign body is linear and it lodges in the proximal small intestine). In longhaired cats, compacted hairballs lodged in the pyrolic antrum and partially in the proximal small intestine may cause occlusion **(Figure 28)**. In the above study, hairballs accounted for 36% of foreign bodies in the stomach.

> Clinical expression

Vomiting is the most commonly described sign of a foreign body in the stomach. Anorexia, dysorexia and prostration are common. Hematemesis is less common. In the event of gastric laceration subsequent to the presence of a linear foreign body the occlusive signs are more characteristic and a state of shock maybe observed.

> Diagnosis

The diagnosis of a foreign body in the stomach is based on radiograph, ultrasound and endoscope examinations. The ultrasound is the complementary examination of choice. When the foreign body is not linear, endoscopy has the advantage of being therapeutic, enabling extraction with various types of forceps. If endoscopic extraction is not possible, surgery is performed.

► Gastric neoplasia

Gastric tumors are much more common than esophageal tumors in domesticated carnivores. The histological and macroscopic characteristics of malignant lesions are different in dogs and cats.

> Different histological types encountered

Benign stomach tumors are uncommon in cats and more common in dogs. They are most often asymptomatic, except when their location or size causes a mechanical problem (exophytic leiomyomas).

The incidence of epithelial tumors in cats varies from 20% to 35% of gastrointestinal neoplasia *(Estrada et al, 1998)* and the stomach is not the most common site. Round cell tumors are common in the stomach of cats. Lymphomas account for the majority of proven neoplasic lesions in cats *(Guilford & Strombeck, 1996c)*. This tumor is considered to be primarily digestive when it is located in the stomach, the intestines and the associated lymph nodes at the time of diagnosis.

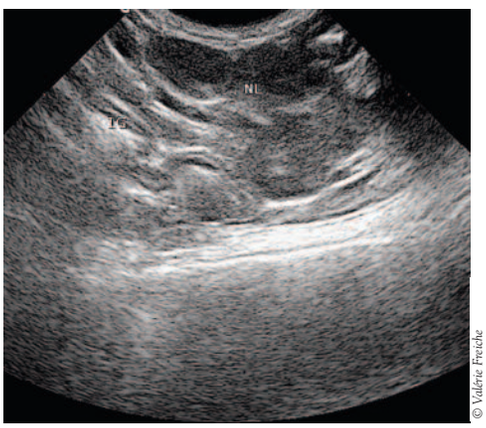

Figure 29 - Ten year old male cat who presented with anorexia and vomiting. *The abdominal ultrasound indicated enlarged lymph nodes. Histopathological analysis of biopsies confirmed the diagnosis of lymphoma.*

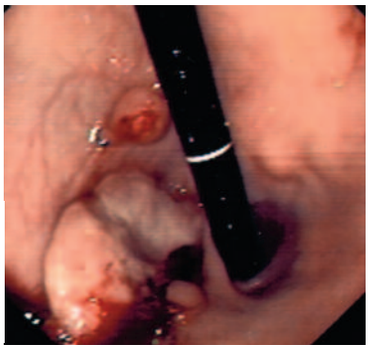
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Figure 30 - 13-year-old female cat who presented for dysorexia, vomiting and weight loss.
Retrovision with the endoscope revealed the presence of parietal mass (es). This appearance is characteristic of one of the forms of lymphoma in the cat.

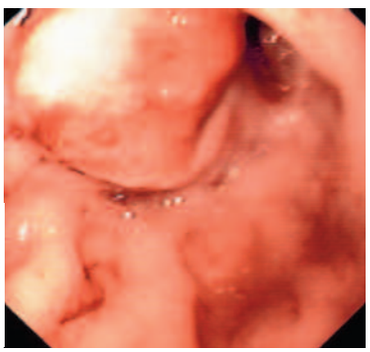
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Figure 31 - Gastroscopy in a 9-year-old Norwegian cat, who presented for gastric retention syndrome.
A large mass is present in the antral area. Enlargement of the abdominal lymph nodes was noted with abdominal ultrasound.

Animals aged ten years or older appear to be most affected **(Figure 29)**, but gastric lymphoma may be diagnosed in young animals.

> Etiology

Contrary to findings in humans, the role of inflammatory or dysplastic lesions (follicular gastritis, intestinal metaplasia or lymphoplasmocytic gastritis) has been hypothesized, but a clear role in the development of gastric neoplasia has not been confirmed in the cat.

In cats, Asiatic breeds are affected most often (Siamese) *(Freiche, 2005a)*. Predisposing factors include the ingestion of carcinogenic factors (nitrosamines, mycotoxins). The role of these substances in carcinogenesis has not been clearly established.

> Clinical signs

The clinical expression of gastric neoplasia in cats is disconcerting and non-specific. Invasive lesions commonly exist without triggering clinical signs for long periods.

Vomiting – of variable frequency and nature – are commonly observed. Vomiting may become refractory to the prescribed symptomatic treatments. The presence of blood is inconsistent and appears in stages. The time between meals and vomiting does not appear to be a reliable sign for objectifying this serious gastric disorder. The presence of food in the vomitus is not systematic, even if proliferative lesions trigger gastric motility problems.

Other less direct clinical signs that may be observed include:
- dysorexia
- prostration
- weight loss
- antalgic positions (less common in cats than dogs).
- isolation of the animal in unusual places

In some cases there is little or no vomiting and owners note only refractory anorexia and/or ptyalism. Abdominal palpation is not very painful and rarely reveals the presence of a mass.

> Diagnosis of gastric neoplasia

Hemato-biochemical modifications

Few of these modifications are likely to provide pointers for the clinician. Iron deficiency anemia is sometimes identified, expressed as bleeding due to chronic erosion of the mucosa.

Traditional radiography techniques

These are not of great help, especially when lesions are just emerging or they are diffuse through the stomach wall (e.g. lymphoma). Images with contrast medium may reveal abnormalities with gastric filling, abnormal gastric folds or parietal ulcerations associated with suspected thickening of the wall or suggest acquired parietal rigidity. These images are technically difficult to produce in cats and do not provide any evidence of an emerging lymphoma.

Abdominal ultrasound

This complementary examination plays an essential role in the diagnosis of stomach neoplasia. It demands good-quality equipment and special training. The ultrasound examination includes a differential diagnosis of the different histological types of gastric neoplasia *(Penninck, 1998)*. Cytological examination by fine needle aspiration may be performed as an alternative to endoscopy, especially for gastric lymphoma **(Figure 30)** if the regional lymph nodes are hyperplastic. Abdominal ultrasound also facilitates disease staging, which is vital prior to medico-surgical treatment **(Figure 31)**.

Gastric endoscopy

This is the diagnostic technique of choice when the indications have been rigorously defined. It immediately visualizes the mucosal surfaces and provides multiple parietal biopsies whose histological analysis confirms the diagnosis, especially in this isolated location. This examination also excludes other digestives disorders with the same clinical signs.

Visual appearance of the lesions

- In cats, *gastric lymphoma* may manifest as an infiltrative form that is typically difficult to diagnose visually. Some lesions resemble chronic isolated gastritis or IBD. As a consequence, only the result of histological analyses can be used to confirm the diagnosis. Folds in the stomach are very hyperplastic and edematous, with a cerebroid appearance **(Figure 32)**. Gastric lymphoma may also take an exophytic form, with a less equivocal appearance in endoscopy. The recent advancement in immunolabeling techniques permits a more precise approach to feline lymphoma by localization of membrane antigens *(Fondacaro et al, 1999)*.

- Other gastric tumors are more occasionally found in cats. Leiomyomas or leiomyosarcomas are expressed by the presence of a sometimes large mass projecting from the gastric cavity and if it is located in the antral region, can obstruct stomach emptying. The diagnosis of these lesions relies on visual aspects as endoscopically obtained mucosal biopsies are often negative (tumor of the muscle layers). *Carcinoid tumors* or gastric *fibrosarcomas* are very uncommon.

- *Benign adenomatous tumors* may be responsible for vomiting and weight loss due to their location close to the pylorus, which causes gastric retention syndrome. These lesions cause major mechanical problems. In this case, excision of the tumor mass plays a curative role.

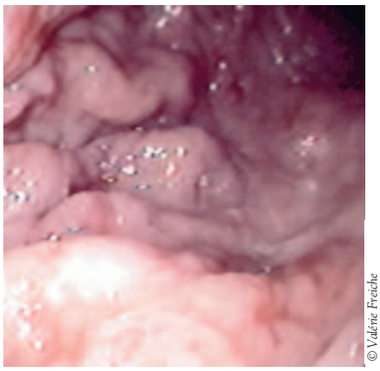
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Figure 32 - Gastric lymphoma in a 10-year-old female European cat. *Cerebroid-like folding, limited response to insufflation, located in the gastric body: the histological diagnosis confirmed the presence of a gastric lymphoma.*

Disease staging

In the event of gastric carcinoma (which is very uncommon in cats) *(Roubardeau & Péchereau, 2006)*, metastasis is initially regional (lymph nodes, liver, spleen, pancreas, peritoneum etc). With lymphoma, regional lymphadenopathy is identifiable at an early stage. Abdominal ultrasound is complementary to endoscopy. Thoracic radiographs rarely reveal pulmonary lesions during the initial diagnosis.

> Prognosis and treatment

The prognosis depends on the histological type of the tumor. In cats with gastric lymphoma, chemotherapy with or without surgery (which is proposed in very specific cases where the lesion is very limited or nodular) produces higher survival rates (often of several months, uncommonly of several years) *(Lanore & Delprat, 2002; Slatter et al, 2003)*.

Leiomyomas, leimyosarcomas and carcinomas should be treated surgically, possibly associated with adjunctive chemotherapy.

9 - Diseases of the intestines and nutritional approach

► Diarrhea in kittens

Diarrhea in kittens is a very common consultation that can be difficult for the veterinarian to manage. It may affect a litter or a colony, or a specific kitten in an age range from two to twelve months. Digestive problems in kittens in the perinatal period and up to the age of 2-3 months are the subject of concern for every breeder and they expect urgent, concrete solutions from their


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Tube feeding kittens requires skill. Breeders should be taught by a veterinarian before attempting the procedure themselves. If the feeding tube is not positioned properly (in the trachea instead of the esophagus) milk may enter the kitten's lungs and cause death.


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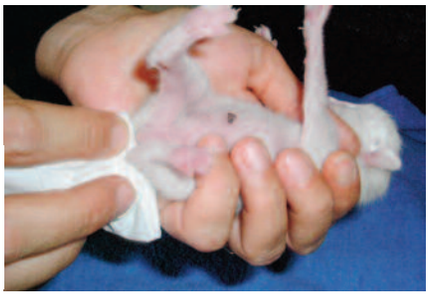
The feces of kittens are usually soft and yellow.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When there is no mother to care for the kitten, elimination must be stimulated after each feeding.

Constipation is quite common in the orphan kitten. In the vast majority of cases, it is linked to a lack of perineal stimulation, which stimulates the elimination of stools. For orphaned kittens, large litters and primiparous mothers, the breeder should ensure that defecation and urination is accomplished effectively. Otherwise, the transit of food through the digestive tract will be slower and will promote the reabsorption of water causing constipation to occur. The administration of paraffin oil is not recommended in the kitten. Repeated stimulation of the perineum and soft washing are preferable. In more serious cases, the veterinarian may need to anesthetize the kitten to administer an enema.

veterinarian. A kitten with diarrhea rapidly becomes dehydrated and requires on average 14-16 mL of water/100 g BW (*Malandain et al, 2006*).

When a kitten is presented with diarrhea and its general condition is satisfactory, the two preferred hypotheses are dietary intolerance or parasitism. The prevalence of parasitic diseases in young carnivores is significant and sometimes underestimated, at both the colony and individual level *(Spain et al, 2001)*.

> Digestive disorders in orphan kittens

This period of life without maternal assistance is complex. Very young animals are poikilothermic, without a layer of fat. Hypothermia always results in paralytic ileus, so prevention is important. In these circumstances, the living environment requires special attention, and dietary standards need to be fulfilled.
The main causes of diarrhea in this period are:
- over-consumption *(Hoskins, 1995)*
- poorly prepared or poorly conserved milk substitute, given at the wrong temperature.

Factors affecting the successful rearing of an orphan kitten are the quality of mother's milk and hygiene during feeding, thermal regulation, the quality of sleep, nursing, external stimuli and socialization.

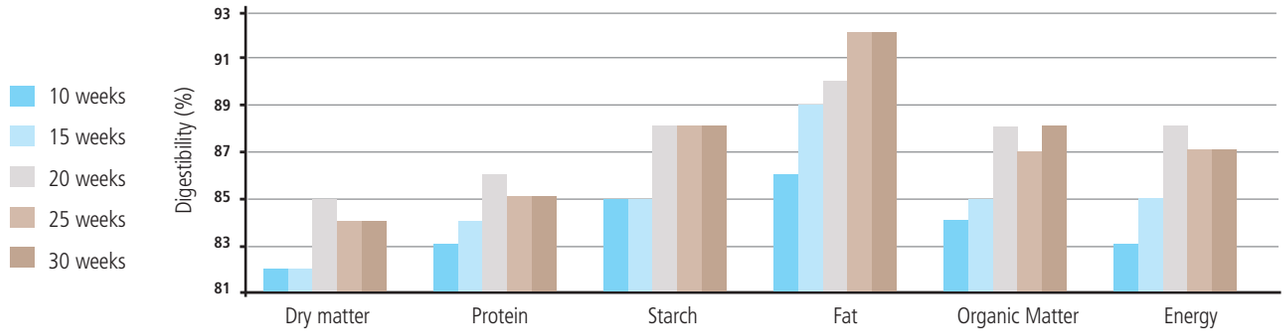
> Digestive disorders caused by the diet during weaning

Physiologically, this is a critical phase for the kitten, who has an immature immune and digestive system **(Figure 33)**, and is therefore vulnerable when placed in an environment with strong infectious and parasitic pressures. During weaning, a kitten faces several types of stress. The most important are:
- change of diet
- detachment from the mother
- acclimatization to a different environment and microbism

It is difficult to suggest recipe-types of weaning modalities. Every method is respectable if the results are good. Weaning begins the fourth or fifth week and most finish by week 7.

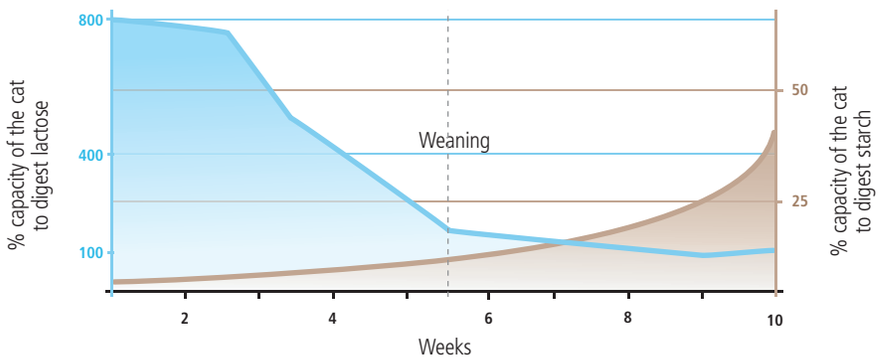
The main causes of diarrhea in this period (not including infectious and parasitic diseases) are:
- poor digestibility of the food
- poor conservation of the food
- over-consumption at mealtimes
- excess starch in the diet **(Figure 34)**.

Figure 33 - Variations in the digestibility of different nutrients during kitten growth
(from Harper & Turner, 2000)



An increase in most parameters is observed from week 20 (n=12).

Figure 34 - Development of the kitten's carbohydrate digestion capacity before and after weaning, compared with an adult's
(from Kienzle, 1993)



> Idiopathic enteritis in kittens

Kittens aged 6-12 months may present with diarrhea that is refractory to the usual symptomatic treatments, and yet resolves spontaneously in a few months *(Hoskins, 1995)*. These cats present with profuse diarrhea, however, they are in good general condition. The diagnostic tests are all within normal limits. The underlying cause maybe due to improper maturation of the digestive tract's absorption and exchange system, exacerbated by errors in dietary supervision.

In practice, weaning can start when the kittens' average daily gain starts to decline. Weaning usually ends around the age of 7 weeks.

> Diagnosis

The clinical signs are not specific to the disease. A methodical approach is necessary to consider the circumstances in which the diarrhea appears, the life context of the animal and the findings of the clinical examination.

A breeder needs to be educated about which clinical signs need to be identified early, the most concerning signs and the criteria for hospitalization. If the kitten is presented by a private individual, a full history (unrestricted access to the outside, contact with sick animals, possibilities that a toxin has been ingested, signs observed) will be needed before the clinical examination can be conducted. The seriousness of the clinical signs is correlated to the origin of the diarrhea.

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Figure 35 - Cytobrushes used for fecal detection of viral enteritis. *PCR is a laboratory technique for amplifying the genetic material of the virus and detecting its presence even at very low quantities. There are various types of applicators or cytobrushes used to collect samples for coronavirus testing (here per rectum).*

The following hospitalization criteria may be employed for kittens *(Battersby & Harvey, 2006)*:
- alteration of the general condition (asthenia, anorexia)
- abnormalities of cardiac rhythm: bradycardia or tachycardia
- hyperthermia or hypothermia
- dehydration
- presence of blood in the feces
- abnormal abdominal palpation (mass, lymph nodes, etc.)
- presence of other clinical signs: frequent vomiting, icterus, etc.

In the event of hospitalization, fluid and electrolyte therapy must be implemented and the kitten placed in isolation, if necessary.

The diagnostic evaluations are adapted to each specific clinical situation and include:
- hemato-biochemical analyses (leucocytosis, anemia, hyper- or hypoproteinemia). Exudative enteropathy is accompanied by hypoproteinemia, while hyperproteinemia is more consistent with feline infectious peritonitis (FIP). The young age of the kitten must not exclude metabolic causes of diarrhea;
- coagulation tests in cases of digestive bleeding
- fecal analyses (fecal cytology, bacteriology, larvae, cysts, protozoans)
- detection of retrovirus (FeLV, FIV)
- PCR on blood and/or rectal sampling (FIV) **(Figure 35)**
- measurement of fTLI, using a specific feline assay.

> Treatment of diarrhea in kittens

A systematic approach is required for acute diarrhea of sudden onset, without alteration of the general condition. Diagnostic examinations must be conducted if the clinical signs persist for longer than a couple of days and a second round of symptomatic treatment should not be started if the first one fails, even if the clinical signs are only a week's duration. Diarrhea is not considered to be chronic until it enters its third or fourth week.

Specific treatment for each disorder must be started. Observance is a limiting factor in cats. It may be difficult for private individuals with many cats or colonies to follow the nutritional instructions. Novel protein diets can be recommended for the dietary treatment of kittens with diarrhea. Low fibre concentrations are probably the best recommendation to start unless there are indications for a large bowel problem. Other helpful supplements are probiotics, that can be helpful in the modulation of the intestinal microbiota *(Guilford & Matz, 2003; Marshall Jones et al, 2006)*. The efficacy of prebiotics such as fructo-oligosaccharides has to be evaluated depending on the individual reaction.

► Infectious gastroenteritis

The term "infectious" is employed liberally here. This section examines forms of viral, parasitic and bacterial gastroenteritis that most commonly affect cats. The exposure of the digestive tract to different pathogenic agents is not always expressed by the appearance of clinical signs *(Guilford & Strombeck, 1996c)*. Any disturbance of the physiological mechanisms of homeostasis is however likely to generate an imbalance in the microflora or induce modifications in local antigenicity, causing diarrhea.

Upon identification of diarrhea in a breeding colony, some practical steps should immediately be implemented: the sick kittens should be isolated, and new kittens, quarantined. Prevention also demands good hygiene and disinfection of the premises.


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> Viral gastroenteritis

The prevalence of all the viruses that infect cats is unknown *(Guilford & Strombeck, 1996c)*. These viral infections provoke highly varied clinical signs: discreet alteration of the general condition or

necrosing enteritis in the event of panleukopenia. These diseases propagate themselves quickly and are highly contagious. Their prevention demands a systematic approach comprising rigorous hygiene measures, the quarantine of new individuals and vaccination wherever possible.

Feline enteric coronavirus

Feline coronavirus shares antigenic and morphological characteristics with the one of FIP. Today, it is commonly thought that a mutation of coronavirus can lead to the expression of FIP. Viral replication occurs in the apex of the microvilli. Infected animals develop moderate and transitory digestive problems. Sometimes there are no visible clinical signs.

Feline infectious peritonitis

This disease manifests in a variety of clinical forms. The most commonly described form is the presence of inflammatory effusion in the cavities. The "dry" form is characterized by granulomatous inflammation of the parenchyma (pancreas, liver, digestive wall, lymph nodes). FIP is therefore not expressed as a common chronic or acute gastroenteritis. It often affects young animals, but not exclusively so. Fever is a common sign. Laboratory evaluation (hematology, biochemistry, PCR, etc.) helps to underpin the clinical suspicion.

A last form – more specific and less well known – is atypical isolated granulomatous colitis. The modifications it produces on an ultrasound are equivocal *(Harvey et al, 1996)*. The prognosis is invariably poor.

Retroviruses (FeLV – FIV)

The FeLV virus is responsible for superacute mortal enterocolitis and lymphocytic ileitis. The FIV virus is most often implicated in episodes of recurring diarrhea. Cats infected with the FIV virus may survive for long periods, during which time they will intermittently present with digestive disorders of varying intensity. Immunosuppression may favor enteric infection *(Battersby & Harvey, 2006)* and the diarrhea will be secondary to other infectious agents rather than to the presence of the FIV virus.

Feline panleukopenia

Feline panleukopenia is due to a parvovirus with epidemiological, physiopathological and hematological characteristics similar to those of the canine virus *(Squires, 2003)*. The pathogenic power of the virus is also expressed on the central nervous system in utero or during the neonatal period (cerebellar hypoplasia) *(Guilford & Strombeck, 1996c)*.

The clinical signs manifest themselves 4-7 days after transmission of the virus by the fecal-oral route. The virus is very stable in the exterior environment. Viral replication occurs in tissues that rapidly multiply: bone marrow, lymphoid tissue, intestinal crypts. The jejunum and ileum are the most often affected digestive segments. Viral replication produces leukopenia and necrosis of the intestinal crypts that leads to hemorrhagic enteritis. The clinical signs are dominated by major asthenia, rapid anorexia and weight loss, vomiting and diarrhea. Death may occur before the appearance of the diarrhea in the superacute forms. Massive bacterial translocation is the cause of septic shock. Liver failure is often the cause of death.

Several other viruses cause acute digestive disorders in cats. These include astrovirus (isolated in kittens) rotavirus (which causes neonatal diarrhea), reovirus and calicivirus. Their identification is difficult and their pathogenic role has not been clearly identified.

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Viral diseases (coronavirus, feline infectious peritonitis, retroviruses, feline panleucopenia) are always likely to appear in a cattery or colony, even when hygiene conditions are good and medical prophylaxis is meticulously observed.

> Parasitic gastroenteritis

Parasitic infestations

The parasitic infestation must be extensive before clinical signs manifest themselves: bloating, vomiting, diarrhea, skin lesions, coughing during larval migration. The incidence of parasitic enteritis is

Figure 36 - Adult roundworms. *Adult roundworms are long and round, measuring 4-10 cm.*

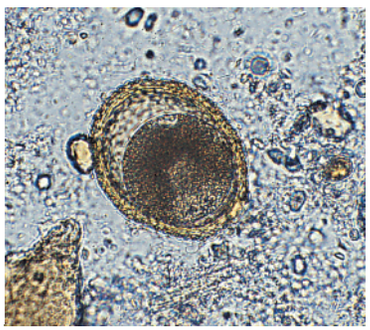


Figure 37 *- Roundworm egg.*

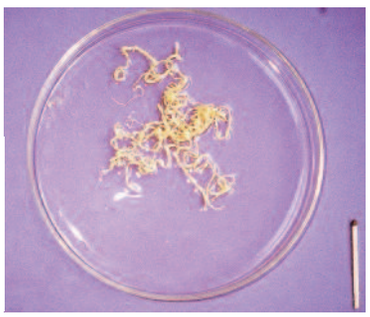


Figure 38 *- Segments of* Dipylidium caninum.

higher in colonies and in young animals. It is underestimated among individual owners *(Battersby & Harvey, 2006)*. Various infestation modes are possible: fecal-oral route, in utero contamination (toxocarosis), transmission through colostrum or milk, ingestion of intermediate hosts (tapeworms).

The location of the parasites is variable. They are often found in the small intestine, but the large intestine is also infested. The presence of these parasites may also cause anemia, melena (hookworm disease), sudden inexplicable deaths in the cattery, stunted growth or fertility problems among breeding stock.

The most commonly encountered parasites are ascarids **(Figures 36 & 37)** *(Toxocara cati, Toxascaris leonina)*, tapeworms (mostly *Dipylidium caninum*) **(Figure 38)**, hookworms *(Ancylostoma tubaeformae)* and *Strongyloides tumefaciens* in tropical areas. The diagnosis is based on fecal evaluation (flotation in zinc sulfate).

The treatment of parasitic enteritis uses anthelmintics, which are available in many forms: oral pastes, small caplets adapted to cats, trans-dermal (spot on). The active substances and their spectrum of action are listed in **Table 7**.

Treatment of the mother is recommended two weeks prior to the birth, then during weeks 3, 5 and 7, to stop the parasitic cycle.

Protozoan diseases

The digestive tract of cats may be colonized by protozoans: Giardia, Coccidia and Trichomonas.

Giardia

Less common in cats than dogs, giardiasis is expressed by digestive disorders that may be intermittent (diarrhea does not present a specific aspect) as well as dysorexia episodes or deterioration in the general condition. An immunosuppressive condition favors the clinical expression of giardiasis.

TABLE 7 - ANTHELMINTIC SPECTRUM OF COMMONLY AVAILABLE ANTIPARASITIC AGENTS

	Nematodes		Cestodes	
Product	Ringworms	Hookworms	Taenia	Dipylidium
Piperazine	■			
Oxibendazole	■	■		
Pyrantel	■	■		
Milbemycin oxime	■	■		
Selamectin	■	■		
Levamisole; Tetramisole	■	■		
Emodepside	■	■		
Mebendazole 2 days	■	■		
Mebendazole 5 days	■	■	■	
Moxidectin	■	■		
Flubendazole 2 days	■	■		
Flubendazole 3 days	■	■	■	
Fenbendazole 3 days	■	■	■	
Niclosamide			■	■
Praziquantel			■	■

Note: the use of these compounds in cats can be restricted according to the licence applicable in each country.

Trophozoites are attached to the brush border of the proximal small intestine. They are periodically excreted in the feces, which is why several fecal examinations spaced over intervals of several days are desirable to avoid a false negative diagnosis. An ELISA diagnostic kit is available for practitioners.

The treatment of giardia uses imidazoles: metronidazole, fenbendazole. With resistant strains, the environment should be properly decontaminated (elimination of feces and disinfection with quaternary ammoniums). Animals must be cleaned as recontamination is possible by the ingestion of oocysts **(Figure 39)** deposited on the coat by licking.

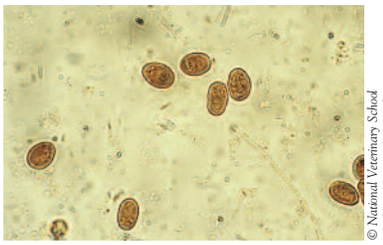


Figure 39 - Oocysts from Giardia. *Oocysts survive in humid environments and some wild animals are reservoirs of this disease.*

Coccidia *(Isospora felis, Isospora rivolta)* (Figure 40)
This protozoan disease is common in breeding colonies and its expression is strengthened by an underlying parasitic condition and unfavorable hygiene. The clinical expression may include the following signs:
- stunted growth in kittens
- abdominal pain
- fever
- tenesmus
- mucoid diarrhea.

Hygiene on the premises is important in prevention. Treatment is based on the association of trimethoprim-sulfonamides with clindamycin or toltrazuril for resistant forms.

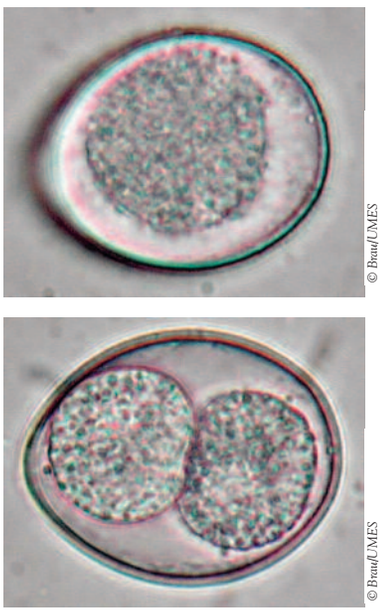


Figure 40 - Oocysts from Isospora felis immature (top) and infectious (lower). *Maturation of the oocysts requires at least 48 hours.*

Trichomonas *(Tritrichomonas fœtus, Pentatrichomonas hominis)*
Trichomoniosis seems to be an under-estimated cause of recurring digestive disorders in young cats, especially in colonies. The pathogenesis of these organisms is multifactorial in interaction with the host's endogenic flora *(Gookin et al, 1999)*. The disease is expressed when hygiene is inadequate: diarrhea predominates with hematochezia and/or mucus, peri-anal inflammation, rectal prolapse. Transmission is directly via the fecal-oral route.

The identification of protozoans by fecal analysis is difficult. They can be easily confused with giardia. Fecal culture tests are commercially available (In Pouch TF©). Their presence in the colon is expressed by an influx of inflammatory cells (lymphoplasmocytes or neutrophilic leukocytes) and sometimes crypt abscesses *(Yaeger & Gookin, 2005)*. Eradication is difficult, as trichomonas are resistant to imidazoles. A recent study mentions the over-representation of purebred cats, especially the Siamese and the Bengal *(Gunn-Moore et al, 2007)*.

> Bacterial gastroenteritis

Some pathogenic bacteria may cause episodes of acute or chronic diarrhea. Unlike protozoans, their presence is clearly overestimated. Antibiotic treatment should only be started after isolation of an enteropathogenic bacterial strain. Inappropriate antibiotic treatment may provoke serious imbalances in the intestinal flora, and favor the development of bacterial antibiotic resistance.

The main pathogenic bacteria described in cats and responsible for digestive disorders include *(Henroteaux, 1996)*:
- *Campylobacter* (possible healthy carrier)
- *Salmonella* (possible healthy carrier, septicemic risk if pathogenic)
- *E. coli* (enteropathogenic strains)
- *Clostridium perfringens*
- *Yersinia enterocolitica*.

Clinically, bacterial diarrhea has strong repercussions on the general condition, as well as fever and the regular presence of blood in the feces. A serum electrolyte profile should be conducted to guide fluid and electrolyte rehydration and to correct the frequent hypokalemia.

The history must probe for sick people that are in contact with the cat. The diagnosis is based on fecal cytology that indicates the presence of leucocytes and bacterial elements. The diagnosis is confirmed by bacterial culture of the feces.

► Acute gastrointestinal diseases

> Etiology

In cats, acute gastrointestinal diseases are most commonly caused by diet, parasites or toxins (see above). They are expressed by the association of vomiting and diarrhea with varying characteristics. Cats sometimes tend to defecate outside the litter box when suffering from this type of diarrhea.

Vomiting predominates in the event of occlusion.

> Procedure for diagnostic evaluation

Diagnostic tests are rarely justified initially. Hospitalization should be proposed according to the same criteria as described for diarrhea in kittens:
- alteration of the general condition and dehydration
- tachycardia and bradycardia
- fever
- hematemesis
- abdominal pain or abnormal palpation
- suspicion of peritonitis.

The sequence of diagnostic tests is dictated by the history and tailored to each case. It includes hematological analyses (leukopenia, leukocytosis, anemia), viral tests (FeLV, FIV), fecal analyses, radiograph and ultrasound examinations if occlusion is suspected.

> Nutritional measures

Acute vomiting and diarrhea usually mean that the patient should be fasted (nil per os [NPO]). Oral feeding is not practicable in cats if vomiting persists or diarrhea is profuse. Because of the consequences of vomiting and diarrhea for the electrolyte and acid-base balance, parenteral fluids with electrolytes and buffering substances should be administered. Oral rehydration can be administered when tolerated. If the water losses are high because of vomiting and severe diarrhea, fluid has to be administered by parenteral application. Fluid should be administered as a mandatory measure if there is evidence of dehydration (>5%) or the patient refuses to drink.

If the condition improves and the animal is willing to accept a small amount of food, frequent small meals should be administered for 24-72 hours depending on individual tolerance. Examples of appropriate homemade diets are boiled rice with 2 parts of boiled lean meat (chicken or turkey) or eggs. Milk and milk products such as low fat cottage cheese (low lactose content) can be used, although the high lactose concentration may be a problem. An alternative is a highly digestible commercial diet with a low-fat concentration. During the acute stage it is often recommended to use a protein source that is not part of the normal diet (sacrificial protein) to avoid sensitization or the development of allergies. The fiber content of diets for patients with acute intestinal problems has to be limited to ensure optimal tolerance and digestibility. The levels of potassium, sodium and chloride should be increased because vomiting and diarrhea induce high electrolyte losses. When clinical signs improve, the usual diet can be reintroduced gradually.

► Inflammatory bowel diseases

Inflammatory bowel diseases (IBD) are the main cause of chronic digestive disorders in domesticated carnivores, especially cats. The term covers a group of idiopathic diseases, while certain pathogens have been implicated in their clinical and anatomicopathological expression (food antigens, parasites, bacteria). Many studies implicate complex interactions between the patient's particular predispositions, immunity problems related to the mucosa and the digestive microflora. Knowledge of IBD has progressed over the last fifteen years, with the advent of ultrasound and endoscopic examinations of the cat's digestive tract.

> Definition

IBD is defined in accordance with the histological criteria: infiltration of the mucosa of the small and/or large intestine by a population of inflammatory cells, most often lymphoplasmocytic **(Figure 41)**, although neutrophilic leukocytes, eosinophilic leukocytes and macrophages may also be involved *(Tams et al, 1996a)*.

The most restrictive definition of IBD entails the presence of lesions only in the small and/or large intestine. However, some authors do not exclude IBD in the event of inflammatory gastric lesions *(Guilford, 1996)*. Very often in fact, intestinal lesions are not isolated and the entire digestive mucosa is affected by the influx of inflammatory cells in the *lamina propria*.

> Clinical reminders

No breed or sex predisposition has been recognized and all age groups may be affected, including young adults. The intensity of the clinical signs varies greatly from animal to animal: chronic digestive disorders (diarrhea and/or vomiting), dysorexia and inconsistent alteration of the general condition. These manifestations may develop 'by crises' for months or even years before becoming permanent. These diseases are better documented in cats than in dogs *(Jergens, 2006)*. At the beginning of the disease, vomiting is predominant and may be the expression of intestinal lesions, even distal ones. The vomiting of gastric juice well after mealtime and in the morning on an 'empty stomach' is common.

Diarrhea may be a sign of lesions of the small intestine (profuse, very watery diarrhea) or a colonic disorder (tenesmus, the presence of mucus or blood, minor undermining of the general condition), but this dichotomy is much less specific in cats than dogs. In other cases, episodes of constipation occur before the appearance of diarrhea.

Abdominal palpation may reveal thickening of the intestinal loops and an increase in the size of the associated lymph nodes. In other cases, abdominal palpation may be perfectly normal.

> Diagnosis

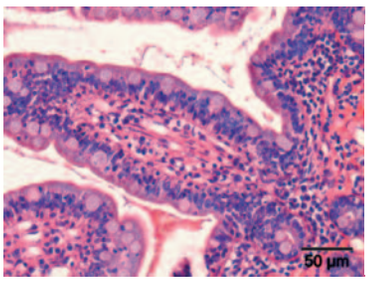
The diagnosis of IBD is by exclusion of other diseases that could cause the clinical signs or an inflammatory influx into the digestive mucosa (neoplastic infiltration, bacterial proliferation syndrome, hyperthyroidism, protozoans) *(Krecic, 2001)*.

Endoscopy is conducted after diagnostic tests for other conditions are completed (CBC, biochemical analyses, fecal examination, basal T_4 measurement, abdominal ultrasound) *(Simpson et al, 2001)*.

Abdominal ultrasound

Abdominal ultrasound precedes endoscopy in the exploration of digestive diseases of the cat. The assessment of the parietal layers **(Figure 42)** and the size of the lymph nodes are essential to help eliminate the hypothesis of lymphoma. Ultrasound also confirms whether there are lesions in the pancreas, liver or bile ducts, as cats with IBD often have concurrent cholangitis.

Figure 41 - IBD in a cat: histological examination.



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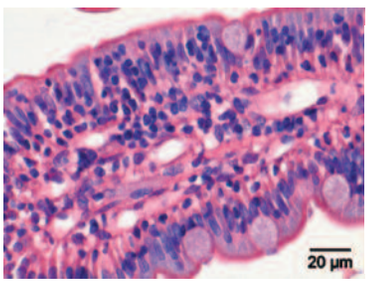
41A - Increased number of intra-epithelial lymphocytes in the villus epithelium as well as increased numbers of lymphocytes in the lamina propria of the villus and the basal mucosa between the crypts.



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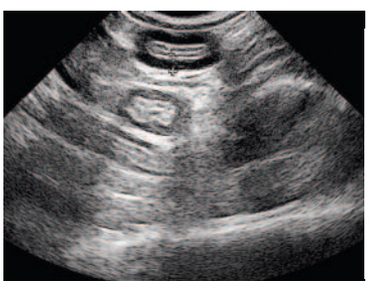
41B - High power magnification of a villus with marked presence of intra-epithelial lymphocytes and lymphocytic infiltration of the lamina propria.

Figure 42 - 3.5 year old female Siamese cross cat, who presented with frequent vomiting.



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Abdominal ultrasound shows an enlargement in the parietal region. Transabdominal biopsies confirmed a diagnosis of severe eosinophilic enteritis.

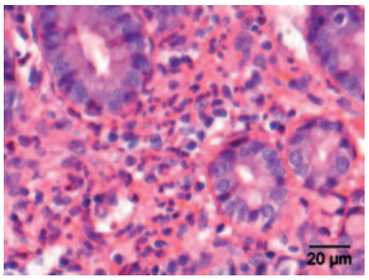

Figure 43 - Eosinophilic colitis in a cat (large intestine).
Marked infiltrate of eosinophilic granulocytes as well as some plasma cells in the lamina propria between the crypts.

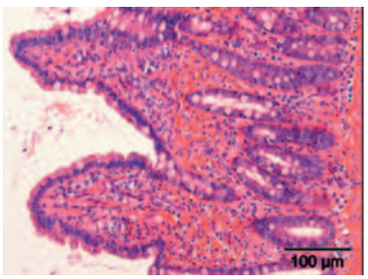

Figure 44 - Chronic eosinophilic enteritis (small intestine).
Villous atrophy with blunted villi, a band of fibrous tissue at the transition between villi and crypts and a moderate infiltrate of eosinophilic granulocytes.

IBD comprises by definition a group of chronic diseases that require protracted treatment. Relapses are common. It is essential to educate the owner about the disease and its management and to set realistic expectations for the care of the cat.

Endoscopy

Both upper and lower gastrointestinal endoscopy is necessary to establish a precise diagnosis. A number of endoscopic biopsies must be obtained from all accessible segments:
- *upper*: stomach, duodenum, proximal part of jejunum
- *lower*: distal part of the ileum, colon.

The histological analysis of biopsies may involve one or more cell types. The most common inflammatory infiltrate is lymphocytic/plasmacytic. The inflammatory infiltration may be polymorphous (the presence of neutrophilic leukocytes, a varied number of eosinophilic leukocytes **(Figure 43)**, histiocytes). Villous atrophy may also be associated with the disease **(Figure 44)**. Its presence often worsens the prognosis.

Visual appearance of the lesions

The visual appearance of the mucosa is never specific. There is poor correlation between the visual appearance and the histological score. In cats, the correlation between the clinical signs and the histological distribution of lesions is unsatisfactory. Visual classification is difficult due to certain subjective parameters that depend on both the operator and the equipment. Endoscopy produces a fairly reliable histological map. It is the fastest exploratory technique and less burdensome for the animal than exploratory laparotomy, which should only be performed in special circumstances. The nature of the inflammatory infiltrate and its distribution along the digestive tract leads to the elaboration of more specific therapeutic protocols *(Strombeck & Guilford, 1991; Sturgess, 2005)*.

Biopsies

Associated parietal fibrosis may be suspected during biopsy (difficulty of taking biopsy fragments of normal size, resistance to traction when the forceps are closed). If this is so, additional biopsies should be performed to obtain samples of sufficient size for reliable histological analysis. This would also permit identification, in the same segment of the digestive tract, of more or less modified sections. Central needle biopsy forceps may also be useful, as they are more effective on a more rigid mucosa surface.

> Management

Medical treatment

Despite the possibility of standardized therapeutic plans, the veterinarian must consider each case as an individual entity. One of the pitfalls of treatment is the lack of observation among cat owners. Treatment comprises the administration of the substances listed below.

- *Digestive flora regulators with immunomodulation properties (metronidazole) (Zoran et al, 1999).*
- Sulfasalazine is tolerated less well in cats than dogs and its indications are specific and limited *(see feline colitis)*.
- *Corticosteroids* are proposed in the most severe cases but large doses are not generally essential to ensure clinical stabilization, as refractory cases are uncommon. The minimal effective dose must be established to enable alternate day corticotherapy at the earliest opportunity. Long-acting corticosteroids are used for cats, but they are less effective than prednisolone administered orally.
- *Other immunosuppressive agents* may be proposed if there is no response to corticosteroids, depending on the histology results of biopsies. These include chlorambucil, cyclosporine and azathioprine *(Zoran, 1999)*. Note that cats are extremely sensitive to the toxic side-effects of azathioprine and its administration requires a close monitoring and reevaluation of the treated cat.

Dietary treatment

Patients with inflammatory bowel disease often suffer from malnutrition **(Figure 45)** due to inadequate dietary intake compared to increased requirements, maldigestion and malabsorption, and excessive fecal nutrient losses.

Exclusion diets and hydrolysed protein-based diets are often favorable in IBD cases because they can positively interact with the mucosal inflammation *(Waly et al, 2006)*. Inflammation of the gut wall itself can impair the absorption of amino acids, peptides and carbohydrates as well as the transport of minerals and fluid. A highly digestible diet may also be beneficial. Most cats can tolerate a high-fat diet (> 20% DMB in a dry food). Some patients may do better on a low-fat diet (≃ 10% DMB) because fatty acids can be hydroxylated in the gut by certain bacteria and stimulate secretory diarrhea. Probiotics and prebiotics may be used as feed additives in IBD patients, although there are no controlled clinical trials providing evidence for their efficacy in IBD cases.


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Figure 45 - *Dietary treatment of IBD cases is similar to the management of dietary allergy.*

► Adverse food reactions

Food allergy, intolerance or sensitivities can be summarized under "adverse food reactions". They are often considered to be a cause of chronic gastrointestinal diseases. Commonly, they are divided into:
- non-immunologically mediated reactions
- immunologically mediated reactions, synonymous to "food allergy" *(German & Zentek, 2006)*.

Clinical signs may affect the gastrointestinal tract or other organs or systems. Dermatological signs are most common in the event of gastrointestinal problems.

> Etiologies

In many cases clinical gastrointestinal signs are caused by food intolerance that is not based on immunological mechanisms. True allergies are difficult to assess in practice and may be less important than commonly assumed. The main compounds in commercial diets that may cause dietary allergy or adverse reactions are protein sources. In principal, all commonly used proteins such as beef, pork, vegetable proteins, and fish have to be considered as potentially problematic.

> Diagnosis

The diagnosis is mainly based on dietary history and clinical investigation. This procedure is subjected to individual influences and the frequency of an "allergy" as a diagnosis is dependent on the investigator.

In all patients that are suspected to have a dietary intolerance, a complete overview of the dietary history of the patient is mandatory, including information on the usual diet, treats or table scraps. In some cases, problematic food compounds can be identified, which is essential for 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 an initial elimination diet depends on the history of ingredients used in the individual's diet.

Specific assays for the characterization of adverse reactions to food are not yet available, so first diagnosis is mostly made on the observation that the disease responds to dietary changes *(Hall, 2002)*. The gold standard of diagnosis involves the response to the exclusion diet and the subsequent challenge with provocation test *(Allenspach & Roosje, 2004)*. A specific diagnosis based on indirect blood allergy tests is questionable and may produce erroneous results.

Common test diets for cats are based on lamb, chicken, rabbit or venison, often in combination with rice or green peas. An improvement in clinical signs is suggestive of food allergy or at least an adverse reaction to food ingredients *(Wills & Harvey, 1994)*. The diagnosis should be confirmed by reverting to the original diet. The development of clinical signs can be expected immediately or within one or two weeks of feeding. Therefore, a trial length of 2-3 weeks would appear appropriate in most GI cases. Food provocation trials can be performed to identify the ingredient causing the problem, adding single protein sources sequentially for 7 days at a time. Most owners will not pursue this if the elimination diet has worked successfully. In conclusion, diagnosis requires dietary elimination-challenge trials and clinical signs; routine clinico-pathological data, serum antigen-specific IgE assay, gastroscopic food sensitivity testing, or gastrointestinal biopsy can only be supportive *(Guilford et al, 2001)*.

> Dietary treatment

Dietary management of adverse reactions to food follows the same principles as discussed for diagnostic procedures. Unfortunately, the practitioner is dependent on the compliance of the owner. This may become critical, as clinical signs can respond slowly or relapse. Dietary protocols should follow a standard concept. In the long run, a balanced diet composition, high digestibility in the small intestine and a restricted number of ingredients are important *(German & Zentek, 2006)*. This facilitates the digestive process, limits the antigenic load in the gut and supports the absorption of nutrients.

Type of diets

Home-prepared diets have a place in the treatment of cats with dietary indiscretions, although commercial diets with limited number of ingredients are often preferred because of the higher safety in application and the greater convenience. Diets with hydrolysed proteins offer an interesting alternative for the treatment of cats with a dietary allergy that is not responsive to "normal" antigen restricted diets.

Dietary change

A dietary change can be helpful regardless of the etiology and can contribute to a better outcome in many cases. A "new" diet may have a beneficial impact on the intestinal digestive processes and it may also influence the composition and metabolic activity of the gut bacteria. A dietary change may limit the growth of undesirable microorganisms and so reduce concentrations of microbial metabolites in the gut. Microbial metabolites like the biogenic amine histamine can have a negative impact on the health of cats.

Once a diet has been selected, it has to be fed as the sole source of food for at least 12 weeks to determine whether the desired response will occur. GI signs will often resolve sooner than dermatological signs.

Protein sources

The choice of the best-suited dietary protein is the key to the outcome of the case.

- **Lamb** has commonly been used, but the widespread use of ovine protein in pet food may make this choice less promising.
- **Fish** is less suitable for cats because many commercial cat foods are fish-based or have fish as a minor ingredient. Fish can be a common cause of adverse food reactions in this species *(Guilford et al, 2001)*.
- **Wheat (and barley, oats) gluten** can cause dietary allergy and celiac disease in humans. Their use is probably also critical in cats, which suggests the need to change the carbohydrate source in all cases with suspected food allergy.

Fat sources may also contain small amounts of protein from the basic animal or plant raw material. Although these traces of protein appear to be of minor importance, they could theoritically affect the result of an elimination trial but this potential influence is strongly debated.

Hydrolysed protein sources are often used in commercially available veterinary diets. Protein is treated enzymatically to alter its structure. They are split by enzymatic treatment into small peptides. The enzymatically released peptides are less likely to interact with the immune system due to their low molecular weight. The high digestibility of these diets may be advantageous in patients with gastrointestinal disorders.

Carbohydrate sources

Generally, a single source of carbohydrate is recommended to avoid misinterpretation. Maize, potatoes, rice, green peas, and tapioca may be suitable.

Minerals, trace elements and vitamins

Minerals and trace elements have to be added to make a diet complete and balanced. However, some sources of mineral salt, like bone meal, contain small amounts of protein, which may itself provoke an adverse reaction.

Supplementation of home-prepared diets with vitamins can also be problematic, since some of the commonly used vitamins are protected by encapsulation with gelatin (usually prepared from pork). Although the production process is strict and most potentially antigenic epitopes are destroyed, traces of proteins or peptides may still be introduced into a diet. One option is to use a home-prepared diet, based on a minimum of dietary ingredients. Adult cats will tolerate this for some weeks without developing severe nutrient deficiencies. However, home-prepared diets need to be balanced and complete if they are fed long-term or nutrient deficiencies will develop.

Medical treatment is based on the therapeutic plans implemented for IBD.

► Diseases of the colon

> Megacolon

Progressive local or total distension of the colon and the loss of motility lead to fecal retention which is characterized by chronic constipation and aggravates over time. Cats are affected more commonly than dogs.

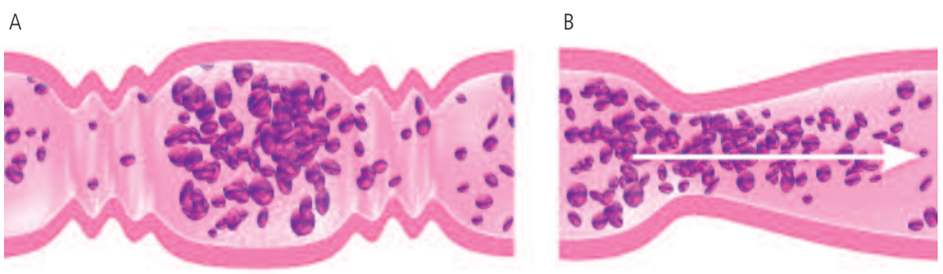
Physiological reminders

The proximal colon plays an important role in the absorption of water and electrolytes from the luminal content. The mucosal parietal cells actively absorb chloride (Cl^-) and sodium (Na^+) ions by ATP dependent pumps. This mechanism results in passive water absorption.

The distal colon permits the storage and periodical elimination of feces. If peristalsis of the colon is passive (the parasympathetic nervous system generates peristaltic contractions, while the sympathetic nervous system regulates segmentary contractions), defecation is a willful act, under the control of the central nervous system. The colonic transit time is variable in carnivores (forty hours or so).

The longitudinal and circular muscle walls are responsible for motility and colon tone. This motility is regulated by gastrointestinal hormones and intrinsic and extrinsic innervation of the colon. There are movements that mix the contents of the colon (rhythmic segmentary contractions) and retrograde contraction waves in cats **(Figure 46)**.

FIGURE 46 - TYPES OF CONTRACTION OBSERVED IN THE COLON



Regular segmentary contractions (A) slow the progress of feces and promote reabsorption of water. Peristaltic contractions (B) favor the advancement of the contents of the colon downstream.

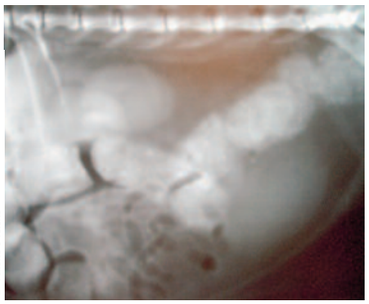

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Figure 47 - Megacolon in a cat who previously suffered from pelvic fractures.

The anaerobic colonic flora participates in a number of reactions: the liberation of medications, and the production of endogenous compounds (volatile fatty acids).

Etiopathogenesis

Congenital megacolon is described in the Siamese. It is said to be due to the absence of ganglion cells in the myenteric and submucosa plexus (aganglionosis).

The acquired forms result from organic lesions (anatomical lesions of the pelvis, neoplasia and intraluminal stricture), metabolic abnormalities (hypokalemia), neurological disorders (dysautonomia) or are of undetermined origins (idiopathic megacolon, which accounts for around 62% of cases according to *Washabau* (2003)).

Clinical expression

Owners report chronic constipation in cats, associated with vomiting. Painful abdominal palpation is evidence of a highly distended, colon that is hardened throughout its length. A rectal swab without sedative will enable elimination of the cause of distal obstruction and deformations of the pelvic canal.

Low occlusion is observed and demands hospitalization of infused animals (renal biochemical values are often high). The fecalith is evacuated under anesthesia, by colostomy in the most severe cases.

Diagnosis

Radiograph examination suffices to establish the diagnosis **(Figure 47)**. An examination of the front of the pelvis is necessary to exclude any old trauma that may have caused modification of the pelvic canal.

Endoscopy is not useful in establishing a diagnosis, unless an endoluminal lesion is suspected that has caused dilatation proximally in the colon.

Medical treatment

Medical treatment is exclusively palliative. Its success is closely linked to the motivation and availability of the owner, as recurrence is immediate without continuous nursing. In the medium term, surgery or euthanasia may be justified by the owner's lack of motivation.

- *Prokinetics:* cisapride was the drug of choice for treating megacolon, however, it is not available in every country.
- *Laxatives*: lactulose (0.2 mg/kg 3 times per day per os) or appetent medicinal oil sometimes delays the need for surgery. Rectal laxatives empty the rectal ampulla but do not have any effect on transit. Enemas are often poorly tolerated by the animal and are irritating in the medium term.

Dietary treatment of constipation

Many cats with constipation respond positively to an increased fiber level, but the physical and chemical properties of fiber sources differ considerably so they should be selected according to the desired effect.

Insoluble fiber

The gut flora ferments dietary fiber sources with low solubility slowly or not at all. Cellulose is a good example of a dietary fiber source with low degradability by intestinal bacterial fermentative processes. It increases the bulk in the large intestine and the increased gut fill helps stimulate intestinal motility. Depending on the structure and chemical composition, some insoluble fiber sources can trap water *(Robertson & Eastwood, 1981)*. The concentration of insoluble fiber should be limited, as insoluble ingredients tend to lower the digestibility of the diet.

Soluble fiber

Typical examples of soluble fiber sources include beet pulp, psyllium, pectin from carrots or fruits, and gum such as guar gum. Soluble fiber has a higher water-holding capacity than insoluble fiber due to its gel-forming capacity *(Robertson & Eastwood, 1981; Rosado & Diaz, 1995)*.

Soluble fiber is generally easily fermented by intestinal bacteria (except psyllium). The fermentation processes induced by the ingestion of fermentable fiber have a strong impact on the colonic milieu, because bacteria release organic acids as metabolism products that tend to reduce the colonic pH. The SCFA produced by bacteria can be utilized as energy yielding substrates by the colonic mucosa. Butyric acid has beneficial effects on the integrity and function of the gut wall and organic acids may also have some regulatory effects on motility.

Negative effects of higher amounts of soluble dietary fiber include an excessive production of SCFA and a risk of osmotic diarrhea.

In practice, it may be necessary to adjust the amount of fiber according to patient tolerance and the clinical effects. In cases of severe problems due to constipation or fecal impaction, the laxative effects of soluble fibrous sources (e.g. psyllium) are used specifically for treatment. Fermentable carbohydrates like lactulose or lactose may be recommended in constipated cats *(Meyer, 1992)*. The dosage needs to be adjusted on a case by case basis to ensure the patient produces a slightly moist stool with increased acidity. The fecal pH will be around 6.5 when adequate amounts of lactulose are ingested. Liver, milk and milk products are diet ingredients with mild laxative properties.

> Colitis

Colonic diarrhea is the result of failure of the colon's water and electrolyte reabsorption function, which determines the water-content of feces. The colon's reabsorption capacity (colonic reserve) can in fact be saturated. It is the proximal part of the colon that is responsible for this regulatory function.

Inflammatory colonopathies are a group of diseases whose pathophysiology is still largely unknown. Some factors have been clearly identified (e.g. parasitic or bacterial causes), but the origin of the colonization of the colonic mucosa by inflammatory cell populations of different histology types remains obscure. The factors involved are highly varied. They include immune-related, medication (NSAID), diet, hereditary (breed colonopathies) and even behavioral factors. In many cases, the pathogenesis proposed in humans is not transposable to domestic carnivores.

Clinical signs

Most colorectal diseases are clinically expressed by diarrhea or constipation. However, it is uncommon for these clinical expressions to provide information on the etiology of the colon.

The owner of a cat often has difficulty gaining insight in the defecation habits of the animal. Diarrhea is suspected when the cat defecates outside the litter box or in the event of soiled hair around the anus. Diarrhea of the large intestine is generally characterized as follows:
- preserved general condition (except advanced neoplasia)
- frequent emission of soft stools, of normal or increased volume, in a pile, the consistency of which changes in the course of the day (gradual softening)
- regular presence of mucus or blood
- observation of tenesmus, anal pruritus.

In cats, flatulence and vomiting complete the clinical signs.

Diagnosis

The anamnesis provides essential pointers, which sometimes provide information on the duration of the disease's development and whether the diarrhea is acute or chronic, permanent or intermittent. Recurring diarrhea is considered to be chronic.

Abdominal palpation must be done very carefully: thickening of part or the entire colon, hyperplasia of the associated lymph nodes, abnormal rigidity, and abnormal content in one or more segments. A *rectal swab* is difficult to perform on cats without sedation.

Complementary examinations

A parasitic fecal examination should always be performed ahead of any more complex examinations of the colon, even if the animal has been properly dewormed. Evaluation using a fecal float is desirable. Parasites and protozoans most frequently implicated in this location are hookworms *(Uncinaria stenocephala)* and some protozoans: mainly giardia, coccidia.

Fecal culture: few cases of colitis are caused by bacteria *(Campylobacter, Clostridia, Yersinia)*. The identification of *Escherichia coli* or *Candida albicans* colonies rarely has pathological significance.

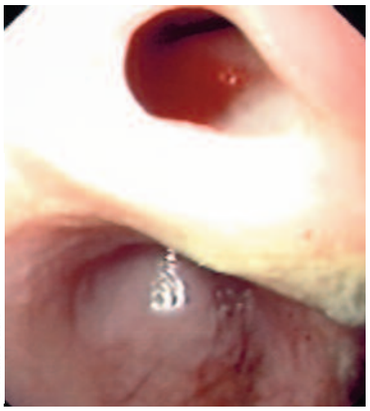
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Figure 48 - Normal ileal papilla identified during coloscopy in the cat.
Needle biopsies in the distal segment of the ileus are essential.

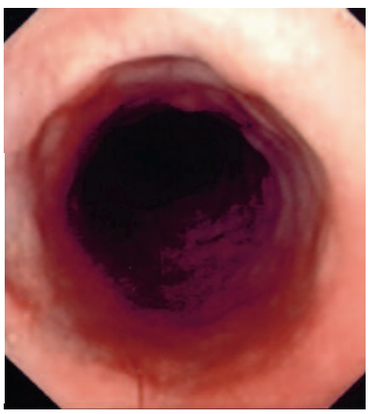
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Figure 49 - Colonoscopy performed on an 11-year-old male Persian.
The colonoscopy reveals an irregularity of the surface of the mucosa in the form of small micronodular bands. This is a case of chronic colitis.

Hematological and biochemical examinations are part of the differential diagnosis (e.g. metabolic diseases), but few changes are observed specifically in terms of inflammatory colonopathies (peripheral eosinophilia in case of parasitism or feline hypereosinophilic syndrome).

Radiography: without contrast agent will generally not reveal most parietal colonic diseases, except if the lesions are very large. If an endoluminal mass is suspected, barium contrast studies of the colon should be performed. However, this examination has largely been superseded by ultrasound and endoscopy.

Abdominal ultrasound: the presence of air in the colon adversely affects the quality of the examination. Ultrasound of the colon may be proposed if the animal cannot be anesthetized or the differential diagnosis has been established between an inflammatory lesion and a neoplastic lesion. The presence of abnormal echogenicity or architectural modifications to the colon wall will reveal whether a lesion is isolated or diffuse, or whether there is a parietal tumor.

Coloscopy: Endoscopy is the diagnostic technique of choice when exploring colonic diseases **(Figure 48)**. Endoscopic biopsies are essential. They provide information on the type of cell infiltrate, the treatment and a precise prognosis.

The following visual abnormalities of inflammatory origin maybe observed during colonoscopy:
- congestion and edema of the mucosa
- thickening of the colonic folds
- heterogeneous coloration of the surface of the mucosa: presence of areas of hyperemia, areas of mottled coloration
- dilatation of the parietal glands: grayish punctuations spread across a segment of the colon surface
- abnormal friability of the mucosa as the endoscope passes through
- changes to the surface of the mucosa: presence of more proliferative areas **(Figure 49)**.

Many biopsies samples are performed during the examination. There is variable correlation between the visual aspect of lesions and the results of histological analysis.

Classification of inflammatory colitis

Lymphoplasmocytic colitis (idiopathic chronic colitis)
This is the most common type. The visual signs include the above changes. In cats, they are among the more general clinical signs of IBD.

Eosinophilic colitis
This may be a component of eosinophilia. Eosinophilic cells often predominant in colitis, but they are always associated with a population of lymphocytes, plasmocytes and possibly neutrophilic leukocytes. Hypersensitivity reactions are implicated in the pathogenesis.

Suppurated colitis
This is a relatively rare type, especially in cats. The clinical signs are often acute, sometimes accompanied by superinfected mucoid feces (pus traces). Ulcerative lesions are often associated with it, as are crypt abscesses. The predominant cell population are neutrophils.

Granulomatous colitis
This is considered to be an atypical and rare form of IBD. The segmentary lesions are observed on part of the small intestine and various parts of the large intestine. These lesions have a proliferative aspect and may sometimes lead to massive thickening of the colon wall, producing stenosis. Clinically, diarrhea is profuse, generally hemorrhagic and contains a lot of mucus. An alteration of the general condition is observed.

Medical treatment of inflammatory colitis

Where possible, the treatment should be etiological if the cause can be identified (parasitic, bacterial, viral colitis) *(Zoran, 1999)*.

Use of antibiotics

The prescription of antibiotics must be limited to highly precise indications and respond to reasonable use. The clinical and hematological criteria may impose the use of certain wide-spectrum substances of low toxicity.

A regulator effect of metronidazole on the digestive flora in domesticated carnivores has been shown during colonopathies. Metronidazole also has an immunomodulator activity.

Benefit of anti-inflammatory substances

Sulfasalazine is an anti-inflammatory agent with an active substance that is cleaved and released in the colon (5-amino salicylic acid). It regulates local prostaglandin production and reduces the influx of leukocytes.

In cats, the recommended dose is either 10 mg/kg BID or 15 mg/kg SID. Several therapeutic plans are available of varying length. Sulfapyridine, which is released into the colon when the substance is cleaved, is responsible for known side effects: hematological disruptions, skin rashes, hepatic lesions, Sjögren's syndrome. Cats maybe more sensitive to the side-effects of sulfasalazine compared to dogs.

Corticosteroids and immunosuppressors

Corticosteroids are an indispensable part of the treatment of a number of chronic inflammatory colonopathies. A medium-size dose has an anti-inflammatory action (inhibition of prostaglandins and antileukotriene effect), while higher doses have an immunosuppressive effect.

Oral administration is preferred to the parenteral route. Cats tolerate corticosteroids better than dogs. They can be administered in a higher dose in the induction phase. The dose should be adapted on the basis of the clinical response.

In the most serious cases or when corticosteroid therapy is contraindicated, additional immunosuppressive treatment may be proposed. Several weeks will be needed to judge effectiveness; and there are many side effects (particularly medullary toxicity) and constraining clinical and hematological checks will be necessary.

Topical agents and dressings

These are adjuvant substances that provide local protection. Some animals are less likely to be effected a second time if a clay bandage (smectite or zeolithe) is used in the medium term. Zeolite, or sodium silicoaluminate, a tetrahedral clay, is capable of adsorbing bacterial toxins, bile acids, and gases. By forming a protective film over the intestinal mucosa, zeolite helps enhance the intestinal mucosal barrier. Compliance is a limiting factor.

Dietary treatment

Although colitis is most frequently diagnosed in dogs, it is becoming increasingly common in cats *(Simpson, 1998)*. Colitis can be beneficially influenced by adequate dietary treatment in cats, although this depends on whether it has mainly an infectious, inflammatory or immune-mediated pathogenesis *(Zentek, 2004)*.

Importance of high-quality protein

Unlike fats and well-cooked starches, which are almost totally digested in the small intestine, the digestibility of proteins varies according to source and treatment. The ingestion of low-quality

proteins – which therefore are also characterized by poor ileal digestibility – leads to an inflow of indigestible protein matter in the colon. Greater putrefaction of proteins leads to an increase in bacterial biomass and a high secretion of water in the colon – simultaneous phenomena that result in poor stool consistency. High protein putrefaction can disrupt the colonic microflora and orient its profile towards potentially pathogenic strains *(Zentek et al, 1998)*. The many aromatic compounds produced (mercaptan, indole, skatole etc) can have a toxic effect on the colonic mucosa in combination with the biogenic amines formed (cadaverin, putrescine, etc) and encourage cancers of the colon and rectum *(MacFarlane & Cummings, 1991)*. The high production of ammonia may ultimately affect DNA synthesis, damage the morphology of the colonocytes and shorten their lifespan *(Visek, 1978)*.

A good selection of proteins and a controlled manufacturing process makes it possible to considerably improve their digestibility, which is essential to good digestive tolerance in cats. Many cats that suffer from chronic diarrhea as a consequence of colonic inflammation will respond to a novel protein elimination diet or a hydrolysed protein-based diet *(Nelson et al, 1984; Guilford & Matz, 2003)*.

Dietary fiber

A hypoallergenic diet can be combined with a fermentable fiber source, such as pectin or guar gum. The addition of fermentable dietary fiber regulates the composition of the colonic microbiota and may reduce the potentially harmful flora.

Soluble fiber is highly fermentable and as such it plays a very important role in the ecosystem of the large intestine. It first acts as a substrate for the bacterial biomass, which provides it with the necessary energy for good growth. The resulting fermentative activity also generates a large quantity of SCFA and lactic acid. Such fermentation products (mainly SCFA) have an extremely important trophic role in maintaining the colonic mucosa in good health. Colon cell atrophy is observed in the complete absence of soluble fiber in food *(Wong & Gibson, 2003)*.

Insoluble fiber (cellulose, hemicelluloses, lignin) is not generally decomposed to any great degree by microflora in the colon, which means they remain virtually intact in the stools. Their high hygroscopic capacity (they can absorb up to 25 times their weight) together with their ability to increase the indigestible residuum of feces help improve fecal consistency but also increase the volume of stools *(Sunvold et al, 1995a)*.

On the other hand, bearing in mind their high fermentability, an excessive quantity of soluble fiber in food is detrimental to good digestive tolerance. The resulting high moisture content, poor consistency and high volume of stools would appear to be explained mainly by a high proliferation of the bacterial biomass *(Sunvold et al, 1995a)* **(Table 8)**.

TABLE 8 - MOISTURE, CONSISTENCY AND VOLUME OF STOOLS IN CATS (N=5) FED WITH A FOOD ENRICHED (~10%) IN DIFFERENT SOURCES OF DIETARY FIBER
From Sunvold et al (1995a)

Diet	Soluble fiber	Insoluble fiber	Digestive tolerance		
			Moisture (%)	Consistency *	g stools/g fiber ingested
Mixture of soluble fiber	+++		74.9[a]	4.2[a]	13.1[a]
Beet pulp	+++	+	74.7[a]	2.3[b]	7.4[b]
Cellulose		+++	52.6[b]	1.8[b]	3.6[c]

** In this study, fecal consistency was assessed on a scale from 1 (hard dry stools) to 5 (diarrheic stools), where 2 is considered optimal. Values with different letters for the same parameter (column) are statistically different ($p<0.05$). A food that is rich in soluble fiber leads to a large quantity of stools, with high moisture content and low consistency. It should also be noted that stools of animals that have eaten a mixture of soluble fiber or beet pulp have a similar water content but very different consistencies. The moisture content of a stool is therefore not always representative of its appearance.*

From practical experience, the addition of moderate amounts of insoluble and soluble dietary fiber is common.

Energy consumption
Cats with enterocolitis often have severe weight loss and anorexia leading to a cachexic body condition *(Hart et al, 1994)*. Therefore, the careful adjustment of energy and nutrient intake is a mandatory part of successful dietary management for these patients. The palatability of a food is another very important criterion, as the nutritional treatment is recommended for several months and boredom should be avoided.

► Small and large intestinal neoplasia

Small intestinal tumors account for 73% of all intestinal tumors in cats (52% adenocarcinomas, 21% lymphomas). Conversely, colonic tumors are uncommon (10-15% of intestinal tumors in cats) *(Estrada et al, 1998)*. The slow appearance of non-specific clinical signs rules out early detection.

Feline intestinal tumors have a better prognosis than esophageal or gastric tumors.

> Small intestinal tumors

Different histological types encountered

The two predominant types of tumor are **adenocarcinomas** *(Kosovsky et al, 1998)* and **lymphomas**. While most cats that present with intestinal lymphoma are FeLV negative, the former presence of the virus is implicated in the neoplastic transformation *(Barr et al, 1995)*.

Other tumors are less common: **leiomyomas, leiomyosarcomas, fibrosarcomas**. Benign tumors of the duodenum, of the **adenomatous** polyp type have been described in cats *(Estrada et al, 1998; Freiche et al, 2005b)*, especially oriental males without known viral impairment by FIV or FeLV.

Mastocytomas exclusively found in the digestive tract are reported in dogs. Some cases have been described in cats, in the colon of aging animals *(Slawienski et al, 1997)*.

Carcinoid tumors (neuroendocrine) are very uncommon. Their clinical expression is generally dominated by the paraneoplastic syndrome *(Guilford & Strombeck, 1996d)*.

Relatively undifferentiated **mesenchymatous tumors** in the intestines are described in cats. Biopsies of mesenchymatous lesions may require specific stains and immunolabeling.

Epidemiology

Breed and sex predispositions have been recognized. In cats, the Siamese is commonly implicated, particularly with carcinoma. Generally speaking, the incidence of intestinal lymphomas appears to be higher in males than females. Whatever the nature of the tumor, affected cats are generally at least 10 or 11 years old, although intestinal lymphomas may be identified in much younger cats. Adenomas are less common in the small intestine and are probably under diagnosed.

Clinical signs

The alteration of the wall of the small intestine may lead to digestive transit or nutrient absorption disorders that have clinical consequences and are responsible for signs of the disease. These signs are not very specific: diarrhea, vomiting, melena. Again, they are shared with other gastrointestinal diseases, which means the etiological diagnosis is sometimes made too late.

The clinical expression of small intestinal neoplasia is linked to the location of the lesion in the intestinal wall:
- the more proximal, the more frequent vomiting will be. Melena is a relatively reliable sign, but inconsistent;
- more distal tumors are expressed by diarrheal episodes that worsen over time. The diarrhea is then characteristic of chronic small intestinal diarrhea. The overall condition of the cat is generally altered, with the presence of weight loss, dysorexia and lethargy.

In some much less common cases, the animal presents with occlusion. General loss of body condition is more visible in later stages of development. Weight loss is a sign. Feline intestinal tumors are sometimes very distal (small-large intestine junction) and are expressed in several forms (isolated, multicentric, diffuse). However, in a large proportion of cases, abdominal palpation does not identify a mass, although diffuse or segmentary thickening of the intestinal loops is often suspected.

Diagnosis

The diagnosis is obtained by traditional techniques.

- **Hematobiochemical analyses** provide few pointers. The differential diagnosis must exclude the metabolic causes of chronic diarrhea. Anemia is an important sign to remember (possible in the event of a lymphoma), but many intestinal neoplasias do not produce blood loss on the CBC. However, intestinal mastocytomas do cause mucosal ulcerations that may result in chronic blood loss.

- **Radiography** may be proposed if no other means of investigation is possible **(Figure 50)**. The association of abdominal ultrasound and endoscopy is greatly preferable to a barium study, which is both difficult to perform and to interpret.

- **Abdominal ultrasound** is certainly the investigation of choice when good equipment is available. Precise signs are described for intestinal neoplasia, based on the same types of changes cited for a gastric lesion. These include modification to the parietal layers with localized or diffuse identification faults, variations in echogenicity (hypoechogenicity), abnormal satellite lymph nodes and localized peristaltic problems *(Penninck, 1998; Hittmair et al, 2001)*.

- **Endoscopy and histological analysis of biopsies** are proposed when the lesion is accessible (proximal and distal small intestine). They are recommended when an abdominal ultrasound has excluded the presence of an isolated lesion of the small intestine. The histological analysis of endoscopic biopsies obtained from several locations can lead to the diagnosis. This examination has two limitations:
  - isolated lesions of the middle of the small intestine are topographically inaccessible
  - isolated tumor cells under the mucosa or the muscles maybe missed.

- **Laparoscopy** permits a beneficial approach, but it demands more sophisticated equipment.

- Trans-parietal biopsies can be performed during an **exploratory laparotomy** if the above examinations are not possible.

In cats, it may be difficult to differentiate intestinal lymphoma in its diffuse form with severe IBD. The visual aspect of the lesions are similar. When there is no logical correlation between the histological analysis of biopsies and the clinical condition of the animal, the diagnosis must be questioned, because diffuse inflammatory lesions of the digestive tract (often lymphoplasmocytic in nature) are almost always associated with feline gastrointestinal lymphoma.

Disease staging

Different types of examination are available to stage the disease: radiology (thoracic imaging), abdominal ultrasound and tomodensitometric examination. These complementary examinations should be used selectively, depending on the case. Metastasis is initially most often regional. Abdominal ultrasound can identify a satellite and/or regional lymphadenopathy, as well as parenchymatous metastasis, while also facilitating fine needle aspiration for an immediate diagnostic approach. The thoracic radiographs can be used to exclude the presence of pulmonary metastasis. The pulmonary tomodensitometric examination is more precise.

Treatment and prognosis

Therapy depends on several factors:
- the animal's general condition and whether medical resuscitation is necessary
- the histopathological nature of the tumor: benign or malignant, risk of metastasis or local recurrence, hematopoietic status

- local and remote disease staging.
When indicated, diffuse hematopoietic intestinal tumors (lymphoma, mastocytoma), will be treated medically *(Lanore, 2002)*. The medical treatment protocols are similar to those for lymphoma and systemic mastocytoma. They vary according to histological type.

Generally speaking, in the event of surgical treatment certain rules need to be observed (*Salwienski et al, 1997)*:
- eliminate all tumor cells and include ganglionic excision when possible
- avoid dissemination of neoplastic cells, locally or remotely.
The enterectomy techniques used on healthy tissue are employed, by means of laparotomy for the different segments of the small intestine.

> Colon neoplasia

Different histological types encountered

Tumors of the colon are uncommon in cats. The carcinoma is the most common histological type. It affects aging animals and males more than females. Rectal tumors are more common than colonic tumors.

The isolated colonic form of lymphoma in cats is not common, although it dominates the incidence of carcinomas in this location. In this species, the ileocolic location must always be examined (lymphoma, carcinoma, mastocytoma).

Benign isolated polyps are less common in domesticated carnivores than in humans. They do not appear to particularly precede the appearance of carcinomas, at least not through the same mechanism as in humans.

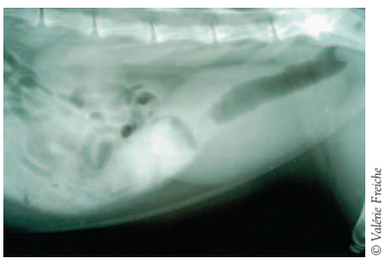
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Figure 50 - Colonic carcinoma revealed by radiography.
The contrast environment generated by distension of the bladder with fluid helps visualize colonic stenosis. The histological diagnosis was achieved by endoscopically obtained biopsy samples. A peripheral lymphadenopathy had been identified during the ultrasound examination.

Clinical signs

All but two of the clinical signs are non-specific. The presence of blood in feces of normal consistency and the presence of abnormally small stools are specific signs. Other clinical signs are identical to those traditionally observed during diarrhea of the large intestine (tenesmus, hematochezia, mucus etc) (*Jergens & Willard, 2000)*.

A rectal swab under anesthesia is necessary, as a large proportion of colon lesions caused by a tumor are located in the last few centimeters of the mucosa. There are few benefits to abdominal palpation (the lesions are not always highly exophytic or indurated).

These neoplastic processes may develop slowly and the diagnosis is made in the later stages as described with gastric carcinoma. The alteration of the general state is slow and inconsistent. The deep infiltrative and/or stenosing forms are more pronounced. Tenesmus and pain are generally very important, except carcinomas located at the colorectal junction, where infiltration is low. The presence of ascites is uncommon at the time of diagnosis.

Diagnostic evaluation

Coloscopy is the diagnostic technique of choice **(Figures 51 & 52)**. It does not demand any specific preparation in cats, as the feline colon is short. The administration of a diet without residue exclusively based on white meat or fish without added fiber or fat for the four days prior to the examination, followed by enemas under anesthesia, is sufficient and not very restricting.

Coloscopy is a tool to address part of the disease staging process and to identify whether there is one or more lesions. Colon neoplasia can present several forms: pedunculated, diffuse, in "graps" or scattered along the colonic wall: it is then difficult to macroscopically predict the histological nature of a colorectal mass. Multiple endoscopic biopsy samples must be obtained.

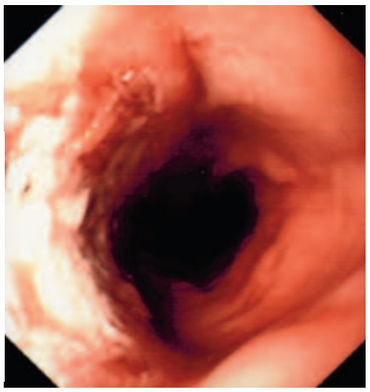

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Figure 51 - Coloscopy in an 8-year-old domestic shorthair cat who presented for defecation disorders and hematochezia.
The examination shows a parietal endoluminal mass which is consistent with a non-pedunculated tumor. The histological nature of the tumor cannot be determined during the examination.

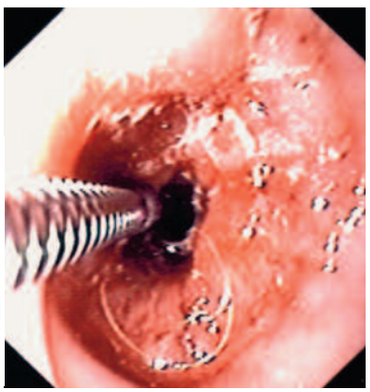

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Figure 52 - 16 year old female cat who presented with constipation and marked depression.
Coloscopy shows endoluminal stenosis, which is responsible for distal occlusion. The distal colic stenosis had a post-inflammatory origin.

Disease staging

Abdominal ultrasound is complementary to coloscopy. It allows evaluation of the regional extension of the tumor process, and must be conducted as soon as possible. Liver and lung metastases are seldom observed during the diagnosis.

Treatment and prognosis

Surgery is the treatment of choice for localized malignant tumors. Palliative surgery may extend the animal's life. In the event of carcinoma, the location of the lesion justifies different surgical approaches, the follow-up of which may be difficult to manage.

Radiation therapy is an excellent complementary treatment to the surgical excision of localized distal recto-colic carcinomas.

The administration of corticosteroids alone, without a chemotherapeutic protocol improves or maintains appetite while reducing the cat's inflammation and pain. Local topical drugs such as anti-inflammatory steroids recommended for humans are not particularly beneficial in cats.

Dietary treatment

Dietary treatment is limited to adjusting the diet composition according to the patient's needs. A higher energy density may be efficiently provided by a higher fat diet. Long chain n-3 fatty acids from fish oil have been shown to be beneficial in different models of neoplastic disorders. Therefore, diets with a higher protein concentration, specifically a balanced spectrum of amino acids (arginine) and higher levels of micronutrients (zinc, antioxidant vitamins) may be favorable in these patients. For further information, refer to chapter 11.

Conclusion

Dietary treatment with adequate medication is the key to successful treatment of gastrointestinal disorders in cats. Depending on the suspected disease, the choice is between highly digestible diets in the case of small intestinal and pancreatic diseases, antigen-reduced diets in the case of dietary sensitivity or allergy, and high-fiber diets when the colon is specifically affected or motility disorders occur. In practice, dietary treatment has to be adjusted individually. The response of the patient is not always predictable and good compliance is needed for optimal success.

Frequently asked questions about the role of nutrition in digestive diseases

Q	A
What type of protein is suitable for a cat with dietary sensitivity?	One solution is to feed the cat with sources of protein to which it has not previously been exposed to e.g. capelin, duck, venison, rabbit etc. The term is an elimination diet, as the purpose is to eliminate protein sources that may trigger undesirable reactions. Another alternative is a hydrolysed protein-based diet. Hydrolysed protein is less immunogenic and produces good results in the event of dietary allergy. Cereals are starch sources that also contain protein. The preferred starch sources are rice, tapioca, potatos, and peas.
What type of diet should I choose for a cat with colitis?	Diets formulated with noval proteins and hydrolysed protein-based diets produce very good results in cats with colitis.
How can I overcome palatability problems in cats?	A cat may develop an aversion to the food it is consuming when digestive problems or vomiting manifest themselves. As a consequence, after the cause of these problems has been treated, it may be necessary to change the food or choose another variety in the same range of products. Dietary aversion is connected to the taste and odor of a particular food.
A laboratory reported high numbers of clostridia in a fecal sample of a patient with chronic diarrhea. What can be done and how should the diet be adjusted?	It is not abnormal to observe a high number of *Clostridia* in the feces of a carnivore. Nutritional action should be considered only in the event of chronic digestive problems. A highly digestible diet should be chosen that is not too rich in animal protein so as not to encourage colic fermentation. This diet must also contain fermentable fiber (beet pulp, fructo-oligosaccharides etc).
Can I use digestive enzymes in the treatment of cats with diarrhea?	Digestive enzymes are indicated only if the cat suffers from exocrine pancreatic insufficiency. This pathology is rare in cats but it does exist. It can be revealed by measuring feline trypsin-like immunoreactivity (fTLI), which is different from canine TLI, so the dog test does not work with cats. The enzymes must be mixed into the food. The powder form is preferable (see the chapter on hepatobilary and pancreatic diseases).
How long do I have to perform an elimination trial in a cat with a suspected dietary allergy?	The test must last at least 12 weeks, but improvement is typically observed in most cats after 4 weeks.
Should I prescribe nutritional supplements for cats with chronic diarrhea?	No, it is better to recommend a high-quality, highly digestible food that contains protein sources the animal has not previously encountered or a hydrolysed protein source. The parenteral administration of vitamin B_{12} is indicated in deficient animals.

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Focus on:

Psyllium fiber

Botanical origins

Psyllium is a small annual plant, with low leaves and white flowers, of the plantain genus, which grow in the sandy soils of the Mediterranean basin. One particular variety *(Plantago ovata)*, which comes from India and Pakistan, is traditionally used in phytotherapy to treat digestive problems. Psyllium is also known as Ispabgol. The whole plant is used in food, as well as nutrition and therapy. The young leaves may be consumed in salads or with vegetables.

Seeds are rich in fiber

The word psyllium is derived from the Greek *psyllia*, meaning flea, which is what the seeds resemble. They are composed of around 57% total fiber, 25% cellulose and 12% soluble fiber, mucilage, which is made of arabinoxylan, an extremely ramified acid.

The mucilage in psyllium seeds is especially beneficial. Once it has been isolated, the seed coat (tegument) contains a high mucilage concentration of 25-30%.

The particular composition of the tegument means that psyllium seeds can absorb up to ten times their weight in water. When purified psyllium seeds are used, the swelling index is between 70 and 85.

Mucilage regulates digestive transit

Psyllium is renowned for its laxative properties. Mucilage behaves like a sponge, absorbing water to swell up and create a viscous gel. Psyllium has an anti-diarrheic effect, by augmenting the viscosity of the intestinal chyme. In human gastroenterology, psyllium is particularly indicated to:
- relieve gastrointestinal inflammations
- treat irritable bowel syndrome
- help treat constipation.

Digestive transit is sometimes slow in sedentary cats due to the lack of physical activity. They often suffer from constipation and digestive problems caused by hairballs. Psyllium has very positive effects on their digestive transit, regulating the advancement of the content of the small intestine and the colon, and the lubrication induced by the psyllium gel facilitates the elimination of feces. Psyllium fiber is only very partially fermented by the bowel flora in the colon and therefore does not alter the consistency of the feces.

Psyllium seeds are traditionally used as appetite suppressors in weight loss diets. Mucilage absorbs water to form a voluminous gel in the stomach.

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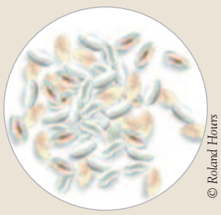

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The fruit of the psyllium is a pod containing two minuscule, flat, oval seeds, that have no odor and scarcely any taste. A thousand seeds weigh less than 2 g.

Digestive problems associated with the formation of hairballs in the cat's digestive tract

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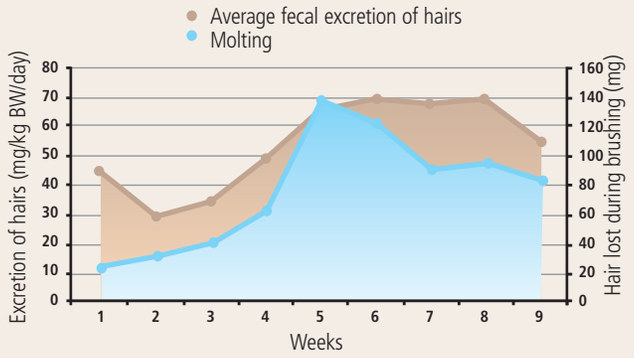
A cat that lives indoors spends around 30% of its time grooming (Benjamin, 1976). *It is particularly sensitive to the formation of hairballs.*

FIGURE 1 - CORRELATION BETWEEN MOLTING AND FECAL EXCRETION OF HAIRS (RESULTS OBTAINED FROM 24 CATS)

(Tournier et al, 2005)



In cats, licking fulfils many different functions:
- it cleans the coat
- it regulates temperature
- it strengthens a bond between animals in the event of mutual grooming
- it helps reduce stress.

The cat's tongue is carpeted with conical dermal papillae that act like a brush to remove dead hairs and foreign bodies in the coat. When licking itself, the cat ingests hairs that it subsequently eliminates through the bowels. A Royal Canin study shows that fecal excretion varies between 30 mg and 70 mg of hair/kg of body weight/day **(Figure 1)**. In a period of molting, the quantity of hairs excreted in the feces may be up to 100 mg/kg of body weight/day, which is a daily volume of around 10 cm^3 for a 4-kg cat *(Tournier et al, 2005)*.

The hairs coalesce in the digestive tract to form a ball (trichobezoar), which is very often regurgitated. In some cases however, they may cause digestive problems *(Barrs et al, 1999)* – vomiting, constipation or intestinal occlusion in the most serious cases. More than half of the veterinarians have had to deal with an intestinal obstruction caused by a hairball and 43% have had to resort to surgery to treat it *(Royal Canin survey, 2004)*.

The formation of hairballs depends on individual factors (connected to the presence of 'retention' pockets in the digestive tract), but mostly on environmental factors. Cats that live indoors are more sensitive than others. When the temperature and lighting are fairly steady, they will molt throughout the year. If they have no access to grass and no opportunity to hunt, they will not ingest the ballast that naturally stimulates intestinal transit.

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The hairs swallowed by the cat are regurgitated in the form of balls or eliminated through the feces. In the course of one year, a cat may excrete 60-120g of hairs, representing a volume of 1.5-3 liters.

Key points
to remember:

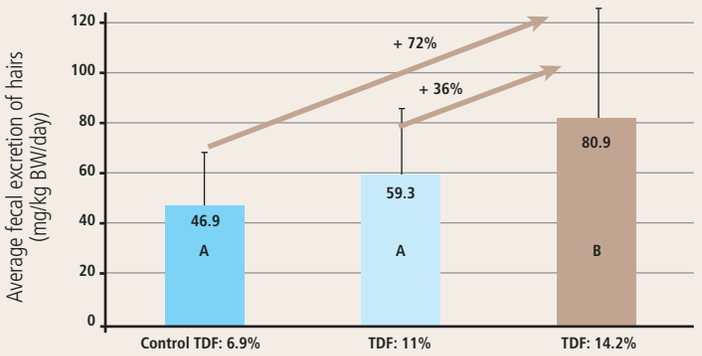
Nutritional factors favoring the natural elimination of hairballs

The natural elimination of hairs may be facilitated by stimulating gastric emptying and intestinal transit. The aim is to prevent the hairs from collecting in the stomach or intestine and forming a ball. This is achieved by increasing the fiber content of the food. This type of diet is especially indicated for cats that live indoors, whose intestinal motility is slowed by the lack of physical activity. Food that activates transit and increases fecal excretion of hairs contains at least 10-15% total dietary fiber **(Figure 2)**.

Fiber constitutes a very heterogeneous material and several types need to be associated to obtain a synergic effect. While the cellulose and other non-fermentable fibers stimulate intestinal transit, some vegetable sources provide fiber with a much more targeted action:

- the fiber in the psyllium tegument favors fecal excretion in constipated cats
- fructo-oligosaccharides provide an energy substrate beneficial to the balance of the digestive flora.

FIGURE 2 - INFLUENCE OF FIBERS ON FECAL EXCRETION OF HAIRS IN A 4-WEEK PERIOD IN 24 CATS
(Tournier et al, 2005)



A specific enrichment with vegetable fiber increases the quantity of hair eliminated through the feces by 72% compared with a control food with a low fiber content. Fecal excretion is measured every week using the method of Hendriks et al. *(1998). The results are mean ± SD. ANOVA measurements are used to interpret the results. The letters A and B signify that the results are statistically different (P<0.05).*

Beet pulp has a mixed chemical composition that enables the combination of the benefits of fermentable (on flora) and non-fermentable fiber (on transit).

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Liver/Pancreas

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ABBREVIATIONS USED IN THIS CHAPTER

AAA: aromatic amino acids
ALP: alkaline phosphatase
ALT: alanine amino transferase
BCAA: branched chain amino acid
CT: computed tomography
DIC: disseminated intravascular coagulation
EPI: exocrine pancreatic insufficiency
FHL: feline hepatic lipidosis
FIP: feline infectious peritonitis
fPLI: feline pancreatic lipase immunoreactivity
fTLI: feline trypsin-like immunoreactivity
γGT: gamma-glutamyl transpeptidase
HE: hepatic encephalopathy
PAA: pancreatic acinar atrophy
PSS: portosystemic shunts
SAMe: S-adenosyl-methionine

Nutritional management of hepatobiliary and pancreatic diseases

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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 the 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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The liver plays a central role in a wide range of metabolic processes and this is reflected in the multitude of pathophysiological derangements that can occur in liver disease. The liver has however a great reserve capacity to perform these functions, and clinical signs occur only when this reserve capacity is exhausted by extensive and progressive disease.

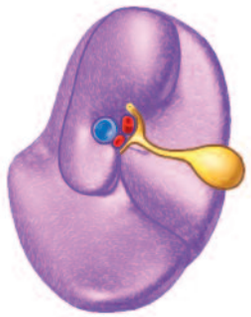
The exocrine pancreas is also essential for the optimal digestion and absorption of nutrients. Conversely to hepatic diseases, disorders of the exocrine pancreas were once believed to be rare in cats, but pancreatitis and exocrine pancreatic insufficiency cases are now recognized with increasing frequency which is likely due to improvements in diagnostic accuracy for this disease. Nutritional support is the keystone in management of cats with liver and pancreatic diseases.

TABLE 1 - MAJOR HEPATOBILIARY FUNCTIONS

Digestive functions
Bile acid synthesis and enterohepatic circulation
- digestion and absorption of lipids
- absorption of vitamins (A, D, E, K)

Detoxification and excretion
Ammonia detoxification (urea cycle)
Drugs and toxins

Storage functions
Glycogen and lipids
Vitamins
Trace elements (copper, iron, zinc, manganese)



Protein metabolism
• Synthesis of albumin, acute phase proteins, coagulation factors
• Amino acid metabolism (plasma free amino acid homeostasis)

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

1 - Hepatobiliary disease

Introduction

The liver is essential for the digestion, absorption, metabolism and storage of most nutrients **(Table 1)**. Liver disease often results in malnutrition, which aggravates the disease process and affects outcome *(Center, 1996; LaFlamme, 1999)*; it is therefore imperative to maintain nutritional status. Early nutritional intervention can reduce morbidity and mortality. Nutritional support is especially important in anorexic cats, since cats are uniquely predisposed to the development of idiopathic hepatic lipidosis when anorexic.

CLINICAL SIGNS

Clinical signs of liver disease in the cat are generally vague and non-specific, and more specific signs such as icterus occur only when the disease is advanced.

In acute liver disease, treatment is mainly aimed at supporting the patient during the process of hepatic regeneration, and cats may fully recover provided there has been only a single sublethal insult to the liver. In chronic liver disease, which is the most common form of liver disease in cats, the emphasis is on supporting the limited remaining metabolic capabilities of the liver and to minimize complications.

TABLE 2 - CLINICAL FINDINGS IN FELINE LIVER DISEASE

Early signs	Common: anorexia; vomiting; depression; weight loss
	Less common: fever (suppurative cholangitis/ cholangiohepatitis); ascites (lymphocytic cholangitis)
Severe hepatic insufficiency	Icterus; Hepatic encephalopathy; Coagulopathy
Major bile duct obstruction	* Acholic (pale) feces

** Specific for hepatobiliary disease, but rarely observed.*

► Diagnosis

> Clinical signs

Cats with liver disease usually do not show any clinical signs until the disease is advanced, and symptoms are vague and variable. Partial or complete anorexia and vomiting are the most common and sometimes the only clinical signs. Other clinical signs include weight loss, depression, vomiting, and occasionally diarrhea **(Table 2)**. Jaundice and abnormal liver size are the physical findings most suggestive of liver disease, but these may also be seen in other diseases not related to the liver. Cats with liver disease tend to have hepatomegaly, but small liver size can be seen in cats with portosystemic shunts or cirrhosis. The only sign specific for liver disease is acholic (grey) feces, found in complete extrahepatic bile duct obstruction, but this is rarely found.

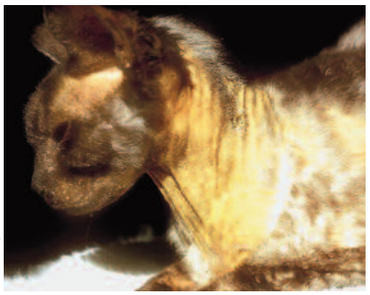


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Figure 1 - Jaundice in a Rex cat.

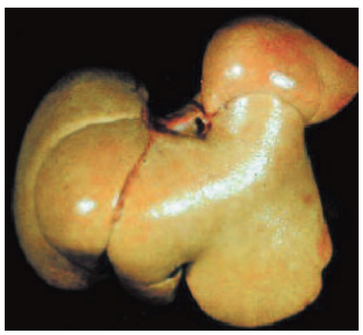

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Figure 2 - Hepatomegaly in a cat.
Enlarged, yellow and friable liver from a cat that died from hepatic lipidosis.

> Differential diagnosis

Jaundice - Jaundice is generally a late sign of liver disease, but tends to occur earlier in the course of feline liver disease than in dogs. It generally signifies severe cholestatic disease, either due to hepatocellular disease or posthepatic causes (extrahepatic bile duct obstruction, biliary rupture) **(Figure 1)**. Hemolytic anemia, which can also cause jaundice, is rare in cats.

Altered liver size - Hepatomegaly **(Figure 2)** is a common finding in cats with both acute and chronic liver diseases, and results from hepatic infiltration with inflammatory cells, fat, neoplastic cells or amyloid. Reduced liver size can however be seen in cats with congenital portosystemic shunts, and in rare end-stage lymphocytic cholangiohepatitis with cirrhosis *(Webster, 2005)*.

Ascites - Cats with liver disease generally do not develop portal hypertension as dogs do, and ascites is therefore an infrequent finding. It may however occur when progressive lymphocytic cholangitis has resulted in cirrhosis, and it then tends to be a modified transudate. The effusion has to be distinguished from that due to protein-losing diseases (transudate), congestive heart failure and neoplasia (modified transudate), and peritonitis, hemorrhage, and ruptured gall bladder (exudates).

> Laboratory testing

Since many of the clinical signs associated with liver disease are non-specific, laboratory assessment is essential to identify and monitor hepatic disease. However, laboratory tests will not recognize specific diseases and may furthermore be influenced by non-hepatic disease (e.g. hyperthyroidism). Baseline tests (hematology, serum biochemistries and urinalysis) are useful in initial screening to look for evidence of hepatic disease as well as other abnormalities.

- *Hematological testing* may reveal anemia or alterations in erythrocyte size and shape, such as microcytosis (e.g. portosystemic shunts), acanthocytes and poikilocytosis. Anemia is usually nonregenerative and most likely associated with chronic disease; a regenerative anemia is uncommon and may reflect infection with blood parasites *(Haemobartonella, Babesia)*, and rarely auto-immune hemolysis. Leukogram changes are inconsistent and depend upon the underlying cause of the disease *(Webster, 2005)*.

- *Serum biochemistries* are usually characterized by increased liver enzyme activities; hyperbilirubinemia is variable. In cats, the half-life of both serum alkaline phosphatase (ALP) and alanine aminotransferase (ALT) is much shorter than in dogs, and liver enzyme induction (e.g. corticosteroids) is uncommon. However, high liver enzymes are frequently seen in hyperthyroid cats. Gamma-glutamyl transpeptidase (γ GT) is a similar enzyme to ALP that increases with cholestasis and is more sensitive for feline inflammatory biliary tract disease than ALP. This may be in part because γ GT arises from predominately bile duct epithelium. Cats affected with idiopathic hepatic lipidosis usually have marked increases in ALP while γ GT concentrations show only mild increases, in contrast to cats with biliary tract disease where there are usually proportionally higher γ GT concentrations than ALP concentrations *(Center, 1996)*.

- *Urinalysis* may show bilirubinuria, which is always abnormal in cats since they have a high renal threshold for bilirubin. Cats with portosystemic shunts may have low urine specific gravity and ammonium biurate crystalluria.

Measurement of fasting and 2-hour post-prandial total serum bile acid concentrations is a sensitive and specific indicator of hepatic function, useful for the diagnosis of subclinical liver diseases and portosystemic shunts. Determination of urine sulfated and nonsulfated bile acids has also been suggested as an alternative diagnostic test for liver disease in cats *(Trainor et al, 2003)*, but this needs further evaluation.

The presence of fasting hyperammonemia can document hepatic encephalopathy (HE), particularly in cats with portosystemic shunts, although not all animals with HE will have abnormal fasting blood ammonia levels. Difficulties in sample handling limit the diagnostic usefulness of this test. Coagulation tests are furthermore indicated in animals with a bleeding tendency and prior to liver aspiration or biopsy *(Lisciandro et al, 1998; Center et al, 2000)*.

> Diagnostic imaging

Survey abdominal radiography can be used to assess liver size and shape, and occasionally radiopaque choleliths **(Figure 3)**, but ultrasonography gives more specific information about alterations in the liver parenchyma, biliary system, and portal vasculature *(Leveille et al, 1996; Newell et al, 1998)* **(Figure 4)**. Ultrasonography performed by an experienced operator has a high accuracy in detecting intrahepatic portosystemic shunts *(Holt et al, 1995)*. Color flow and pulse wave Doppler ultrasonography gives the additional advantage of visualization of blood flow direction and measurement of portal blood flow velocity *(d'Anjou et al, 2004)*. Ultrasonography can furthermore be used for cholecystocentesis and culture in cats with suspected suppurative cholangiohepatitis, and for precision ultrasound-guided hepatic biopsy. Mesenteric portography can be used before or during surgery to confirm the diagnosis and establish the morphology of the shunting vessel. Suspected portovascular anomalies can also be evaluated by contrast nuclear scintigraphy; this is however limited to research institutions due to the need for radioactivity.

> Biopsy and surgery

The ultimate diagnosis of feline liver disease other than that caused by a congenital portosystemic shunt is usually made by histological examination of a liver biopsy **(Figure 5)**, which is essential to clarify the cause of abnormal liver tests and/or size and to develop an appropriate treatment plan **(Figure 6)**. Samples can be obtained by fine needle aspiration, percutaneous ultrasound-guided biopsy or surgically. Fine needle aspiration can give useful information in cats with diffuse diseases such as hepatic lymphoma or idiopathic hepatic lipidosis, and may indicate the presence of inflammatory liver disease, but in most cases a biopsy is preferred for assessment of cellular changes and structure of the hepatic parenchyma *(Wang et al, 2004)*. Coagulation status must be assessed prior to the procedure, since hemorrhage is the most common complication. Cats with cholestatic disease rapidly develop fat-soluble vitamin deficiencies, and coagulopathies responsive to vitamin K_1 administration can be seen in feline hepatic lipidosis or severe cholangiohepatitis *(Center et al, 2000)*.

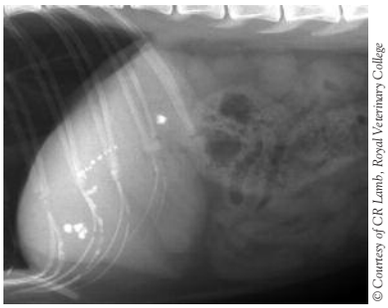
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Figure 3 - Lateral abdominal radiograph of a cat with cholelithiasis. *Cholelithiasis is visible as multiple radiopaque densities.*

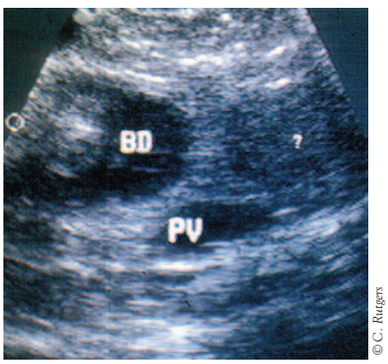

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Figure 4 - Ultrasound of a cat with cholestatic jaundice. *The ultrasound shows a dilated common bile duct (BD), portal vein (PV), and a hypoechoic hepatic mass.*

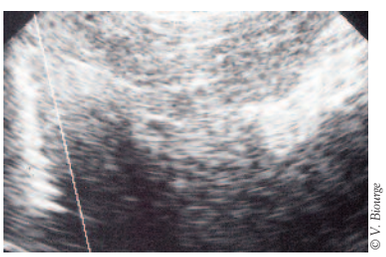
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Figure 5 - Liver biopsy. *Biopsy is essential to clarify the cause of abnormal liver tests and/or size.*

FIGURE 6 - DIAGNOSIS OF LIVER DISEASE

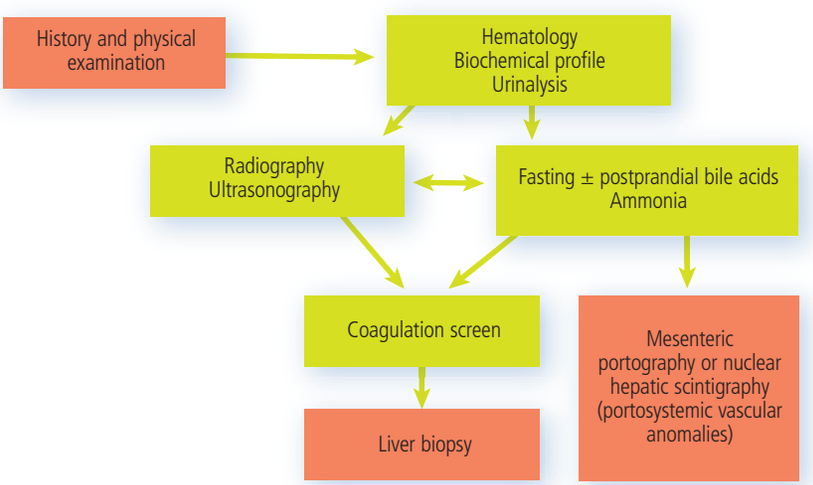


Table 3 – Hepatobiliary diseases in the cat

Inflammatory	Infectious: - Bacterial (suppurative cholangitis/cholangiohepatitis complex*, abscess, bartonellosis) - Viral (feline infectious peritonitis) - Protozoal (toxoplasmosis)
	Non-infectious: - Lymphocytic cholangitis* - Toxic and drug-induced (diazepam, acetaminophen, tetracyclines, stanozolol)
Non-inflammatory	- Metabolic disorders (idiopathic hepatic lipidosis*, amyloidosis) - Congenital portosystemic shunts - Hepatobiliary neoplasia* (primary or metastatic)

* *Most common*

► Feline hepatobiliary diseases

The incidence of feline liver disease is relatively common. The cholangitis/cholangiohepatitis complex and feline hepatic lipidosis are the major causes of hepatobiliary disease in cats, followed by neoplasia (lymphoma, bile duct). Other inflammatory liver diseases include infectious diseases such as feline infectious peritonitis (FIP) and toxoplasmosis. Hepatotoxicities are uncommon and most often associated with administration of drugs such as acetaminophen, diazepam and tetracyclines. Extrahepatic bile duct obstruction may be related to cholelithiasis or external compression (neoplasia and/or pancreatitis). Hepatic cysts are an infrequent finding and seldom cause problems. Metabolic diseases, like hepatic amyloidosis, are rare **(Table 3)**.

> Cholangiohepatitis/cholangitis complex

The cholangiohepatitis/cholangitis complex is a common but ill-defined inflammatory disorder of the hepatobiliary system in cats. It is distinctly different from dogs, where inflammatory disease is usually centered on the hepatic parenchyma (hepatitis). In cats, the inflammation is almost always centered on the bile ducts. The classification has been complex, but it is now subdivided according to the type of cellular infiltrates into suppurative (neutrophilic) cholangitis/cholangiohepatitis, chronic (mixed inflammatory cell population) and lymphocytic cholangitis *(Gagne et al, 1999; Weiss et al, 2001; WSAVA Liver Standardization Group, 2006)*. Lymphocytic portal hepatitis is furthermore a common finding in older cats, but is now thought to be of questionable clinical significance.

Suppurative cholangiohepatitis/cholangitis may begin as an ascending bacterial infection of the biliary tract, which results in neutrophilic inflammation of the bile ductules and portal triads. It is more common in males. Cats with acute suppurative cholangitis present acutely ill with fever, anorexia, vomiting and lethargy *(Caney & Gruffydd-Jones, 2005)*. They are frequently icteric, and have neutrophilia and raised liver enzymes. Coliforms *(E. coli)* are the most common bacteria, but there is often a mixed infection including common components of the enteric flora. A positive bacterial culture of the bile or liver of affected cats may help in identifying causative organisms, although the incidence of positive cultures is inconsistent. Complications include sludged (inspissated) bile and cholelithiasis, which can cause partial or complete biliary obstruction and require treatment before the cholangiohepatitis can be controlled or resolved.

Feline **suppurative cholangitis** frequently coexists with other diseases, particularly pancreatitis and inflammatory bowel disease *(Weiss et al, 1996)*. This association has been referred to as triaditis, and may be due to the fact that the pancreatic ducts and bile ducts join before entering the duodenum, allowing bacteria to enter in both. Ascending bacteria initiate the acute disease, and over time it can become chronic. The predominant signs of suppurative cholangiohepatitis are however usually attributable to hepatobiliary disease. It is nevertheless important to look for underlying disease, since these may affect the management and response to treatment (e.g. correction of cobalamin deficiency in cats with concurrent inflammatory bowel disease).

Treatment for cats with suppurative cholangiohepatitis includes fluid and electrolyte therapy as needed, nutritional support, antibiotic and choleretic therapy. In the longer term modified diets formulated for liver support are indicated, but in the early stages maintenance of caloric intake is the priority. Surgical intervention may be indicated for biliary decompression or to remove choleliths. The choice of antibiotics is ideally based upon bile and/or liver culture and sensitivity testing, but effective empirical choices are ampicillin (10-20 mg/kg IV, IM SC q6-8h), amoxicillin (11-22 mg/kg IM, SC or PO q8-12h), and cephalexin (20-20 mg/kg PO q8-12h). Metron-

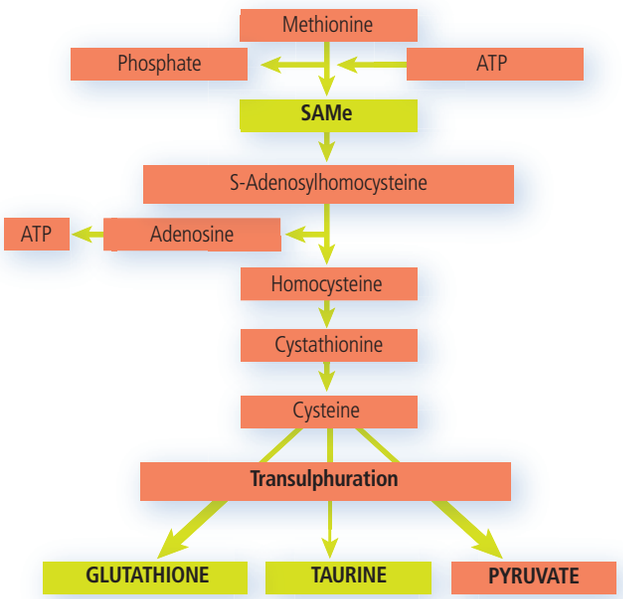
idazole (7.5-10 mg/kg PO q12h) can be used in combination with a penicillin, and has a good anaerobic spectrum. Metronidazole is metabolized by the liver, and the dose should be reduced if there is severe hepatic insufficiency. Long-term antibiotic treatment for at least 2 months is recommended, since short duration of therapy may result in reoccurrence of clinical signs.

Choleretic therapy with ursodeoxycholic acid (10-15 mg/kg PO q24h) is of value in restoring bile flow, provided there is no biliary obstruction. Ursodeoxycholic acid also has anti-inflammatory, immunomodulatory and antifibrotic capacities, probably through changing the composition of the bile acid pool by reducing the proportion of hydrophobic bile acids that have toxic effects on hepatocellular membranes *(Nicholson et al, 1996; Webster, 2006)*. Antioxidant therapy with vitamin E and S-adenosyl-methionine (SAMe) is furthermore useful to reduce oxidative stress associated with liver disease and cholestasis *(Caney & Gruffydd-Jones, 2005)*.

One beneficial effect of S-adenosyl-methionine (SAMe) is believed to be the restoration of hepatic glutathione levels that are reduced in liver disease, leading to increased oxidative damage and exacerbation of liver disease. SAMe is critical in the defence against free oxygen radicals. Other beneficial effects may be due to increasing taurine levels **(Figure 7)**, since taurine is required for bile acid conjugation and has a cytoprotective effect.

Chronic cholangiohepatitis with a mixed inflammatory cell population is thought to be the result of progression of the acute suppurative form. This is generally due to an ascending biliary infection from the gut; liver flukes *(Platynosomum concinnum)* may be a rare contributing factor in endemic tropical areas *(Haney et al, 2006)*. Presenting signs are intermittent vomiting, lethargy and anorexia, weight loss, and jaundice. A liver biopsy confirms the diagnosis, but concurrent pancreatitis and inflammatory bowel disease have to be taken into consideration. Treatment is empirical with immunosuppressive therapy (prednisolone, tapering over 2-4 weeks to 0.5-1 mg/kg once daily or every other day), antibiotics if indicated, choleretic therapy with ursodeoxycholic acid, and antioxidants. Liver fluke infestation is diagnosed upon hepatic biopsy or fecal examination, and treated with praziquantel (20 mg/kg/day for 3 days). This disease is slowly progressive, and may eventually result in cirrhosis, which has been compared to human biliary cirrhosis.

FIGURE 7 - PRODUCTION OF CYSTEINE AND TAURINE FROM S-ADENOSYL-METHIONINE (SAME)



Lymphocytic cholangitis is thought to be immune-mediated, and is characterized by lymphocytic infiltration around the bile ducts *(Day, 1996)*. Persian cats are predisposed, but there is no sex bias *(Lucke & Davies, 1984)*. The condition appears to be very chronic and slowly progressive, and affected cats present with a prolonged history of weight loss, anorexia and variable icterus; in addition, they often have hepatomegaly and a protein rich abdominal effusion. Hypergammaglobulinemia is common and may reflect the chronic nature of the disease, but needs to be differentiated from feline infectious peritonitis (FIP). Treatment is by immunosuppressive therapy with corticosteroids, which have both anti-inflammatory and anti-fibrotic properties. Prednisolone is commonly used at an initial immunosuppressive oral dose (2-4 mg/kg q12h), which is gradually reduced over 6 to 12 weeks according to the patient's response. It should then be tapered to the lowest effective dose. The use of azathioprine should be avoided, since it may have severe adverse effects in cats. Alternative immunosuppressive agents include cyclosporine, chlorambucil, methotrexate and cyclophosphamide, but experience of their use and value is limited. Ursodeoxycholic acid, antioxidant therapy with SAMe and vitamin E, and nutritional support are furthermore important components of the management.

If ascites is severe, particularly if this is causing dyspnea due to pressure on the diaphragm, drainage by abdominal paracentesis may be indicated. Loop diuretics such as furosemide (1 -2 mg/kg q12h) combined with restriction of dietary salt may be helpful in mild ascites. Potassium-sparing diuretics (e.g., spironolactone) are alternative agents for treating ascites.

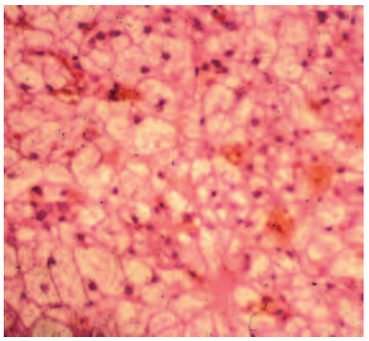


Figure 8 - Liver biopsy of a cat with hepatic lipidosis.
Notice the progressive diffuse lipid vaculolization. The brown areas indicate cholestasis (H&E).

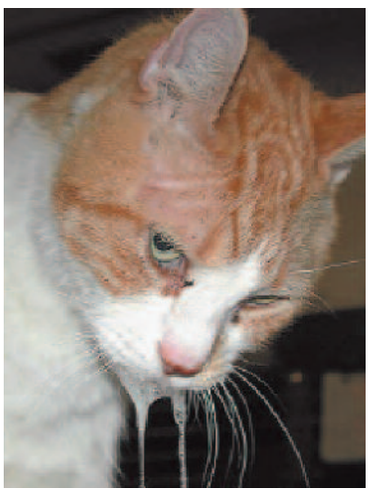


Figure 9 - Ptyalism associated with feline hepatic lipidosis.
Some cats develop remarkable ptyalism, thought to reflect hepatic encephalopathy.

> Feline hepatic lipidosis

Feline hepatic lipidosis (FHL) is a unique syndrome characterized by severe hepatocellular accumulation of triglycerides **(Figure 8)** with resulting intrahepatic cholestasis and liver dysfunction. Cats that were previously overweight and are undergoing rapid weight loss are at increased risk *(Biourge et al, 1994c)*; affected animals often have an underlying disorder that causes anorexia and catabolism *(Scherk & Center, 2005)*. It occurs primarily in middle-aged to older cats, and there is no breed or sex predisposition.

The etiology is incompletely understood but likely related to metabolic characteristics peculiar to cats, which are obligate carnivores with high requirements for protein, essential amino and fatty acids. Cats also have a high tendency to accumulate triglycerides in their hepatocytes, which is augmented during fasting after weight gain, resulting in progressive hepatocellular vacuolation. In hepatic lipidosis, the rate of peripheral fat mobilization exceeds that of hepatic triglyceride mobilisation and fat oxidation. Hepatic fat accumulation and vacuolation become so severe that it promotes oxidant injury, intrahepatic cholestasis and ultimately liver failure *(Scherk & Center, 2005)*.

The cause for the rapid mobilization of peripheral fat is as yet unknown. When anorexic, cats lack essential amino acids that are necessary for mobilization of fat stores as very low-density lipoproteins *(Biourge et al, 1994a)*. In addition, several nutritional deficiencies develop including protein malnutrition, which aggravate the liver disease *(Center, 2005)*. Cats with liver disease, including hepatic lipidosis, often have reduced hepatocellular levels of the endogenous antioxidants vitamin E and glutathione. This increases oxidative stress and aggravates hepatocellular damage *(Center et al, 2002)*. Hepatocellular carnitine deficiency has furthermore been documented and may promote lipid accumulation in the liver; carnitine supplementation has been shown to be helpful to prevent hepatic lipidosis in obese cats during complete fasting *(Blanchard et al, 2002)*, but it's role in the management of this disease is still controversial *(Ibrahim et al, 2003)*.

Cats with FHL usually present with a history of prolonged anorexia, rapid weight loss and vomiting. There is typically a significant loss of muscle mass while abdominal and inguinal fat stores are spared. On initial presentation, these cats are jaundiced, lethargic and have hepatomegaly. Some cats develop remarkable hypersalivation **(Figure 9)** as a result of hepatic encephalopathy. Hyperbilirubinemia, marked elevations in serum ALP but moderate elevations in serum γGT, and increased serum bile acids are consistent findings. Monitoring of ALP is a useful way to assess liver lipid accumulation: in anorexic cats, SAP is consistently above physiological range three weeks before hyperbilirubinemia and clinical signs appear *(Biourge et al, 1994b)*.

Cats with FHL should be investigated for the presence of underlying disease, particularly pancreatitis and inflammatory bowel disease. Nonregenerative anemia, hypokalemia and coagulation abnormalities may be present. Serum vitamin B_{12} level determination is useful to rule out coexistent hypocobalaminemia, which adversely affects liver function.

A definitive diagnosis requires a liver biopsy and hepatic cytology. It is advisable to do this only after administration of at least three doses of vitamin K_1 (0.5-1.5 mg/kg q12h), since fat-soluble vitamins are often deficient in view of the severe cholestasis.

Treatment for idiopathic hepatic lipidosis needs to be aggressive, since otherwise mortality rates are high. Initial therapy requires rehydration with balanced electrolyte solutions; replacement of potassium depletion is important as normokalemia improves survival. Adequate nutrition is however the cornerstone of treatment and prevention of feline hepatic lipidosis *(Center, 2005)*. Since these cats are typically profoundly anorexic, tube feeding is usually initially necessary to provide the essential nutrients. Oral force-feeding is generally contra-indicated, since this can lead to further food aversion. Initially, a nasoesophageal tube may be used **(Figure 10)**, and once the patient is more stable an esophageal or gastrostomy (PEG) tube can be inserted for longer-term use. Feed-

ing a high quality diet for 2-6 weeks, or until the cat begins to eat on its own again, is the most important aspect of treatment. Dietary protein content is important since it helps hepatic regeneration. For most cats with hepatic lipidosis, proteins can represent 35-50% of dietary calories. If a cat exhibits signs of hepatic encephalopathy, the dietary protein content can then be progressively lowered to the minimum level of 25%.

Other supportive measures aim at controlling vomiting and providing nutritional supplements:
- L-carnitine supplementation (250 mg/cat/day) to improve lipid metabolism
- antioxidant therapy with SAMe (200 mg/day; 20 mg/kg q12h when given with food) and vitamin E (20-100 IU daily PO)
- B vitamins are advised since these cats will have depleted hepatic stores, and it will improve appetite and cellular metabolism. Parenteral vitamin B_{12} supplementation (1 mg IM) is suggested because of the multifactorial causes of FHL, many of which lead to vitamin B_{12} deficiency.


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Figure 10 *- Nasoesophageal tube as a supportive measure for anorexic cats.*

> Toxic hepatopathies

The liver is uniquely susceptible to toxicities, since it detoxifies all agents coming from the portal blood. Acute toxic hepatopathies are however rare in cats and usually due to administration of certain therapeutic agents, such as diazepam, tetracyclines, acetaminophen, stanozolol, and methimazole *(Harkin et al, 2000, Hooser, 2000)*. Signs appear within a few days or weeks following administration and are characterized by anorexia, increased liver enzymes, hyperbilirubinemia, and may progress to acute hepatic failure unless the drug is discontinued at the first sign of increases in serum ALT levels. Histopathology mainly reveals hepatic lobular necrosis. Discontinuing the drug is essential for recovery, coupled with fluid, electrolyte and nutritional support, and antioxidant therapy. The cat's susceptibility to adverse drug reactions may be partially due to its inability to glucuronidate some metabolites in combination with its tendency for accelerated depletion of glutathione stores; however, some drug reactions are idiosyncratic.

Hepatic copper accumulation is very rare in cats, in contrast to dogs. Liver disease associated with periacinar copper accumulation has been described in a small number of Siamese cats, and some cats with chronic lymphocytic cholangitis were reported to have copper positive granules within portal hepatocytes *(Haynes & Wade 1995; Fuentealba & Aburto 2003)*. There are no reports of treatment.

> Portosystemic shunts

Feline portosystemic shunts (PSS) are less common in cats than in dogs. They are usually congenital, single and extrahepatic **(Figure 11)**, and are in most cases found in cats less than 2 years of age. Cats very rarely develop acquired portosystemic shunts due to portal hypertension *(Langdon et al, 2002)*.

Most cats with PSS are domestic shorthairs, but in purebreds there may be a breed predisposition in Persians and Himalayans *(Levy et al, 1995)*. The history most commonly includes failure to thrive or weight loss, and variable signs of hepatic encephalopathy (lethargy and depression, ataxia, seizures, behavioral changes, blindness; intermittent hypersalivation can furthermore be a symptom of HE in cats) and occasionally ammonium biurate urolithiasis. There may also be a history of tranquilizer or anesthetic intolerance. Affected cats sometimes have copper colored irises, but this is not specific for shunts.

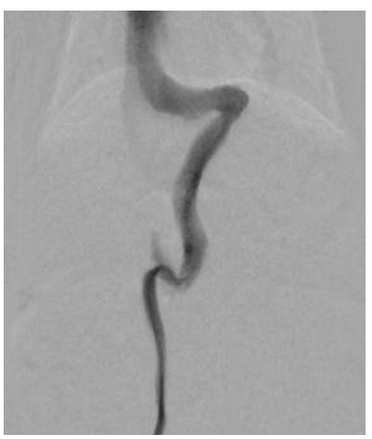
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Figure 11 - Digital subtraction angiogram of cat with congenital extrahepatic PSS.
Before ligation: the perfusion of the liver is altered.

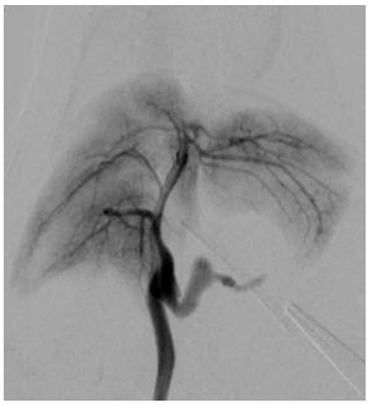

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Figure 12 - Digital subtraction angiogram of cat with congenital extrahepatic PSS after ligation. *Satisfactory perfusion of the liver.*

Hematological and biochemical abnormalities may include anemia, red cell microcytosis, increased ALT, and decreases in serum glucose and cholesterol. Cats with PSS can have normal albumin concentrations. Urinalysis abnormalities include low urine specific gravity and ammonium biurate crystalluria. Because of increased urinary excretion of ammonia and uric acid, dogs and cats may also develop uroliths. Urate uroliths are often radiolucent and therefore may not be detectable on survey radiographs unless they are combined with struvite. Elevations of both pre- and postprandial serum ammonia concentrations, or marked elevation of the postprandial values in relationship to the preprandial ones are common. Radiography usually shows small liver size, and ultrasonography is useful to detect the presence and location of a shunt.

Medical management of HE with lactulose, oral antibiotics and a protein-restricted diet stabilizes cats in anticipation of surgery and is also used for those patients in which surgical correction is not possible. Surgical options for PSS occlusion are shunt ligation, or attenuation and slow vessel occlusion using ameroid constrictors or cellophane banding *(Kyles et al, 2002; Hunt et al, 2004)*. Complete ligation of the shunt **(Figure 12)** in a single procedure is possible in less than half of the cases. Partial ligation however commonly results in recurrence of clinical signs *(Schunk, 1997)*. Repeated staged surgeries to completely ligate the shunt vessel may be more effective in these cases *(Tillson et al, 2002)*, with a good long-term prognosis if complete ligation eventually is achieved.

> Hepatic amyloidosis

Hepatic amyloidosis has been described as an uncommon familial disorder in young adult Oriental shorthair and Abyssinian cats.

Systemic amyloidosis also involving the liver is generally secondary to chronic systemic inflammatory responses. However, predominant hepatic amyloidosis has been described as an uncommon familial disorder in young adult Siamese and Oriental shorthair cats, and as sporadic cases in other breeds *(van der Linde-Sipman et al, 1997)*. Hepatic involvement has also been described in familial amyloidosis of Abyssinian cats, but signs of renal disease predominate in this breed. Clinical signs may be vague and suggestive of liver disease, but accumulation of hepatic amyloid sometimes results in spontaneous hepatic rupture and acute hemorrhagic abdominal effusion *(Beatty et al, 2002)*. Diagnosis is based on cytology of a liver aspirate or a biopsy, which have been stained with Congo-red. There is currently no treatment for this condition in cats.

© Yves Lanceau/Royal Canin/ Oriental shorthair

> Hepatobiliary neoplasia

Hemolymphatic neoplasia, mainly including lymphoma, is the most common form of hepatobiliary neoplasia in the cats. Primary hepatobiliary neoplasms occur uncommonly. Clinical signs are often vague and nonspecific, and cats may also be asymptomatic. Finding a cranial abdominal mass or hepatomegaly is the most frequent physical abnormality. Diagnosis is by ultrasound and confirmatory biopsy. Lymphoma may be amenable to chemotherapy protocols, some smaller primary tumors could be explored surgically to see whether they can be excised.

Table 4 - Purebred breed predisposition in feline liver diseases

Cholangiohepatitis	Congenital portosystemic shunts	Hepatic amyloidosis
Lymphocytic cholangitis is more commonly seen in Europe, with a predisposition in **Persian cats**.	Congenital portosystemic shunts are most frequently seen in domestic shorthair cats, but two related breeds, **Himalayans and Persians**, are at increased risk *(Levy et al, 1995)*.	This is a familial disorder in **Siamese, Oriental and Abyssinian cats**. The amyloid protein in Siamese cats differs from that in Abyssinian cats, which suggests that the Siamese has a unique isotype *(van der Linde-Sipman et al, 1997)*.

► Epidemiology

> Breed predisposition

In general, breed predisposition to the development of hepatic disease is difficult to ascertain in cats, due to the high numbers of domestic shorthair cats that are of mixed breeding. Increased incidence in specific breeds may be significant, although numbers are often small **(Table 4)**.

> Risk factors

Feline hepatic lipidosis

It is well established that there are two predisposing factors for most cases of idiopathic lipidosis: **obesity and anorexia**. Regardless of the cause of anorexia, an anorectic obese cat **(Figure 13)** is likely to develop hepatic lipidosis. The process may begin after only a few days of anorexia, but it usually does not become clinically significant until at least a few weeks.

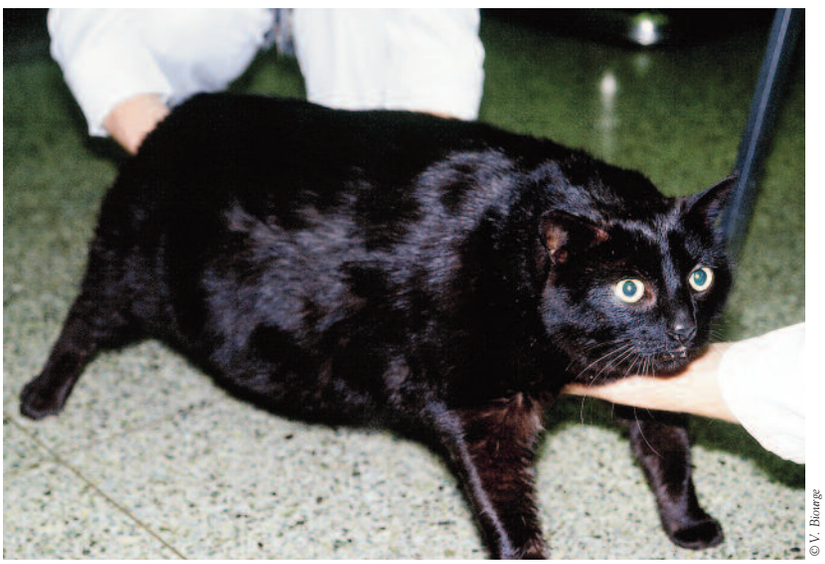
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Figure 13 *- Obesity is a major predisposing factor for feline hepatic lipidosis.*

Drugs

Certain drugs may provide a risk factor for development of acute liver disease in cats, with acetaminophen, diazepam and tetracyclines the best recognized *(Center et al, 1996; Hooser, 2000)*.

► Pathophysiological mechanisms

Hepatocellular dysfunction is associated with a number of metabolic disturbances that alter the utilization of nutrients **(Table 5)**. These are compounded by cats' nutritional peculiarities, which are due to their development as strict carnivores. Cats have very high daily protein requirements and they utilize protein for gluconeogenesis and energy production, even when the diet is high in carbohydrates. They have very limited ability to down-regulate this continuous protein catabolism *(Zoran, 2002)*. Hepatic glycogen stores are relatively small in cats, and blood glucose concentrations are maintained through gluconeogenesis from amino-acids.

Anorexia and malnutrition therefore rapidly result in augmented protein catabolism and peripheral lipolysis, and progressive loss of fat and muscle. The major consequences of malnutrition are decreased immunocompetence, decreased tissue synthesis and repair, and altered intermediary drug metabolism.

Cats are obligate carnivores with high daily dietary requirements for protein and certain amino acids (arginine, taurine), and a limited ability to digest, absorb and metabolize carbohydrates. Other nutrients considered essential in feline diets are vitamins A, D, niacin and arachidonic acid.

Hepatocellular dysfunction often causes metabolic disturbances that are compounded by malnutrition, which is a common complication of liver disease. Anorexia and malnutrition furthermore predispose cats to the development of idiopathic hepatic lipidosis.

Table 5 - Nutritional consequences of feline hepatobiliary disease

Substrate	Clinical effect
Protein metabolism	
Increased catabolism	Malnutrition, weight loss, HE
Impaired urea cycle (decreased urea production)	HE
Decreased synthesis of coagulation factors	Coagulopathy
Decreased albumin synthesis	Hypoalbuminemia
Fat metabolism	
Increased lipolysis	Malnutrition, hepatic lipidosis
Decreased excretion of bile acids	Malabsorption of fat and fat-soluble vitamins; steatorrhea, coagulopathy
Carbohydrate metabolism	
Decreased hepatic glycogen storage	Hypoglycemia (acute disease)
Increased gluconeogenesis	Loss of muscle, malnutrition
Glucose intolerance and insulin resistance	Hyperglycemia (chronic disease)
Vitamin metabolism	
Decreased storage	Vitamin B deficiency
Decreased absorption of vitamins A, D, E, K	Oxidant damage
Minerals and trace elements	
Decreased zinc levels	Decreased antioxidant protection
Detoxification and excretion	
Decreased excretion bilirubin	Jaundice
Decreased detoxification (drugs, ammonia)	Toxic hepatopathies, HE

HE = hepatic encephalopathy

> Protein, fat and carbohydrate metabolism

Protein

The liver has a large functional reserve and is able to preserve homeostasis and minimize catabolism for a long time, despite extensive damage. Cats are expert in hiding signs of disease, and appearance of metabolic alterations and clinical signs of liver dysfunction signify advanced disease.

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 *(Center, 2000a)*. Albumin has a relative priority for synthesis, although hypoalbuminemia is relatively uncommon in feline liver disease; it does not occur until the disease is chronic and is compounded by malnutrition.

The liver furthermore synthesizes the majority of the coagulation factors. Lack of synthesis in liver failure may lead to prolonged coagulation times, but only when factors are reduced to less than 30% of normal. Disseminated intravascular coagulation (DIC) is yet the most common coagulopathy associated with liver disease, and the most likely to cause spontaneous hemorrhage. Decreased absorption of vitamin K in chronic cholestasis may also lead to prolonged clotting times, but these can be corrected by parenteral administration of vitamin K_1 *(Bauer, 1996)*.

In acute disease, functional proteins in skeletal muscle and other tissues are catabolized to meet the demands for the synthesis of host defense proteins. In chronic liver disease, the etiology of the catabolic state is multifactorial *(Bauer 1996; Krahenbuhl & Reichen 1997)*. 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 clinical significance in the cat is unknown.

Protein catabolism is increased in all liver diseases. Protein breakdown is augmented in patients with infections or gastrointestinal hemorrhage, which can precipitate HE due to increased ammonia production.

Deficiency of specific amino acids may furthermore play a role in feline liver disease. Cats have a relatively high dietary requirement for arginine (recommended allowance: 1.93g/1,000 kcal ME: *NRC 2006*) because they lack alternative synthetic pathways, and thus rely on dietary arginine to drive the urea cycle. Arginine-free diets will result in hyperammonemia and HE within hours, whereas diets low in arginine will propagate HE in a later stage. Cats also need dietary taurine, (recommended allowance: 0.1g/1,000 kcal ME: *NRC 2006*) which is essential to conjugate bile acids and promote choleresis; in addition, it has a mild antioxidant function. Dietary requirements are higher when cats are fed canned diets, since these promote increased growth of enteric flora, deconjugation of bile acids and degradation of taurine *(Kim et al, 1996)*. NRC 2006 recommends an allowance of 1.0g of taurine/kg dry diet, whereas the allowance for canned diets is 1.7g/kg diet.

Cats may furthermore develop L-carnitine deficiency in liver disease, due to insufficient intake of L-carnitine or its precursors, reduced hepatic synthesis, or increased turnover. L-carnitine supplementation may be protective against the development of hepatic lipidosis in obese and anorexic cats, although this is still unproven *(Biourge, 1997)*.

Carbohydrate

The liver is responsible for the maintenance of blood glucose levels because it is the primary organ for glycogen storage and glycogenolysis. In liver disease, serum concentrations of glucagon and insulin are increased due to reduced hepatic degradation, with the effects of hyperglucagonemia generally predominating *(Marks et al, 1994; Center 2000a)*. 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 HE. 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 chronic liver disease (esp. cirrhosis) due to peripheral insulin resistance related to an increase in glucagon levels.

Fat

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, 1994; Marks et al, 1996)*.

Through its synthesis of bile acids and secretion of bile the liver plays an important role in the digestion and absorption of fat and fat-soluble vitamins (A, D, E, K). Fat malabsorption is nevertheless not common in liver disorders, since some dietary triglycerides can still be absorbed in the complete absence of bile acids. However, in severe cholestatic liver disease the reduced availability of enteric bile acids can cause malabsorption of fats, fat-soluble vitamins (especially vitamins E and K) 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 *(Center, 2000a)*.

> 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 *(Center, 1998)*. Vitamin C can be synthesized in cats but is not stored. Its synthesis may be affected by liver disease *(Center, 2000a; Marks et al, 1994)*.

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; vitamin E deficiency is particularly common in chronic liver disease *(Center, 1996)*. Deficiencies of vitamins E and K are most significant.

- Vitamin E is an important antioxidant that protects lipoproteins and cell membranes from lipid peroxidation. Vitamin E deficiency is important since it causes an increased susceptibility to oxidative stress, which perpetuates ongoing liver injury *(Sokol, 1994)*.
- Vitamin K deficiency is less common but more easily recognized since it develops rapidly and results in a clinically detectable bleeding tendency.

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 HE.

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 companion animals. 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. Hepatic copper accumulation is rare in cats, but it has been reported in cats with cholestatic liver disease *(Fuentealba & Aburto, 2003)* and as a possible primary copper hepatotoxocosis *(Meertens et al, 2005)*. In physiological hepatic concentration, copper is complexed by proteins but excessive hepatic accumulation of copper results in mitochondrial injury, generation of reactive oxygen species and free radicals*, and hepatocellular damage *(Sokol et al, 1994)*.

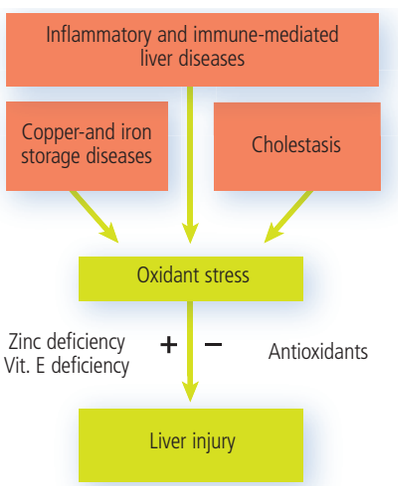
$$* \; 2Cu^{2+} + 3\,H_2O_2 \;>\; 2Cu^{3+} - 2\,H_2O + 2\,OH^{\bullet} + O_2$$

Zinc is an essential cofactor in many biological processes; it has an antioxidant role, anti-fibrotic properties, and enhances ureagenesis *(Marchesini et al, 1996)*.

TABLE 6 - HEPATIC ANTIOXIDANT DEFENSES

Dietary antioxidants	Endogenous antioxidants
Vitamin E Vitamin C Taurine Glutamine S-adenosyl-methionine (SAMe)	Glutathione Superoxide dismutase Catalase

FIGURE 14 - ETIOLOGY OF OXIDANT STRESS IN LIVER DISEASE



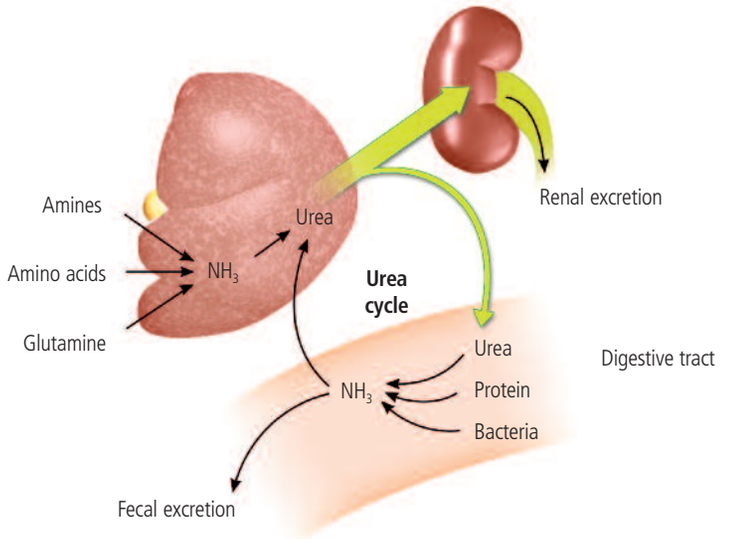
Antioxidants

Free radicals are generated in many types of liver disease, and play an important role in perpetuating hepatic pathology. 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)*. Endogenous enzymatic antioxidant defense systems that hold the generation of free radicals in check may become deficient during liver disease **(Table 6)**. All antioxidant systems work synergistically to prevent cellular damage. A disruption in these natural defense systems results in oxidant stress **(Figure 14)**. Nutritional antioxidants include vitamins E and C as well as SAMe whereas taurine and zinc have also a weak antioxidant effect.

Detoxification and excretion

The liver is the primary site of detoxification of both endogenous by-products of 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. Ammonia is the substance most commonly linked with HE, although serum ammonia

FIGURE 15 - AMMONIA METABOLISM



levels correlate poorly with the degree of HE *(Maddison, 2000)*. A large part of this ammonia is produced in the gastrointestinal tract by urease-producing bacteria **(Figure 15)**.

► Nutritional management

> Nutritional goals

Effective management of hepatobiliary disease requires both treatment of the underlying disease and nutritional support. Nutrient requirements of cats with liver disease are the same if not higher of those of normal animals, with those for protein and micronutrients even greater *(Michel, 1995)*. The diet must be highly palatable and provide adequate energy, protein, fat, and all essential micronutrients. Care must be taken to avoid overwhelming the remaining metabolic capacities of the diseased liver. It is furthermore becoming increasingly evident that it is possible to modulate metabolic and pathological processes through the use of specific nutrients and metabolites *(Remillard & Saker, 2005)*.

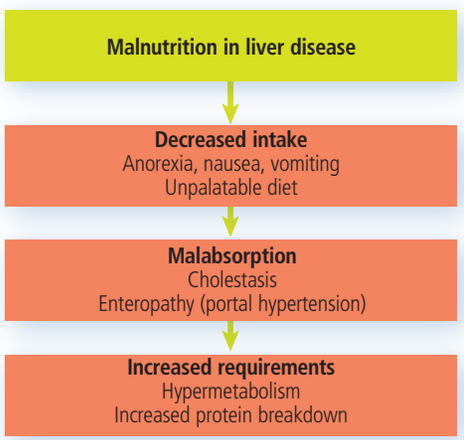
The aims of dietary management of feline liver disease are:
- to supply adequate energy and nutrients to fulfill basic energy requirements and prevent/correct malnutrition
- to limit further hepatocellular damage by reducing oxidative stress
- to support hepatocellular regeneration by providing limiting nutrients, especially protein
- to prevent or minimize metabolic complications such as HE.

ENERGY

Cats with liver disease are usually catabolic and have increased energy requirements.

Malnutrition is common in cats with hepatobiliary disease, due to decreased intake and the metabolic consequences of the disease **(Figure 16)**. Negative protein and energy balance have a harmful influence on hepatocellular regeneration and repair, reduce immune response, alter intermediary metabolism, promote HE, and increase mortality *(Biourge, 1997; Center, 1998)*. Correction and prevention of malnutrition are essential in management. Maintaining adequate nutritional intake is furthermore the only effective treatment in cats with hepatic lipidosis. Providing several small and palatable meals throughout the day will help to promote food intake and nitrogen balance. Cats that are anorexic for more than 3-5 days require tube feeding, whereas immediate tube feeding is usually recommended in cats with hepatic lipidosis. Force feeding and appetite stimulants are not recommended in cats in order to avoid learned food aversions *(Remillard & Saker, 2005; Delaney, 2006)*.

FIGURE 16 - ETIOLOGY OF MALNUTRITION IN LIVER DISEASE



PROTEIN

- Provision of adequate high-quality protein as well as calories is essential to ensure a positive protein balance and enable hepatic regeneration.
- Cats have high dietary protein requirements which are often increased in liver disease. Dietary protein should not be restricted unless there is clear evidence of hepatic encephalopathy and hyperammonemia.

The diet should have a high palatability and energy density, since cats with liver disease usually have reduced appetites. An adequate supply of energy (50-60 kcal/kg/day) and protein is essential to prevent catabolism and manutrition *(Biourge, 2004; Remillard & Saker, 2005)*. The use of nonprotein calories is important to prevent the use of amino acids for energy and reduce the need for gluconeogenesis. In cats, nonprotein calories should mainly come from fat sources and include some highly digestible carbohydrates (e.g. rice).

Fat is a highly palatable and concentrated source of energy, and the diet's caloric density is proportional to its fat content. Cats with liver disease can tolerate larger quantities of fat in the diet (30-50% of calories) than previously assumed. Fat restriction should only be considered in cats with severe cholestatic liver disease and suspected fat malabsorption, although adequate essential fatty acids must be provided. Incorporation of medium chain triglycerides in the diet is not recommended, since they may decrease palatability.

Altered carbohydrate metabolism in feline liver disease usually presents as a problem in maintaining euglycemia. Cats have a limited ability to digest, absorb and metabolize carbohydrates, and are often glucose intolerant in chronic liver disease. Carbohydrates should not represent more than 35% of the calories of the diet. Boiled white rice is useful because of its high digestibility, providing non-encephalopathogenic energy *(Center, 1998)*. Complex carbohydrates such as soluble fiber can be useful in cats with cirrhosis and a tendency to hyperglycemia, because they smooth the postprandial glycemic response and prolong glucose delivery to the liver.

Incorrect protein restriction in cats with liver disease causes further 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 hepatic encephalopathy *(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. As protein deficiency appears to be important in the pathogenesis of hepatic lipidosis, clinicians should provide patients the highest level of protein they will tolerate as soon as possible *(Biourge, 1997)*. Protein digestibility and amino acid content are important. Although vegetable, soy or dairy proteins may be better tolerated than meat proteins in HE.

BCAA (branched chain amino acid) supplementation has been advocated in people with advanced liver disease and HE, since a decreased plasma ratio of BCAA to AAA (aromatic amino acids) has been considered an important pathogenic factor in its pathogenesis. The use of BCAA supplementation is expensive and controversial, and has not been investigated in cats.

Deficiencies of specific amino acids have furthermore been speculated to occur in feline liver disease, but study results have been conflicting and speculative. However, there is evidence that L-carnitine supplementation may protect cats against hepatic lipid accumulation and thus may be an useful dietary supplement for patients with liver disease *(Ibrahim et al, 2003)*. A suggested dose is 250-300 mg/day. L-carnitine is a quaternary ammonium compound, and is an essential cofactor for the transport of long chain fatty acids into the mitochondria for subsequent oxidation and energy production *(Remillard & Saker, 2005)*. It is normally synthesized in the liver from the amino acids lysine and methionine.

Fiber

Moderate quantities of dietary fiber can have several beneficial effects in liver disease. Soluble fiber is of benefit in managing HE. Colonic fermentation of soluble fiber (e.g. fructo-oligosaccharides) lowers the intraluminal pH and thus reduces the production and absorption of ammonia, the effects of which are similar to that of lactulose. Colonic fermentation also favors the growth of acidophilic bacteria (e.g. *Lactobacillus spp*) that produce less ammonia and promote incorporation and excretion of ammonia in fecal bacteria.

Fiber (both soluble and insoluble) binds bile acids in the intestinal lumen and promotes their excretion. Insoluble fibers (lignin, cellulose) act by increasing transit time, preventing constipation and adsorbing toxins. Diets high in soluble fiber and with some insoluble fiber should therefore be useful in the long-term dietary management of cats with HE *(Center, 1998)*. Foods low in fiber can be supplemented with psyllium (1/2 tsp per 2.5 kg body weight per meal).

Minerals

Potassium and zinc deficiencies are most frequent. Hypokalemia **(Figure 17)** is a common precipitating cause of HE in cats with liver disease *(Center, 1998)*, and may be corrected by fluid therapy and dietary supplements. It usually occurs due to a combination of anorexia, vomiting or diarrhea, or excessive use of diuretics in the management of ascites. Zinc deficiency is related to reduced intake and is aggravated by the liver disease.

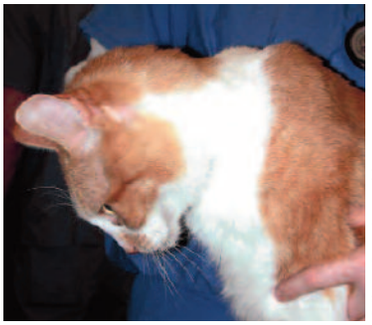


Figure 17 - Head/neck ventroflexion in a cat with severe hypokalemia associated with hepatic lipidosis. *A cat with feline hepatic lipidosis demonstrating severe head/neck ventroflexion (this is a very rare clinical sign). This cat had severe hypokalemia and hypophosphatemia; correction of the electrolyte imbalances resolved these clinical signs.*

Zinc benefits the urea cycle and central nervous system neurotransmission, has hepatoprotective effects against a variety of hepatotoxic agents and has antioxidant functions *(Feher et al, 1998, Marchesini et al, 1996)*. Zinc supplementation is furthermore useful to prevent hepatic copper accumulation in copper hepatotoxicosis, since zinc inhibits the absorption of copper from the gastrointestinal tract by causing induction of the intestinal copper-binding protein metallothionein. Dietary supplementation with zinc in cats with liver disease is done empirically, including zinc acetate (2 mg/kg per day), gluconate (3 mg/kg per day) or sulphate (2 mg/kg per day) divided into two or three daily doses. Zinc acetate is preferred because it is less irritating to the stomach; it should be given 1-2 hours before or after feeding. Serum zinc concentrations should be determined before and regularly after treatment is started in order to prevent iatrogenic zinc toxicity. Diets high in zinc (58 mg/1000 kcal) are furthermore useful for all patients with liver disease.

Zinc supplementation may reduce lipid peroxidation, has antifibrotic properties, prevents hepatic copper accumulation, and can reduce the severity of hepatic encephalopathy.

Vitamins

Vitamin deficiency is common in chronic feline liver disease. Water-soluble vitamins, especially B vitamins, which are essential for hepatic metabolism of nutrients; may be lost through vomiting or urinary losses or can become deficient as a result of anorexia, intestinal malabsorption, or decreased hepatic metabolism *(Remillard & Saker, 2005)*. High daily B vitamin intakes are recommended for cats with chronic liver disease; this is safe since excesses are excreted in the urine. The diet should furthermore contain adequate levels of vitamin C in order to take advantage of its antioxidant properties.

Fat-soluble vitamins (vitamins A, D, E, and K) may become deficient in cholestatic liver disease, because their absorption depends on the availability of bile salts. Vitamin E is an important endogenous free radical scavenger that protects against oxidative injury. Supplementation (400-600 IU/day) is particularly indicated in cholestatic 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 are preferred, since a certain level of enteric bile acids are required for its absorption.

Vitamin K deficiency is mostly relevant in cholestatic disorders, although it also may become depleted in severe chronic liver disease. Deficiency is documented by demonstration of prolonged coagulation times and normalization after parenteral administration of vitamin K_1. Coagulopathies secondary to vitamin K deficiency should be treated with two or three doses of vitamin K_1 (0.5-1.0mg/kg intramuscular or subcutaneously every 12 hours). The same dose can be given biweekly or monthly in chronic disorders in which continued repletion of vitamin K is required.

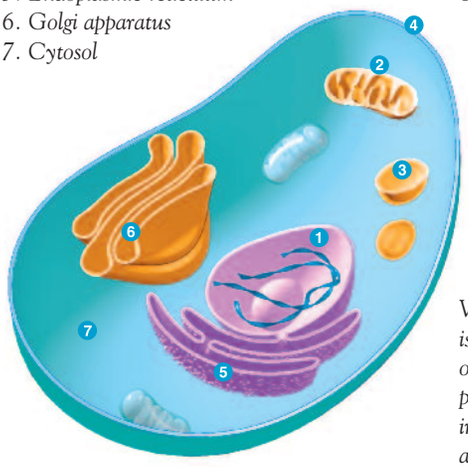
Antioxidants

Liver disease is associated with increased generation of free radicals **(Figure 18)**. Supplementation with antioxidants such as vitamins E and C, as well as taurine, is essential in order to minimize oxidative injury. A combination of dietary antioxidants is better than a single one, since they

FIGURE 18 - ANTIOXIDANT ACTION SITES IN THE CELL

1. *DNA*
2. *Mitochondria*
3. *Lysosomes*
4. *Cell membrane*
5. *Endoplasmic reticulum*
6. *Golgi apparatus*
7. *Cytosol*

Polyphenols > 1 2 5 6
Vitamin C > 7
Vitamin E > 4
Lutein > 3 5 6
Taurine > 7



Vitamin E supplementation is indicated in various forms of chronic liver disease. It protects against oxidative injury due to free radicals and it may slow down the progression of the disease.

act synergistically. A good balanced diet should also contain nutrients such as zinc, manganese and selenium, which are normally incorporated in enzymatic antioxidant systems.

SAMe is a nutraceutical that may be helpful in reducing hepatic oxidative injury. It is a precursor of glutathione, an important hepatic antioxidant enzyme that is often reduced in liver disease *(Center et al, 2002)*. Oral supplementation helps to replenish hepatic glutathione stores and may thus improve antioxidant function. In addition, SAMe has anti-inflammatory properties. It is given as an enteric-coated tablet at 20 mg/kg/day. Side effects of the drug are rare.

► Nutritional management of specific feline liver diseases

> Acute liver disease

Cats are more likely to have chronic liver disease, since they are good at hiding early signs of any disease. Acute liver disease is mostly caused by hepatotoxins, and its management includes removal of the toxin (if known), and supportive treatment with fluids and antioxidants (vitamin E, SAMe). Tube-feeding may be necessary if the cat remains anorexic, since anorexia may predispose it to the development of hepatic lipidosis.

> Chronic liver disease

Dietary management is particularly important in chronic liver disease. Treatment is essential in restoring the energy balance, especially by providing protein. The amount fed should at first be based on an estimation of the cat's energy requirements. Every effort should be made to get the cat to eat voluntarily, although force-feeding should be avoided in order not to create food aversion. Food should be palatable and fed in small portions several times daily. Cats that refuse to eat or consume insufficient amounts to meet minimum requirements require tube feeding, usually initially via an indwelling nasoesophageal tube, in order to halt the vicious cycle of excessive muscle catabolism and worsening signs of liver dysfunction. Protein restriction should only be instituted when there are signs of HE. It is also essential that the diet contains increased zinc levels and a mixture of antioxidants including vitamin E and C. Zinc supplementation is useful because it is an antioxidant, and also has antifibrotic properties and can reduce the severity of HE.

> Hepatic lipidosis

The key to treatment is for the cat to receive adequate protein and fat calories via tube feeding to correct the nutritional imbalance that has been created by the disease **(Figure 19)**. Since these cats are usually profoundly anorexic, tube feeding is indicated as an initial treatment. An esophagostomy or a gastrostomy feeding tube should be placed as soon as the cat is stabilized. Ideally, a moderate to high protein (30-40% of calories), complete and balanced diet that has been specifically formulated for cats should be utilized unless the cat has or develops signs of HE. The energy requirements of cats with hepatic lipidosis are presumed to be similar to healthy cats (50–60 kcal/kg/day), divided into equal sized portions. In addition, a predisposing condition (e.g. stress, pancreatitis, cholangiohepatitis) should be investigated and managed. Attention should also be given to appropriate protein intake, at least 3.8-4.4 g/kg/day. The goal is to restore the energy bal-

ance and supplement amino acid deficiencies, especially arginine and taurine. L-carnitine may also be an important nutritional factor because as it may help the beta oxidation of fatty acids by the hepatocytes.

Cats should derive their caloric intake via the feeding tube for the first 7–10 days of therapy. At this time, the cat can be offered food orally. If the cat remains anorexic, tube feeding should continue for another 5–7 days prior to offering food again. The feeding tube can be removed after the cat has has started eating voluntarily and is maintaining its caloric intake and body weight. Several dietary supplements have been recommended, but not critically evaluated by various authors. These include L-carnitine (250–500 mg/cat/day), taurine (250–500 mg/cat/day), vitamin B complex, zinc (7–10 mg/kg elemental zinc/day), and vitamin E (20–100 mg/cat/day). Weekly parenteral vitamin K_1 (0.5–1.5 mg/kg SQ) is indicated for those cats with documented coagulopathies.

Hepatic encephalopathy

HE is a metabolic disorder affecting the central nervous system, which develops secondary to hepatic disease *(Michel, 1995)*. In cats, it is usually a result of congenital portosystemic shunts and less commonly due to severe hepatocellular disease. 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 cats with congenital 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.

Cats with signs of HE are initially offered a protein-restricted diet (<20-25% of calories) in combination with medication aimed at reducing colonic absorption of ammonia (lactulose, oral antibiotics) **(Figure 20)**. Protein quantity is gradually increased at weekly or biweekly intervals when the cat becomes neurologically asymptomatic. Serum protein should be monitored to prevent hypoalbuminemia, in which case dietary protein content should be increased in association with more aggressive adjunct treatment. Maintenance of a positive nitrogen balance is essential in reducing the risk of HE.

The source of proteins is important in the management of HE, since ammonia production and absorption can be minimized by providing highly digestible sources of protein. When hepatic encepalopathy persists despite a protein-restricted diet and adjunct medication, it may be helpful to replace meat proteins with highly digestible vegetables (e.g. soy hydrolysate) and/or milk proteins (e.g. casein, cottage cheese). Milk and vegetable proteins are better tolerated in human patients with hepatic encephalopathy. Soy and milk protein diets are low in nitrogen compared to meat diets, which could contribute to their beneficial effects.

The addition of soluble fiber (psyllium 1-3 tsp mixed with food daily) adds bulk to the stool and prevents constipation.

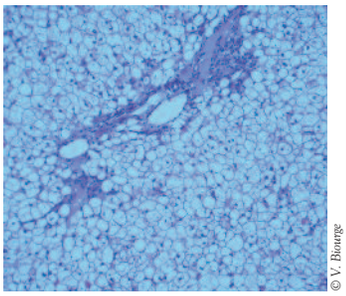
Homemade versus commercial diets

Commercial diets are preferred above homemade ones because they are nutritionally complete. It is difficult to create homemade diets that are balanced enough to be used for prolonged periods.

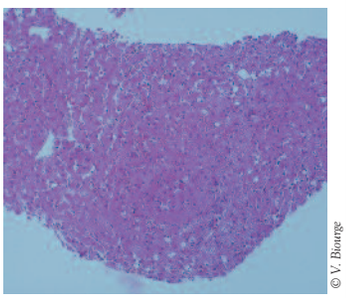
Conclusion

Diets for cats with liver disease should be highly digestible with a high energy density provided by fat and carbohydrates **(Table 7)**. Protein restriction should be avoided as much as possible, especially in cats with acute inflammatory hepatic disease or necrosis. Moderate protein restriction may be necessary in cats with clinically evident HE, but in general, it is important to feed cats the highest level of protein they can tolerate without precipitating signs of encephalopathy.

FIGURE 19 - LIVER HISTOLOGY OF A CAT ILLUSTRATING THE CAPACITY OF THE CAT TO RECOVER QUICKLY FROM HEPATIC LIPIDOSIS

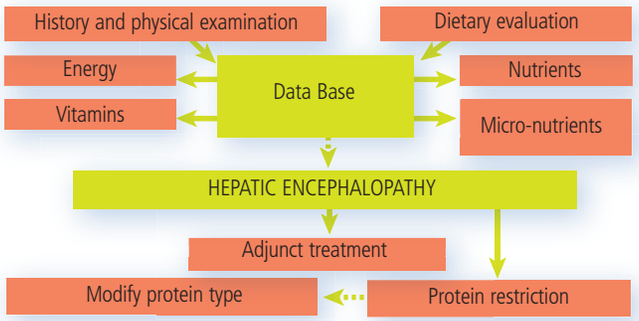


At the end of the fasting period (severe hepatic lipidosis).



After 5 weeks of adequate nutritional support.

FIGURE 20 - OVERVIEW OF NUTRITIONAL MANAGEMENT OF CATS WITH LIVER DISEASE



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 sodium (<0.5 g Na/1000 kcal) in case of ascites, and a moderate amount of predominantly soluble fiber.

Correction of enteric bleeding, constipation, infection, alkalosis, hypokalemia and azotemia is important in reducing the risk of hepatic encephalopathy. Maintenance of a positive nitrogen balance (muscle mass) is essential.

TABLE 7 - DIETARY RECOMMENDATIONS FOR THE MANAGEMENT OF LIVER DISEASE IN CATS

• Individualize management per cat and type of liver disease
Energy • High palatability and high energy density • Small meals fed frequently • Prolonged anorexia necessitates placement of an enteral feeding tube, BUT cats with confirmed hepatic lipidosis should be tube fed immediately
Provide adequate protein – AVOID negative nitrogen balance • Protein should be of high quality and digestibility • Do not restrict protein unless encephalopathic • Provide essential amino acids
Fat • Normal levels (30-50%) of dietary calories • Restrict only with severe cholestasis and/or steatorrhea
Carbohydrates • In glucose intolerance: avoid simple sugars, increase complex carbohydrates
Fiber • Moderate amounts, predominantly soluble fiber
Provide adequate vitamins and minerals • Increased vitamins B and E • Moderate restriction of sodium • Restricted copper • Increased zinc (>43 mg/1000kcal)
Include additional antioxidants • Zinc, vitamin E, vitamin C, taurine
Management of complications • Hepatic encephalopathy: - restrict dietary protein if necessary to control HE - increase dietary protein tolerance with adjunctive treatment (lactulose, metronidazole, neomycin, soluble fiber) - ± vegetable or dairy proteins - correct precipitating factors (e.g. hypokalemia) • Ascites - dietary sodium restriction (<0.5 g Na/1000kcal) - adjunctive treatment (spironolactone, furosemide)

Frequently asked questions about the dietary treatment of feline hepatobiliary diseases

Q	A
Cats 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. Slightly warming the food, and feeding small amounts frequently can increase palatability. Force-feeding is in most cases contraindicated since it can lead to learned food aversion. Tube feeding, initially via a nasoesophageal tube, may be required in cats that are anorexic, since correction and prevention of malnutrition are essential to provide the building stones for hepatic repair and regeneration, and to prevent or treat hepatic lipidosis.
How do you feed a cat diagnosed with idiopathic hepatic lipidosis?	The key to treatment of cats with hepatic lipidosis is to supply adequate nutrients in order to reverse increased peripheral fat metabolism and metabolic derangements. Since these cats are typically profoundly anorexic, this is done usually through a feeding tube (esophagostomy or gastrostomy tube) until their metabolism normalizes. Feeding a high quality, moderate to high protein diet until the cat begins to eat on its own again, in general after 2-6 weeks, is the most important aspect of treatment.
What is the role of antioxidants in the diet of a cat with liver disease?	There is mounting evidence that free radical production is increased in many liver diseases and that it can play an important role in initiating and perpetuating liver injury. Cats with liver disease, especially hepatic lipidosis, also appear to have decreased liver concentrations of the endogenous antioxidant glutathione, and thus may be at greater risk of oxidant damage to hepatocytes. The diet should therefore contain adequate to increased amounts of antioxidants such as vitamin E and S-adenosyl-methionine. A combination of dietary antioxidants is better than a single one, since they appear to act synergistically.
Do cats with liver disease need additional vitamins?	Stores of B-vitamins are often depleted in liver disease, and supplementation of B vitamins is suggested to improve appetite and cellular metabolism. Some cats with severe cholestatic liver disease will develop malabsorption of fat-soluble vitamins, and added vitamin E and K may be necessary as well.

2- Exocrine pancreatic disease

Introduction

The exocrine pancreas is essential for the optimal digestion and absorption of nutrients **(Table 8)**. Pancreatic acini synthesize and secrete digestive enzymes such as trypsin, lipase and amylase, which break down proteins, lipids and carbohydrates in the proximal duodenum. Bicarbonate rich secretions are released with pancreatic enzymes to maintain an optimal pH for enzyme activity, and secretion of pancreatic intrinsic factor enables the absorption of cobalamin (vitamin B_{12}). In addition, the exocrine pancreas produces bacteriostatic peptides that regulate the upper gastrointestinal flora, and has a role in maintaining the integrity of the intestinal mucosa. The pancreas also has an inbuilt mechanism to prevent it from premature intrapancreatic activation of digestive enzymes and autodigestion.

TABLE 8 - FUNCTIONS OF THE EXOCRINE PANCREAS

Secretion of digestive enzymes	Trypsin, lipase, amylase
Secretion of bicarbonate	Neutralizes gastric acid emptied into the duodenum, creating a neutral pH for optimal digestive enzyme absorption
Facilitation of cobalamin absorption	Secretion of pancreatic intrinsic factor that enables absorption of cobalamin (Vitamin B_{12})
Secretion of antibacterial factors	Production of bacteriostatic peptidases (pancreatic secretory trypsin inhibitor) and defensins that regulate the upper GI flora
Modulation of intestinal mucosal function	

Pancreatitis is the most common feline exocrine pancreatic disorder, followed by exocrine pancreatic insufficiency; exocrine pancreatic neoplasia and other miscellaneous conditions are less commonly seen in cats.

► Pancreatitis

Feline pancreatitis can be difficult to diagnose as clinical signs, laboratory findings and imaging results are often nonspecific *(Ferreri et al, 2003)*. However, pancreatitis has now emerged as a significant disease in cats. It may be acute or chronic and of variable severity. The etiology of most cases of feline pancreatitis is idiopathic. Chronic pancreatitis is the most common form of the disease in cats *(De Cock et al, 2007)*. It is usually mild, and may be only recognized by the development of secondary diabetes mellitus or exocrine pancreatic insufficiency *(Steiner & Williams, 2005)*.

Pancreatitis is sometimes only diagnosed when related conditions, such as hepatic lipidosis, are being investigated. Severe acute pancreatitis (necrotizing, hemorrhagic) can result in extensive pancreatic necrosis and multisystemic complications; however, fulminating pancreatitis associated with severe systemic complications is rare in cats.

> Diagnosis

History and physical examination

Clinical signs of pancreatitis in cats are nonspecific, including anorexia, lethargy and weight loss. Diagnosis can therefore be difficult, and requires a combination of clinical suspicion, appropriate physical examination findings, elevations in pancreas-specific enzymes and abdominal ultrasonography.

Clinical signs vary depending on the severity of the disease. The most common signs are lethargy, anorexia and dehydration, which are symptoms seen in many feline diseases *(Mansfield & Jones, 2001b)*. Vomiting and cranial abdominal pain are far less common than in dogs with pancreatitis. Cats diagnosed with acute pancreatitis and with concurrent hepatic lipidosis are more likely to be cachectic and have coagulation abnormalities. Some cats with acute pancreatitis are presented because of icterus due to extrahepatic bile duct compression *(Zoran, 2006)*. Severe acute pancreatitis may infrequently result in systemic vasodilatation leading to hypotension and sometimes renal failure. Because cats display less commonly key clinical signs observed in dogs, the diagnosis of pancreatitis is much more difficult and a high index of clinical suspicion is warranted.

Chronic pancreatitis may be subclinical and may cause anorexia and weight loss.

TABLE 9 - LABORATORY FINDINGS IN FELINE PANCREATITIS

Hematology and serum biochemistries	- Inconsistent anemia and leukocytosis - Hypoalbuminemia - Hyperglycemia / glucosuria - Increased liver enzymes - Hyperbilirubinemia - Azotemia (prerenal most common) - Hypokalemia - Hypocalcemia
Serum vitamin concentrations	Decreased serum cobalamin (vitamin B_{12}) concentration
Pancreas-specific enzymes	Increased serum fPLI concentration (most specific) Increased serum fTLI concentration

fPLI – feline pancreatic lipase immunoreactivity
fTLI – feline trypsin-like immunoreactivity

> Diagnostic tests

Hematology, biochemistries and urinalysis (Table 9)

Routine laboratory findings are generally nonspecific and cannot distinguish between acute and chronic pancreatitis *(Ferreri et al, 2003)*. Leukocytosis and neutrophilia are more common in acute pancreatitis, and nonregenerative anemia can be found in both acute and chronic disease. Serum biochemical abnormalities are highly variable; most common are elevations in serum liver enzyme activities (alanine amino-transferase [ALT], alkaline phosphatase [ALP]). Severe acute pancreatitis can cause hyperbilirubinemia due to extrahepatic bile duct compression. Azotemia is variably present, and may be pre-renal or renal, either due to dehydration or rarely due to acute renal failure secondary to pancreatitis.

Electrolyte abnormalities (hypokalemia, hypocalcaemia) are frequently seen in severe cases. Hypocalcemia (total and serum ionized) appears to be a more frequent finding in cats than in dogs; it may result from several mechanisms, including peripancreatic formation of calcium salts with fatty acids (fat saponification), and is associated with a worse prognosis *(Kimmel et al, 2001)*. Other abnormalities may include hypoalbuminemia, hypercholesterolemia and hyperglycemia.

Urinalysis often reveals an elevated urine specific gravity secondary to dehydration. In severe cases acute renal failure may ensue, resulting in reduced urine specific gravity and casts in the sediment.

None of these findings are specific, but the tests are nonetheless important because they serve to rule out disorders other than pancreatitis and to assess the overall status of the patient.

Pancreas specific enzymes

Measurement of serum lipase and amylase activities is very insensitive and of no clinical value in the diagnosis of feline pancreatitis. Determination of serum feline trypsin-like immunoreactivity (fTLI), which is specific for exocrine pancreatic function, is more helpful but its sensitivity for detection of pancreatitis in cats is less than 50%, making it a suboptimal diagnostic test *(Swift et al, 2000; Steiner, 2003; Forman et al, 2004)*.

Recently, a serum feline pancreatic lipase immunoreactivity (fPLI) test has been validated, which appears to be a more sensitive and specific test for the diagnosis of feline pancreatitis, more so for acute than chronic pancreatitis *(Forman et al, 2004; Steiner, 2004)*.

Diagnostic imaging

Radiography – The sensitivity of abdominal radiography is generally low for the diagnosis of feline pancreatitis, and especially for chronic pancreatitis. Radiographic abnormalities in acute pancreatitis may include a generalized or focal loss of serosal detail (suggesting peritonitis or peritoneal effusion), increased opacity or the presence of a mass in the area of the pancreas, displacement of the duodenum and/or a dilated and hypomotile duodenum. Cats with concurrent hepatic lipidosis often have hepatomegaly. These changes occur much less commonly than in canine acute pancreatitis, and are not specific *(Whittemore & Campbell, 2005)*.

Ultrasonography – Abdominal ultrasonography is more specific and sensitive for detecting pancreatic abnormalities, and is currently one of the most commonly used tools for the diagnosis of pancreatitis in cats. It also allows the evaluation of concurrent disease, e.g. liver disease or biliary obstruction. Ultrasound is widely available today, although sonographic examination of the pancreas requires a high level of operator expertise. Changes identified include pancreatic swelling, changes in echogenicity of the pancreas (hypoechogenicity in acute pancreatitis and hyperechogenicity in chronic pancreatitis and fibrosis) **(Figures 21 & 22)**, hyperechoic peripancreatic fat and mesentery, abdominal effusion, a dilated common bile duct, and less frequently a mass effect in the area of the pancreas **(Figure 23)**. Cavities of the pancreas are generally due to abscesses or pseudocyst formation, and appear as anechoic or hypoechoic cavities, possibly with a thickened wall **(Figure 24)**. Mild pancreatitis may however be more difficult to diagnose via abdominal ultrasound.

Computed tomography (CT) – Other imaging modalities, such as CT-scanning, are more expensive and thought to be less helpful than abdominal ultrasonography *(Gerhardt et al, 2001; Forman et al, 2004)*.

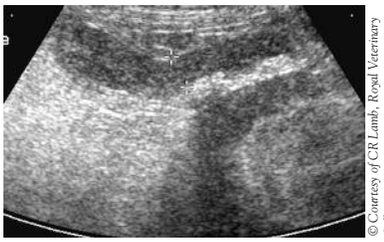


Figure 21 - Ultrasound image of a cat with acute pancreatitis. *The cat had a serum fTLI concentration >400 mg/L. Ultrasound shows a diffusely hypoechoic parenchyma. The pancreas is not enlarged.*

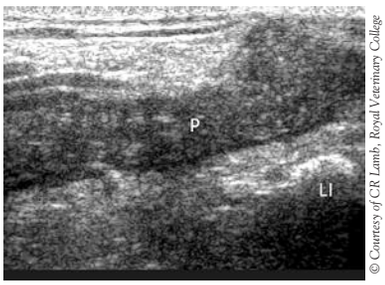


Figure 22 - Chronic active pancreatic necrosis in a diabetic cat. *Ultrasound shows a diffusely hypoechoic, enlarged pancreas.*

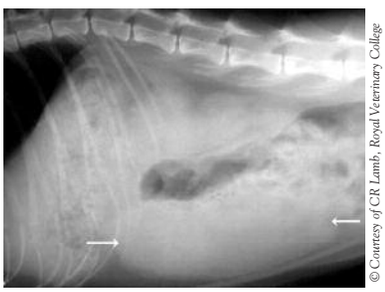


Figure 23 - Pancreatic pseudocyst in a cat. *The lateral abdominal radiograph indicates an oblong soft tissue opacity along the ventral abdomen.*

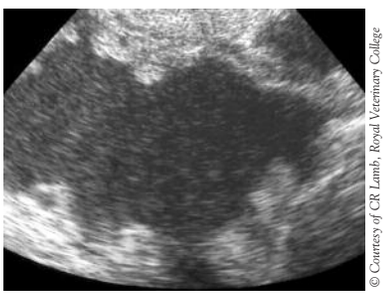
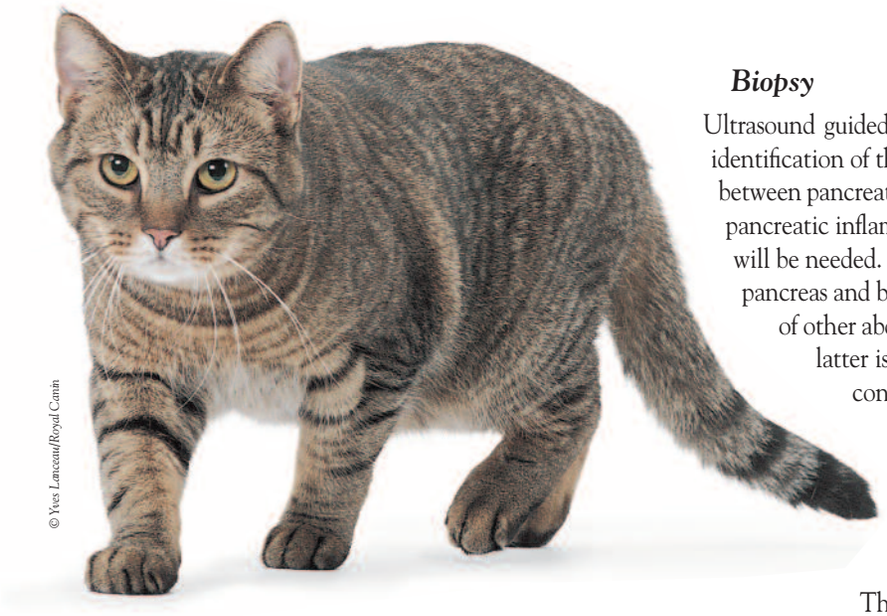


Figure 24 - Ultrasound scan of a cat with a pancreatic pseudocyst. *The ultrasound scan shows a cavitary mass with thick irregular walls.*



Most cases of pancreatitis are seen in domestic short-hair cats. There is no breed or sex predisposition.

Biopsy

Ultrasound guided fine needle aspiration is relatively safe and helps in identification of the underlying pancreatic disease, e.g. in differentiating between pancreatitis and neoplasia. However, the patchy distribution of pancreatic inflammation can limit its usefulness, and multiple aspirates will be needed. Laparoscopy and laparotomy allow visualization of the pancreas and biopsy of parts that look abnormal, as well as inspection of other abdominal organs (e.g., liver, biliary tract, intestine). The latter is important in the cat because of the high incidence of concurrent disease in this species. Surgical biopsy procedures are however expensive and invasive, while cats with acute pancreatitis may be poor anesthetic risks.

Differential diagnosis

The clinical signs of feline pancreatitis are nonspecific, but this disease should however be suspected in any cat with evidence of hepatic, biliary or inflammatory bowel disease.

Pancreatic neoplasia is much less common than pancreatitis, but signs and ultrasonographic findings can be similar in cats *(Seaman, 2004; Hecht et al, 2007)*. Identification of a pancreatic mass and lymphadenopathy upon ultrasonography may be helpful, but fine-needle aspiration or surgical biopsy is needed for definitive diagnosis.

> Epidemiology

Etiology

Most feline pancreatitis cases are idiopathic, and causes and risk factors have been described in only a small number of cases. Traumatic pancreatitis associated with road traffic accidents or falls from a great height ("high rise syndrome") has been reported in some cases. Several infectious agents have been implicated, although a cause-and-effect relationship has only been established for *Toxoplasma gondii* and in very rare cases aberrant migration of the feline liver fluke *(Amphimerus pseudofelineus)*. Feline herpesvirus, coronavirus (feline infectious peritonitis -FIP-) and panleukopenia virus are putative causative factors for pancreatitis in cats, but there is little or no scientific evidence to support this *(Steiner & Williams, 1999; Mansfield & Jones, 2001a)*. Drugs have been implicated as causing pancreatitis in humans and dogs, but this is poorly documented in cats. Pancreatitis was reported in two cats following topical administration of the organophosphate fenthion *(Hill & Van Winkle, 1993)*.

Risk factors

There are few known risk factors for the development of pancreatitis in cats. Many cats with chronic pancreatitis have concurrent biliary tract and/or gastrointestinal tract disease ("triad disease"), but the cause-and-effect relationship remains unclear. The incidence of chronic pancreatitis is however significantly correlated with increasing age *(De Cock et al, 2007)*. In contrast to dogs, there is no evidence that overweight body condition, nutritional factors (ingestion of high-fat meals) or endocrine diseases (hyperadrenocorticism) play a role in the etiology of feline pancreatitis. Pancreatitis may occur in cats of any breeds. An older report suggesting that Siamese cats were at increased risk has not been confirmed in recent studies. There is no sex predisposition.

> Pathophysiological mechanisms

Regardless of the initiating cause, pancreatitis is thought to be due to premature intrapancreatic activation of trypsinogen which, when activated to trypsin, activates other digestive proenzymes resulting in a local and systemic inflammatory response. Under normal conditions this does not happen due to a number of protective mechanisms, which include:

1) synthesis, storage and secretion of pancreatic enzymes as zymogens (inactive proenzymes) that must be activated by trypsin within the gut prior to being functional
2) strict segregation between lysosomes and zymogens
3) secretion of pancreatic secretory trypsin inhibitor.

Pancreatitis develops when all these protective mechanisms are overwhelmed, resulting in fusion between lysosomes and zymogens, and intrapancreatic activation of digestive enzymes *(Steiner & Williams, 1999)*.

Acute mild pancreatitis can be self-limiting, and usually has few symptoms. Severe acute pancreatitis is uncommon in cats, but can have serious local and systemic complications. Activated digestive enzymes cause local effects, such as inflammation, hemorrhage, acinar cell necrosis, and peripancreatic fat necrosis **(Figure 25)**. Cytokines released into the blood stream may cause systemic effects, including systemic inflammatory changes, vasodilatation leading to hypotension, pulmonary edema, disseminated intravascular coagulation (DIC), central neurological deficits, and multi-organ failure. Depletion of pancreatic acinar glutathione can furthermore stimulate oxidative stress that contributes to tissue injury. However, the exact pathophysiology of spontaneous pancreatitis in cats remains speculative.

> Treatment

Medical management

Acute pancreatitis

Treatment for feline acute pancreatitis is mainly supportive and aimed at restoring and maintaining fluid and electrolyte balance, inhibiting inflammatory mediators and pancreatic enzymes, controlling pain and vomiting, and management of complications and/or concurrent diseases *(Simpson, 2005)*. Initial fluid therapy is usually with Lactated Ringers solution; potassium and glucose should be added where necessary based upon the results of serum biochemistries. The type of fluid should then be adjusted based upon measurements of electrolyte levels and pH. Efforts should also be made to identify and remove an underlying cause; however, more than 90% of cases are idiopathic.

In severe acute pancreatitis, other therapeutic strategies may furthermore involve plasma administration (20 mL/kg IV) to replenish α2-macroglobulin, a scavenger protein for activated proteases in serum. However, although it has been reported to be of value in dogs with pancreatitis, little is known about its usefulness in cats.

Abdominal pain is commonly recognized in humans and dogs but not in cats with pancreatitis, likely because many cats do not show clear signs of abdominal discomfort. They may however benefit significantly from analgesic therapy, and the presence of abdominal pain should be suspected. Treatment with analgesic drugs e.g. (buprenorphine 0.005-0.1 mg/kg SC q 6-12 hrs) can help cats with acute pancreatitis to feel better and promote eating *(Whittemore & Campbell, 2005)*.

It is common practice to give parenteral antibiotics during this supportive period, but cats with pancreatitis seldom have infectious complications. Antibiotic administration is best avoided unless the cat is febrile and/or has toxic changes on the white blood cell count.

The goals of management are removal of the inciting cause if possible, provision of supportive and symptomatic therapy, and monitoring for and treatment of complications. Nutritional support is especially important in cats since anorexia predisposes them to hepatic lipidosis.

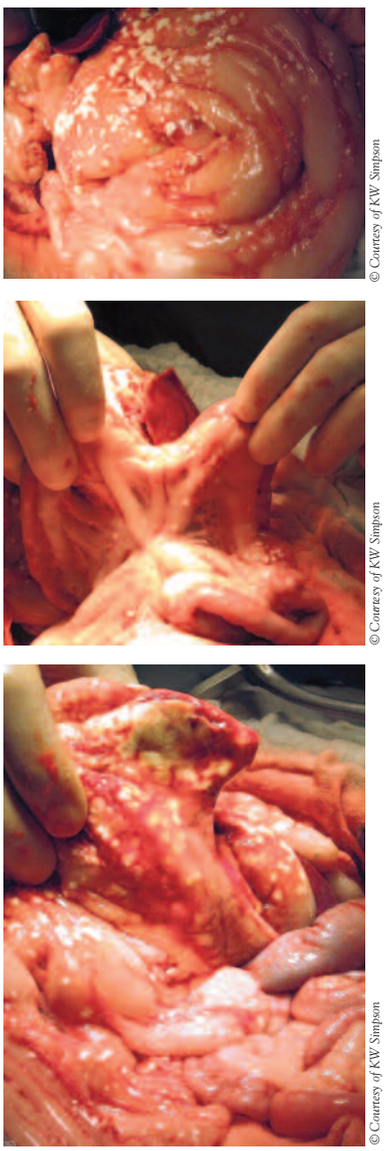


Figure 25 - Peripancreatic fat necrosis. *Exploratory laparotomy and histopathology confirm severe multifocal fat necrosis in a cat with fatal acute pancreatitis.*

Concurrent diseases are common in feline pancreatitis, and need to be addressed to improve response to therapy *(Simpson, 2005)*. Associated diseases include inflammatory bowel disease, cholangiohepatitis and interstitial nephritis *(Weiss et al, 1996)*. Concurrent hepatic lipidosis is common *(Akol et al, 2001)*, which emphasizes the need for early nutritional support.

Chronic pancreatitis

Medical management is supportive and mostly focuses on treatment of secondary diabetes mellitus and/or exocrine pancreatic insufficiency. Whenever possible the underlying cause should be removed. Exposure to unnecessary drugs should be avoided, and consideration should be given to the treatment of pancreatic flukes, especially in areas where they are known to be prevalent. Concurrent diseases, notably inflammatory bowel disease, cholangiohepatitis and interstitial nephritis, are common in cats with chronic pancreatitis, but little is known about how to best treat these in conjunction with managing the pancreatitis *(Ferreri et al, 2003)*.

Abdominal pain is frequent in people with chronic pancreatitis and is likely to occur in cats as well, although it is generally poorly recognized. Meperidine or butorphanol can be used parenterally. This has not been documented in cats, but trial therapy with pancreatic enzymes should be considered in patients with chronic pancreatitis that show either abdominal pain or anorexia attributable to abdominal discomfort *(Steiner & Williams, 2005)*. Supplementation with pancreatic enzymes may be helpful to reduce abdominal pain by a negative feedback on endogenous pancreatic enzyme secretion.

Nutritional support is essential in cats with acute pancreatitis, since they are generally anorexic and often have concurrent hepatic lipidosis. Nutrition furthermore helps tissue repair and recovery, and can modulate the inflammatory response.

TABLE 10 - RECOMMENDATIONS FOR MANAGEMENT OF EXOCRINE PANCREATIC DISEASE IN CATS

Provide adequate energy	- High diet palatability and energy density - Small meals fed frequently - Moderate fat intake
Provide adequate protein	- Protein should be of high quality and digestibility - Do not restrict protein
Fiber	- Moderate amounts, predominantly soluble fiber
Provide adequate vitamins and minerals	- Increase vitamin B and E - Parenteral cobalamin supplementation
Include additional antioxidants	- Vitamins E and C, taurine
Management of complications	• Persistent anorexia - Enteral tube feeding - (Parenteral nutrition) • Exocrine pancreatic insufficiency - Exogenous pancreatic enzyme supplementation mixed within each meal • Diabetes mellitus - Exogenous insulin

Nutritional management (Table 10)

To feed or not to feed

The traditional recommendation for patients with acute pancreatitis is not to feed orally for three to four days in order to prevent further pancreatic stimulation ("rest the pancreas"). This recommendation is justified in patients that vomit, but most cats with acute pancreatitis do not vomit. The issue is complicated further in cats by the fact that cats with severe pancreatitis are anorexic and often develop hepatic lipidosis, which worsens their prognosis *(Akol et al, 2001)*. Pancreatitis is a catabolic state in which metabolic and energy demands can be very high. Starvation will only serve to compound malnutrition and will also adversely affect immune response and bowel mucosal integrity. Cats with pancreatitis should therefore receive nutritional support at an early stage. There is no clinical impression that such enteral nutrition exacerbates the course of pancreatitis, and in fact cats clearly do better overall when nutritional support is given.

If the cat is not eating on its own within three days, nutritional support via a feeding tube is indicated to prevent or treat hepatic lipidosis, protein/calorie malnutrition and immunosuppression.

How to feed

Oral force feeding is not recommended since it is difficult to achieve the appropriate levels of caloric intake by this method, and also because it can induce food aversion. The choice is then between enteral or parenteral nutrition. There is increasing evidence in humans and animals that enteral nutrition is superior to parenteral nutrition in the treatment of acute pancreatitis *(Marik & Zaloga, 2005; Simpson, 2005; Makola et al, 2007)*. Enteral nutrition prevents intestinal mucosal atrophy and bacterial translocation which accompany parenteral nutrition. It is also more economical, has less risk of septic complications and is far less complicated to use. The simplest and most widely used methods of enteral feeding are via a nasoesphageal, esophagostomy or percutaneous endoscopic gastrostomy (PEG) tube **(see chapter 12)**. Postpyloric feeding via a jejunostomy tube (distal to the site of pancreatic stimulation) has the theoretical advantage of minimizing pancreatic stimulation, but there are now several studies in human patients that the nasogastric route may be just as effective and safer. Jejunostomy tube placement historically required invasive surgery, but recently a percutaneous endoscopic transpyloric placement technique has been described *(Jergens et al, 2007)*. It remains however open whether cats with acute pancreatitis really require jejunal feeding.

Parenteral nutrition may be necessary for cats in which persistent vomiting cannot be controlled by anti-emetic treatment; it is however expensive, difficult to administer in practice, and may cause complications such as sepsis.

What diet to feed

The diet for patients with pancreatitis should be highly digestible. Dietary fat restriction is recommended for human and canine patients with pancreatitis in order to reduce pancreatic stimulation, but is less applicable to felines. Cats are obligate carnivores and require fairly high dietary fat levels, and in contrast to dogs there is little clinical evidence to suggest that dietary fat restriction influences the outcome of feline pancreatitis. In addition, low-fat diets are energy restricted and not a good choice for sick cats with poor appetites. The best compromise is to select a palatable, complete and balanced diet formulated for maintenance with a moderate fat content (10-12% on a dry matter basis). The important thing is to stay away from a high fat diet (> 16 % fat on a dry matter basis), especially in those cats that have both pancreatitis and diabetes mellitus *(Steiner J, personal communication 2007)*.

Dietary protein should be of good quality and meet the cat's requirements for maintenance and tissue repair. However, diets excessively high in protein should be avoided in order to minimize pancreatic stimulation by peptides. Novel antigen diets may be useful in cats with pancreatitis and concurrent inflammatory bowel disease *(Biourge & Fontaine, 2004)*.

Dietary supplements

Antioxidants – Oxidative stress caused by inflammatory mediators can aggravate severe acute pancreatitis in humans *(Schulz et al, 2003)*, although the role of antioxidant treatment in its management is controversial *(Johnson, 2007)*. There are no data about the role of antioxidants in the management of feline pancreatitis.

Fatty acids – Supplementation with n-3 polyunsaturated fatty acids (fish oil) can ameliorate inflammation through modulation of eicosanoid synthesis. A clinical trial in human patients with acute pancreatitis suggested a clinical benefit based upon shortened time of hospital stay and jejunal feeding *(Lasztity et al, 2005)*. Its use in cats with exocrine pancreatic disease has not yet been evaluated.

Cobalamin – Cobalamin malabsorption is common, because intrinsic factor (IF), a cobalamin binding protein that promotes cobalamin absorption in the ileum, is produced only by the pancreas in cats (as opposed to the stomach and pancreas in dogs). Cobalamin deficiency is even greater in cats with concurrent small intestinal disease. Cats with subnormal serum cobalamin concentrations should be supplemented parenterally (SQ or IM, 250 µg once a week for six weeks and then monthly) *(Simpson et al, 2001)*. The necessity for further treatments should be assessed by regular measurement of serum cobalamin concentrations.

Vitamin K – Coagulation abnormalities should be treated with parenteral vitamin K; in cats with severe necrotizing pancreatitis, the possibility of disseminated intravascular coagulation should be assessed, which may require administration of fresh frozen plasma (10-20 mL/kg).

► Exocrine pancreatic insufficiency

> Introduction

The exocrine pancreas plays a central role in the digestion and absorption of nutrients. Pancreatic acinar cells synthesize and secrete enzymes that digest proteins, fats and carbohydrates (protease, lipase and amylase). Pancreatic duct cells furthermore secrete bicarbonate to maintain an optimal pH for digestive and absorptive function, as well as intrinsic factor to facilitate cobalamin absorption.

Exocrine pancreatic insufficiency (EPI) results from deficient synthesis and secretion of pancreatic digestive enzymes. The lack of digestive enzymes in the duodenum leads to maldigestion and malabsorption of intestinal contents. The exocrine pancreas has a large functional reserve capacity and clinical signs of maldigestion do not occur until 90% of secretory capacity is lost.

> Diagnosis

Overview

EPI is an uncommon cause of chronic diarrhea in cats; however, in the past it has been under diagnosed due to the lack of specific clinical and laboratory findings. Diagnostic accuracy has now been facilitated by the fTLI test, which is a species specific radioimmunoassay.

Clinical signs

Clinical signs in affected cats are not specific for EPI: the most commonly reported clinical signs in cats with EPI are weight loss and soft voluminous feces *(Steiner & Williams, 2005)*. Polyphagia despite weight loss is not as commonly seen as in dogs. Many cats also develop a greasy, unkempt hair coat, especially in the perianal and tail regions, resulting from the high fat content of their feces. Some cats have watery diarrhea secondary to intestinal disease. Affected cats may also have a previous history of recurring bouts of acute pancreatitis (e.g., anorexia, lethargy, vomiting) that resulted in chronic pancreatitis and EPI. Concurrent disease of the small intestine, hepatobiliary system and endocrine pancreas may be present.

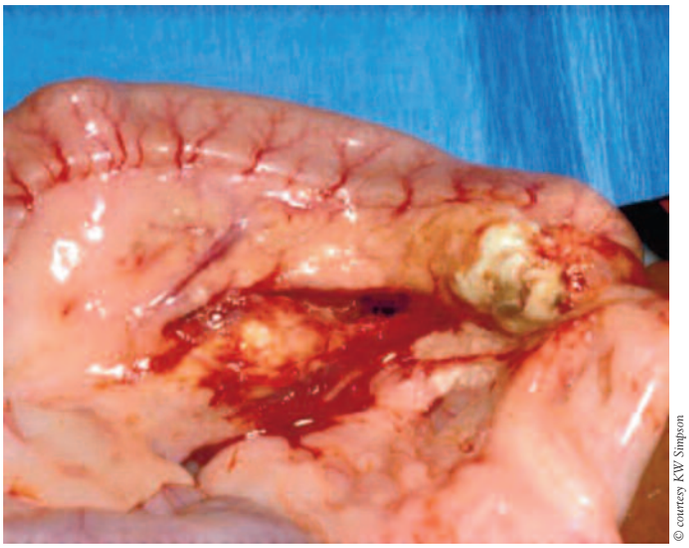
Differential diagnosis

The main differential diagnoses for a cat presented with diarrhea, weight loss and changes in appetite are hyperthyroidism, diabetes mellitus and chronic small intestinal disease (most commonly inflammatory bowel disease). Physical examination may help in differentiating these, e.g. by palpating a thyroid nodule or thickened intestinal loops. However, these diseases may be coexisting, especially in older cats, and laboratory testing and imaging (particularly ultrasound) are mandatory.

Laboratory testing

Routine laboratory tests

Results of hematology and serum biochemistries are generally within normal limits or show nonspecific changes. Older cats may have evidence of concurrent renal disease, whereas cats with hyperthyroidism often have increased serum liver enzyme concentrations. Microscopic examination of feces will demonstrate steatorrhea and undigested fat, but this is not pathognomonic for EPI.



© courtesy KW Simpson

Figure 26 *- Chronic pancreatitis is the most common cause of EPI in cats.*

Serum concentrations of cobalamin and folate should also be determined in all cats with suspected EPI, because of the common occurrence of low levels (especially for cobalamin) *(Steiner & Williams, 1999)*.

Pancreas-specific tests

A feline-specific radioimmunoassay for trypsin-like immunoreactivity (fTLI) has now been developed and validated, it is sensitive and the test of choice to diagnose EPI in cats. Fasting serum fTLI concentrations less than 8 µg/L (reference range = 17-49 µg/L) are diagnostic for feline EPI *(Steiner & Williams, 2000)*. When the fTLI concentration is between 8-17 µg/L, the test should be repeated ensuring adequate fasting; it is also possible the cat has partial EPI that in time may progress to complete EPI. The TLI test is a simple and reliable way of confirming the diagnosis of EPI; however; it is essential to use an assay specific for feline TLI since there is no cross reactivity between canine and feline TLI.

Diagnostic imaging

Imaging findings are inconsistent; abdominal radiography and ultrasonography generally do not show any abnormalities.

> Epidemiology

Risk factors

Chronic pancreatitis is the most common cause of feline EPI **(Figure 26)**, occurring mainly in mature and older cats. In most cases, it is idiopathic. Rare causes of feline EPI without chronic pancreatitis are pancreatic duct obstruction by liver flukes or pancreatic neoplasia (adenocarcinoma), leading to acinar atrophy. Fecal examination can help in the diagnosis of a fluke infestation, whereas abdominal ultrasonography is essential in detecting a pancreatic mass.

Pancreatic acinar atrophy (PAA) similar to the disease commonly observed in dogs has not been documented in cats.

Breed and sex predisposition

There is no breed or sex predisposition for the development of EPI in cats.

> Pathophysiology

Cats with EPI have an extensive and chronic disease, which is usually due to chronic and irreversible pancreatitis.

The typical signs of EPI (diarrhea, weight loss and polyphagia) are due to decreased intraduodenal concentrations of pancreatic digestive enzymes and bicarbonate with resultant malassimilation of fats, carbohydrates and proteins. This leads to malabsorption, osmotic diarrhea and steatorrhea, and malnutrition. In addition, there are secondary disturbances of intestinal mucosal growth and transport mechanisms that aggravate malabsorption. Cats normally have high numbers of anerobic organisms in their proximal small bowel *(Johnston et al, 1993)* and it is not known whether they develop changes in the nature and number of small intestinal flora, which is common in dogs with EPI.

Fat malabsorption may result in deficiencies of the fat-soluble vitamins (esp. vitamins K and E). Vitamin K-dependent coagulopathy has been reported in a cat with EPI *(Perry et al, 1991)* and may occur in other cases as well. Vitamin E deficiency could aggravate oxidative stress, but there are no reports documenting this in feline EPI.

Many cats with EPI have low serum cobalamin concentrations, which impairs their response to treatment. Cobalamin is absorbed in the distal small intestine after it has formed a complex with intrinsic factor, a protein that in cats is exclusively secreted in the pancreatic juice *(Fyfe, 1993)*. The lack of pancreatic intrinsic factor in EPI impacts severely the ability to absorb cobalamin. In addition, concurrent small intestinal disease *(Weiss et al, 1996)* may further impair cobalamin absorption in cats. Cats seem predisposed to develop markedly reduced serum cobalamin levels under those circumstances *(Simpson et al, 2001)*. Uncorrected cobalamin deficiency may lead to villous atrophy, intestinal inflammation and worsening malabsorption, with resultant failure to respond to pancreatic enzymes alone.

EPI in cats is usually due to chronic pancreatitis, and many cats have concurrent diseases (inflammatory bowel disease, cholangiohepatitis, and diabetes mellitus) that may require additional treatment.

Serum folate concentrations may be decreased in the case of concurrent small intestinal disease resulting in malabsorption of folate. This differs from the situation in canine EPI, where folate levels are often increased due to secondary small intestinal bacterial overgrowth. Cats have however normally high levels of bacteria in their small intestine and bacterial overgrowth is not a recognized syndrome in this species *(Johnston et al, 1993; 2001)*.

> Treatment

Enzyme supplementation

Adequate management of cats with clinical EPI depends on long term enzyme replacement and dietary manipulation.

Addition of exogenous pancreatic enzymes to the food is essential for resolution of clinical signs.

Synthetic dried pancreatic extracts are available in several forms.
Powdered pancreatic extracts are most commonly used due to their effectiveness and ease of use. Tablets, capsules and enteric-coated tablets are not recommended since they are usually less effective *(Steiner & Williams, 2005)*. The powdered extract should be mixed within the food immediately prior to feeding (0.5 to 1 tsp per meal twice daily); pre-incubating the enzymes with the food or concurrent antacid therapy are unnecessary *(Steiner & Williams, 1999)*. The amount should be adjusted based on its efficacy in resolving clinical signs; it is common practice to start with the higher dosage, after which it can be gradually decreased to the smallest dose that maintains remission.

It is important that dietary management and enzyme supplementation are kept constant, since variation and especially the consumption of a non-supplemented meal can cause a return of the diarrhea.

Raw chopped pancreas (30-90 g per meal twice daily) may be used as an alternative and can be very effective. It can be stored frozen for at least three months, but is generally less convenient to use and has the potential for causing gastrointestinal infections (e.g., *Salmonella, Campylobacter*). Bovine pancreas is safest, since there is always a risk of transmitting Aujeszky's disease when using

porcine extracts. Raw chopped pancreas can however be a solution when the cat develops aversion to the powdered extract.

Vitamin supplementation

Cats with EPI almost always have marked depletion of body cobalamin stores and severely decreased serum cobalamin concentrations. In addition, many cats with EPI have concurrent small intestinal disease which further impairs cobalamin absorption. Supplementation is by parenteral cobalamin (250-500 µg/kg subcutaneously every two or three weeks) to maintain normal serum concentrations of cobalamin *(Ruaux et al, 2005)*.

Cats with EPI with or without concurrent small intestinal disease may also have low serum folate concentrations and should be treated with oral folate at 400 µg once daily for 2-4 weeks or longer, until serum levels have normalized.

Malabsorption of fat-soluble vitamins (vitamin A, D, E and K) may occur in EPI, although the clinical importance in cats is unknown. Cats with evidence of a coagulopathy should be supplemented with vitamin K. It may also be helpful to increase dietary vitamin E levels because of its antioxidant function, especially in cats that do not respond to enzymes and supportive management alone and especially in cats with concurrent diseases.

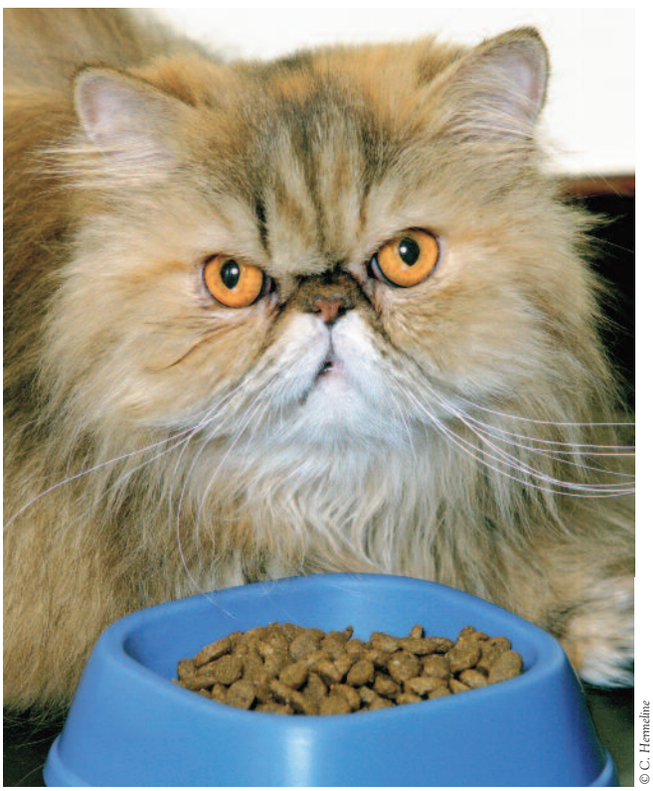
Management of concurrent diabetes mellitus

Cats with chronic pancreatitis resulting in EPI as well as diabetes mellitus will need insulin treatment in addition to management of the EPI.

> Nutritional management (Table 10)

High digestibility is a mainstay of dietary management, since it requires less gastric, pancreatic, biliary and intestinal secretions for digestion, and thus facilitates absorption in the upper small intestine. Dietary modification may be required in cats that present with severe weight loss and protein-calorie malnutrition, and also in cats that do not respond adequately to this management.

Cats with EPI should be fed a highly digestible, good quality and energy dense diet, with an appropriate pancreatic enzyme supplement mixed into it (Simpson, 2005).



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Protein

The diet during early refeeding should contain higher protein levels, since many patients with EPI suffer from protein-calorie malnutrition. If response to treatment is poor, concurrent intestinal disease has to be investigated further, e.g. by a dietary trial with an antigen restricted diet. A diet based on rice and soy protein hydrolysate proved to be beneficial in the management of canine EPI *(Biourge & Fontaine, 2004)*. This strategy remains to be validated in cats.

Fat

Fat malabsorption and steatorrhea are major signs in patients with EPI *(Williams, 2005)*. However, fat restriction is of questionable benefit for cats, especially since this species needs a relatively high-fat diet. In addition, there is evidence that higher fat diets promote better digestibility *(Suzuki et al, 1999)*. The cause is unclear, but it may be related to improved preservation of exogenous pancreatic enzymes, particularly lipase. Furthermore, a higher fat and thus more energy dense diet will help an animal in poor body condition to regain its optimal body weight faster. Dietary fat levels can therefore be within the normal range, but high digestibility is essential.

Fiber

Diets containing moderate amounts of fermentable fiber will help to improve GI health by its positive actions upon the mucosal barrier.

Carbohydrate

Cats are poorly adapted to handling carbohydrates, so excessive amounts should be avoided.

Trace elements and vitamins

The diet should contain high-normal concentrations of B-vitamins, since body stores are often depleted.

> Treatment failures

Reconfirm EPI

- Make sure the diagnosis is correct, and resubmit an fTLI.
- One should also ensure that serum cobalamin and folate concentrations are managed appropriately.

Inadequate enzyme supplementation

Ensure that the enzyme supplement being fed is appropriate (non-enteric coated powder), not out-of-date, and fed at the right dose with each meal.

Small intestinal disease

Concurrent small intestinal disease may cause continued malabsorption despite adequate enzyme supplementation. Dietary modifications, e.g. to an antigen-restricted or protein hydrolysate diet, can help to evaluate for dietary intolerance/sensitivity. The diet should be fed exclusively, with added enzyme supplementation, for at least two to three weeks. If gastrointestinal signs resolve after the dietary trial, the cat should be challenged with components of its former diet in order to confirm a diagnosis of dietary intolerance/sensitivity.

If dietary modification is not effective, the cat should be investigated for structural intestinal disease (e.g. inflammatory bowel disease) with abdominal ultrasound and endoscopy with intestinal biopsy. Cats with concurrent inflammatory bowel disease usually can be successfully managed with oral prednisolone (*Steiner & Williams, 2005*).

Conclusion

Feline exocrine pancreatic disease, particularly acute pancreatitis, is more common than previously thought. It however requires a high level of clinical suspicion. Assay of serum fPLI combined with abdominal ultrasound is recommended for the diagnosis of pancreatitis, whereas a severely decreased serum fTLI concentration is diagnostic for EPI in the cat. In both pancreatitis and EPI, concurrent diseases should be assessed and addressed as necessary.

Provision of adequate calories and nutrients is essential in the management of cats with exocrine pancreatic disease. Supportive therapy is important to prevent complications and decrease mortality in acute pancreatitis, and early enteral feeding may be required in order to prevent secondary hepatic lipidosis. Cats with EPI will at least require dietary supplementation with pancreatic enzymes for resolution of clinical signs, and additional treatment with parenteral cobalamin is necessary in many cases.

Frequently asked questions about the dietary treatment of feline pancreatic diseases

Q	A
How should I feed a cat with acute pancreatitis?	Most cats with acute pancreatitis are anorexic, which puts them at risk of developing hepatic lipidosis. It is therefore important that they receive nutritional support at an early stage, provided they are not vomiting. In most cases this is done via an enteral feeding tube. Cats with intractable vomiting that do not respond to anti-emetic treatment may need parenteral nutrition.
Should cats with pancreatic disease be fed a fat-restricted diet?	There is no evidence that dietary fat levels play a role in feline pancreatic disease, nor that fat restriction improves the cat's response to treatment. In addition, cats require a relatively high-fat diet and need the calories from fat to improve their often poor body condition.
What are the dietary recommendations for cats with EPI?	It is best to divide daily intake in at least two or three meals to reduce dietary overload and osmotic diarrhea. Ensure you add the enzyme supplementation to each meal and mix thoroughly. The diet should have high diet palatability and energy density, contain normal levels of fat (which protects the enzymes, provides energy as well as palatability), adequate levels of high quality protein and contain some fermentable fiber.
Do I have to pre-incubate the food with the pancreatic enzymes before feeding it to a cat with EPI?	No, enzymes will only work in the right condition of pH and moisture, pre-incubation is therefore of no use but the enzymes must be carefully mixed with the food.
My cat doesn't like the powdered enzyme supplement. What else can I use?	You can try raw, chopped pancreas, which can be stored frozen for several months.

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Focus on:

Vitamin B_{12} (cobalamin)

Definition and origins

The anti-anemic qualities of calf liver were first discovered in 1925. They were linked to the existence of an "extrinsic dietary factor", which was only isolated mid-century. Given the name vitamin B_{12} or cobalamin, this substance is mainly found in animal products (fish, meat and offal). Whatever the source, vitamin B_{12} is always synthesized by microorganisms. It is very stable during the heat treatment of food products.

Formula

Vitamin B_{12} is the only vitamin to incorporate a mineral element in its chemical formula, namely cobalt.

The molecule's nucleus is a tetrapyrrole with a central cobalt atom, linked to 4 pyrrolic nitrogen atoms, 1 ribonucleotide and 1 anionic ligand (X). There are several types of cobalamin, depending on the nature of the ligand, including:

X = CN (cyanide): cyanocobalamin

X = CH3 (methyl): methylcobalamin

X = OH (hydroxyl): hydroxocobalamin

X = 5'dAd (5'deoxyadenosyl): adenosylcobalamin

In cats, cobalamin is mainly found in the form of hydroxocobalamin and adenosyl cobalamin.

Biological roles

Cobalamin plays an essential role in the synthesis of nucleic acids (in synergy with folic acid). A deficiency disrupts protein synthesis, especially for fast-regenerating tissues like hematopoietic tissue.

Risk of vitamin B_{12} deficiency in cats

A fall in the body's cobalamin reserves is seen in cats suffering from pancreatic or hepatic disease.

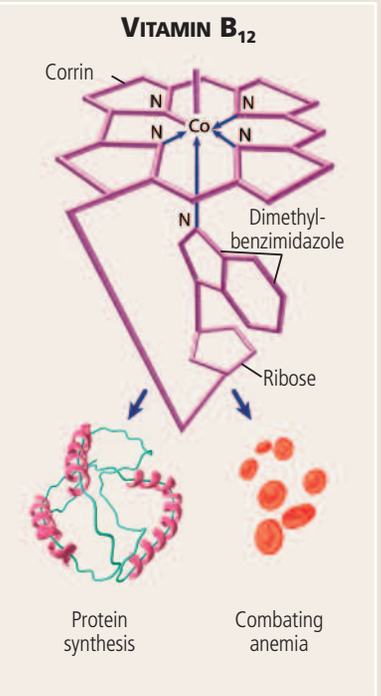
The depletion of reserves may be explained by chronic dysorexia or intestinal malabsorption reducing the quantity of cobalamin available to the animal. The deficiency may also be secondary to an insufficiency of intrinsic factor essential to the absorption of cobalamin. In cats, this glycoprotein is synthesized only by the pancreas, so pancreatic disease is a risk factor for deficiency. Any imbalance in the intestinal bacterial flora is also likely to reduce the absorption of cobalamin, as intestinal bacteria use vitamin B_{12} and may also form connections to intrinsic factor.

Cobalamin supplementation

Cats are not able to store large quantities of cobalamin in the body and quickly become deficient when their homeostasis is disrupted. Supplementation of vitamin B_{12} is essential in the event of pancreatic or hepatic disease. It is also indicated when an underlying intestinal disease is suspected. Because of the above assimilation problems, oral supplementation is ineffective, so parenteral administration is required.

The plasma concentration of cobalamin should be measured prior to initiating supplementation. It is generally recommended to first administer 250-500 µg/kg (on average 1000 µg / cat) SC. Depending on the cobalamin plasma concentration, this dose may be repeated every two to three weeks until the plasma cobalamin concentation normalizes. The benefit of long-term supplementation should be evaluated on the basis of the underlying disease and the response to treatment.

The potential toxicity of large cobalamin doses administered to cats has not been addressed in any publications.



Feline idiopathic hepatic lipidosis

Feline hepatic lipidosis is characterized by the excessive accumulation of hepatic lipids (triglycerides). When associated with other pathologies (e.g. diabetes mellitus, renal insufficiency, chronic enteritis) it is qualified as secondary, otherwise it is known as idiopathic hepatic lipdosis (IHL).

Epidemiology

Cats suffering from hepatic lipidosis are generally aged 4-12 years. No particular breed appears to be predisposed, but IHL is most common in neutered cats.

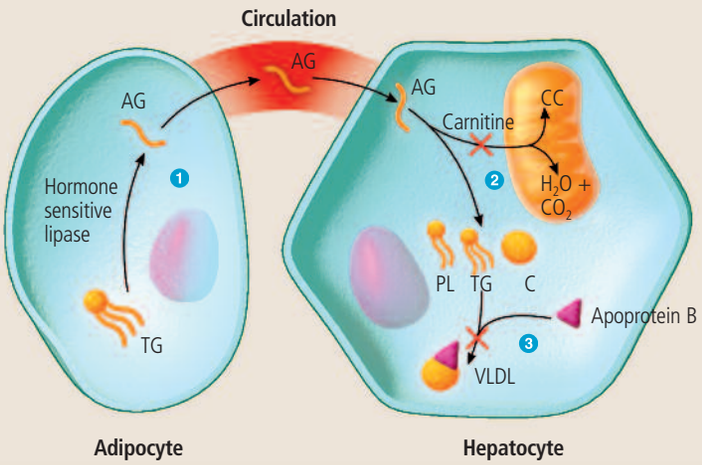
Most cases of IHL are observed after prolonged fasting (4-7 weeks) in cats that were previously obese, although most have already lost at least 30% of their body weight by the time they are taken to the veterinarian. The trigger for anorexia is yet to be identified. Stress factors that should be considered are moving, vacation, arrival of another cat or a baby in the home and poorly palatable food. IHL is said to be more common in cats that live in a group than in those that live alone. IHL "epidemics" are not uncommon in cat colonies in the event of a change of environment or food.

Pathophysiology

Contrary to the process in humans, obesity does not lead to hepatic lipidosis in cats. Some endocrine and/or nutritional imbalances – diabetes mellitus, hyperthyroidism, choline and essential amino acid deficiency, energy overdose during parenteral feeding and a severe diet – do however induce lipidosis in cats. In these situations, lipidosis is generally moderate and does not lead to clinical signs.

The pathophysiological mechanisms responsible for the accumulation of hepatic lipids during prolonged fasting in cats have not yet been fully described **(Figure 1)**. This observation constitutes a metabolic particularity in cats, as fasting and hepatic lipidosis are not associated in humans, dogs or rats. In cats, the lipids accumulate from the beginning of the period of fasting **(Figure 2)**, but the clinical [anorexia,

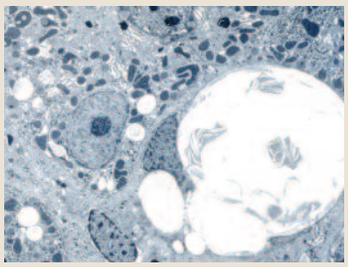
FIGURE 1 - PATHOPHYSIOLOGICAL MECHANISMS INVOLVED IN HEPATIC LIPIDOSIS



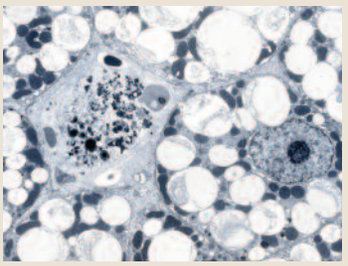
FA: fatty acid
C: cholesterol
K: ketones
PL: phospholipids
TG: triglycerides
VLDL: very low density lipoprotein

Metabolic alterations responsible for the accumulation of hepatic lipids might be the result of:
- *excessive mobilization of peripheral lipids (1)*
- *inhibition of fatty acid oxidation (2)*
- *inhibition of the synthesis and/or transport of lipoproteins (3).*

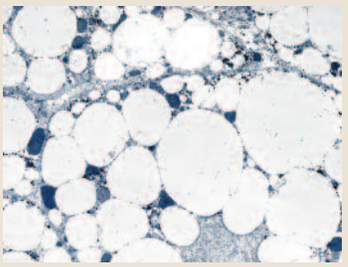
FIGURE 2 - HEPATIC BIOPSIES (AS SEEN WITH AN ELECTRONIC MICROSCOPE)



Obese cat. *Presence of small vacuoles in the hepatic parenchyma and of a larger vacuole in an endothelial cell.*



After 2 weeks of fasting: severe hepatic lipidosis.



After 6 weeks of fasting: very severe hepatic lipidosis. *The cell is filled and the nucleus is compressed by the accumulation of intracellular lipid vacuoles.*

It is important to note that such histological pictures can be observed in cats who do not present any clinical sign of hepatic lipidosis.

muscular atrophy] and biochemical signs [elevated hepatic enzymes and serum bilirubin **(Figure 3)**] only appear when the lipidosis becomes very severe.

A preliminary work suggests that cats are not able to efficiently save protein during prolonged fasting. It is therefore possible that the deficiency of one or more indispensable amino acids causes dysfunction in hepatic lipid metabolism, leading to pathological lipidosis.

These observations suggest prudence with respect to a low-calorie diet for cats. Veterinarians must advise owners to make sure their cat actually consumes the recommended food. In case of doubt, the measurement of alkaline phosphatase in the serum can be used as a marker of hepatic lipidosis **(Figure 4)**.

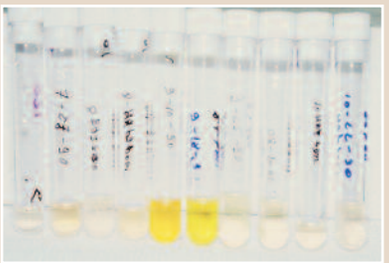
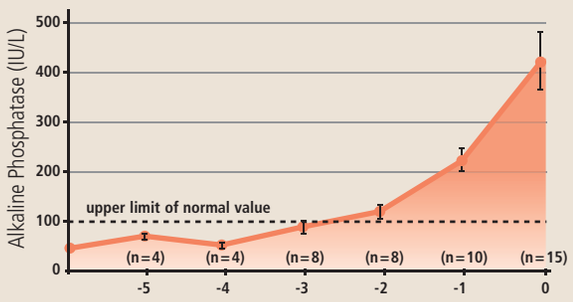
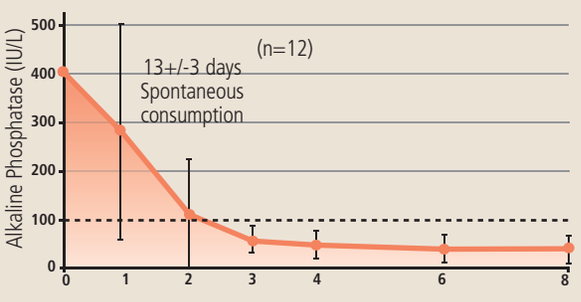


Figure 3 - Visible hyperbilirubinemia. *During the evolution of hepatic lipidosis, the color of the serum changes very quickly: the transformation happens about 3 weeks after alkaline phosphatase has started to increase.*

FIGURE 4 - SERUM CONCENTRATIONS OF ALKALINE PHOSPHATASE





4A - Before the appearance of hyperbilirubinemia (week 0) in anorectic cats. *The concentration of alkaline phosphatase is a marker of hepatic lipidosis.*

4B - After re-feeding of cats suffering from hepatic lipidosis. *The concentration of alkaline phosphatase improves dramatically after 2 weeks and returns to normal within 3 weeks after cats have started to eat again.*

Dietary recommendations

Aggressive nutritional support is the treatment of choice. Our own observations as well as those of other authors show that a highly digestible complete food that respects the following nutritional balances would appear to be appropriate:

- 30-50% calories from protein

- 35-50% calories from fat

- 20-30% calories from carbohydrate

Cats with IHL are glucose-intolerant and preparations rich in rapidly assimilated carbohydrates present a risk of hyperglycemia. In the event of hepatic encephalopathy, limiting the protein content to 20-25% of calories is recommended.

The supplementation of certain nutrients (choline, arginine, citrulline, taurine, thiamine, vitamin C and zinc) has been recommended for the nutritional treatment of IHL. The efficacy of these supplements has not been scientifically demonstrated.

A properly balanced nutritional diet will reduce the bilirubin and the serum hepatic enzymes within 1-2 weeks. They typically return to physiological levels within 4 weeks. Most cats accept food after 2-3 weeks of enteral feeding. The liver regains its normal histological structure within 4-8 weeks.

Feeding practice

The treatment of hepatic lipidosis demands constant attention of the veterinarian. It is not uncommon for the clinical signs to appear to worsen at the start of treatment. It is important to monitor the potassium concentration and reintroduce the cat to food very gradually.

Type of food

Cats with IHL require assisted feeding. A nasoesophageal enteral feeding tube is a cost-effective, rapid and safe way to administer liquid nutrition or wet food homogenized with water. Tube placement requires local anesthesia without expensive equipment. In our experience, it does not prevent cats from eating normally. If the food is not liquid enough, nutritional assistance may be provided via the placement of a gastric or esophageal enteral feeding tube.

It is vital that the cat continues to be fed through vomiting or diarrhea, which are both common during the first week. If the digestive problems are uncontrollable, temporary parenteral feeding may be initiated.

Rationing

During the first day of hospitalization, it is recommended to feed the cat four times at intervals of at least three hours and to limit the serving to 25 mL. Over the following days, increase the serving by multiples of 5 mL until the cat is consuming 60 kcal/kg body weight/day. This will generally be achieved within 5-7 days. Increasing the serving very gradually limits vomiting and diarrhea. After ten days, meal frequency should be reduced to three times per day. If given time to adapt, cats will comfortably tolerate up to 120 ml per serving.

Preventing food aversion

Cats are likely to refuse to eat a food they associate with digestive disorders (nausea, vomiting) that appear during the consumption period. This type of food aversion appears to be a major component in the anorexia associated with hepatic lipidosis.

Recommendations to reduce the risk of food aversion:

- Do not offer multiple types of food to confirm the anorexia
- Use exclusively a feeding tube throughout the period of assisted feeding during the first 10-15 days of treatment
- After 10-15 days of treatment, propose a diet that the cat has not consumed since it has been sick. Don't insist if the cat does not eat immediatly. Repeat the operation after 48 hours until the cat feels like eating spontaneously.

Conclusion

The prognosis of IHL has greatly improved since the recognition of the importance of nutritional support in its treatment. It is nevertheless more reserved when the hepatic lipidosis is complicated by another underlying disease (e.g. chronic gastroenteritis, chronic kidney disease etc.).

Feeding protocol during the first week of treatment	
• **Day 1:** - 25-50% of MER - 20-25 mL/serving, 4 servings/day	• **From day 5-7:** - Up to 100% of MER (60-80 kcal/kg) - Up to 120 mL/serving, 3-4 servings/day

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ABBREVIATIONS USED IN THIS CHAPTER

AST: arginine stimulation test
BID: twice daily
DM: diabetes mellitus
1DM: type 1 diabetes mellitus
2DM: type 2 diabetes mellitus
DMB: dry matter basis
GIP: glucose-dependent insulinotropic peptide, or gastric inhibitory polypeptide
GK: glucokinase
GLP-1: glucagon-like peptide-1
GLUT 1, 2 or 4: glucose transporter type 1, 2, or 4
GST: glucagon stimulation test
IAPP: islet amyloid polypeptide
IDDM: insulin-dependent diabetes mellitus
IGF-1: insulin-like growth factor 1
IL-1β: interleukin beta
IVGTT: intravenous glucose tolerance test
IST: insulin stimulation test
NEFA: non-esterified fatty acid
NIDDM: non-insulin-dependent diabetes mellitus
PPAR γ: peroxisome proliferator-activated receptor gamma
PUFA: polyunsaturated fatty acid
PUFA n-3: omega-3 polyunsaturated fatty acid
TDF: total dietary fiber
TFA: trans-fatty acid
TNF-α: tumor necrosis factor alpha

Feline diabetes mellitus: nutritional strategies

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Diabetes mellitus is a common endocrinopathy in cats. Its prevalence has risen over the last 30 years and on average reaches around 1 case per 200 cats. This increase may be directly related to the higher prevalence of obesity in cats. Feline diabetes shares many features of human type 2 diabetes (2DM) in respect to its pathophysiology, underlying risk factors and treatment strategies. General recommendations for feeding diabetic cats has changed over the last few years and now the focus is on diets relatively high in dietary protein and low in carbohydrate. It is clear that not all authors have the same understanding of the composition of high protein or low carbohydrate diets. As a general rule, these terms refer to a protein content (on DMB) of approximately 50% protein or more, and less than 15% carbohydrates. The values will be specified in the chapter when necessary. This high protein, low carbohydrate feeding regimen, combined with rigid and well supervised insulin therapy has resulted in a sharp increase in the remission rate of diabetes mellitus. The present chapter reviews the pathophysiology of feline diabetes and discusses treatment strategies, especially in light of the cats' specific nutrient requirements and the recommended use of high protein, low carbohydrate diets.

1 - Prevalence of feline diabetes mellitus

Diabetes mellitus (DM) is a common endocrinopathy in cats. Its prevalence has been reported to be in a range of approximately 1:400 to 1:100 *(Panciera et al, 1990; Rand et al, 1997)*. Based on the number of cases presented to veterinary teaching hospitals, a retrospective study showed that the prevalence of feline diabetes increased by a factor of more than 10 over the last 30 years. While in 1970, less than 1 case in 1000 cats was reported, this number increased to more than 12 cases per 1000 cats in 1999 *(Prahl et al, 2003; 2007)*. At the same time, however, the fatality rate decreased markedly from over 40% to less than 10% indicating that diabetic cats can be successfully treated. Part of this is certainly due to the better understanding of the pathophysiology of feline diabetes. Important risk factors for the development of the disease are age, gender, neuter status and obesity **(Table 1)**.

TABLE 1 - RISK FACTORS FOR THE DEVELOPMENT OF DIABETES MELLITUS IN CATS
(Nelson, 2005; Rand & Marshall, 2005; McCann et al, 2007)

Age	feline DM occurs more often in old cats
Gender	male cats are affected more often than female cats
Neutering	no independent risk factor, but neutered cats have higher risk to develop obesity
Obesity	increased risk of developing DM in obese cats
Physical activity	feline DM occurs more often in physically inactive cats
Breed	Burmese breed?
Drug treatment	megestrol acetate, glucocorticosteroids
Underlying disease	systemic infection, stomatitis

► Feline diabetes mellitus is associated with obesity

The latter factor is most likely responsible for today's increased prevalence of feline DM because feline obesity is directly associated with insulin resistance *(Scarlett et al, 1994; Hoenig, 2006a; 2007a; see also Pathophysiology of feline diabetes)*, and obesity in cats is much more common in today's cat population: at least 20% but more likely 35-40% of cats are considered overweight or obese *(Baral et al, 2003; Lund et al, 2005; Diez & Nguyen, 2006; German, 2006)*.

► Influence of age

Feline DM usually affects middle-aged and older cats with a sharp increase beyond the age of 7 years. Cats below 1 year of age are 50 times less likely to develop diabetes than cats beyond the age of 10 years *(Prahl et al, 2003)*.

► Influence of gender and neutering

Male cats seem to be at higher risk of developing diabetes than females. While this situation is similar in humans at least before the average age of menopause, the reason for the gender difference in feline diabetes is unknown at present. The difference seems unlikely to be directly related to the concentration of sexual hormones because most male cats are castrated, and because neutering is not an independent risk factor for the development of diabetes when controlling for body weight (BW) and age *(Prahl et al, 2003)*.

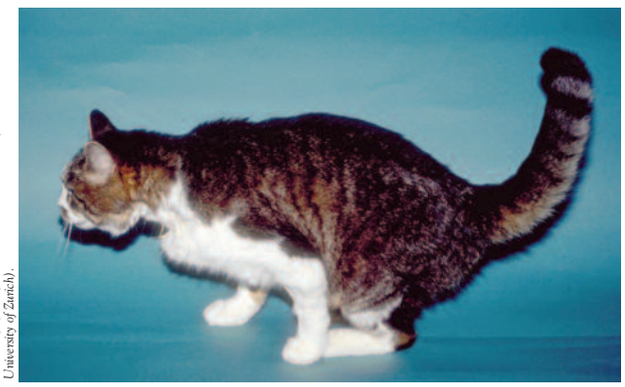
► Breed differences

Only a few studies have investigated the possible breed differences in the prevalence of feline diabetes. While a retrospective study in the USA provided no evidence for a higher prevalence in certain breeds of cats with purebred cats actually being at lower risk than mixed breed cats *(Prahl et al, 2003)*, some studies performed in Australia reported a higher prevalence among Burmese cats *(Rand et al, 1997)* **(Figure 1)**. A similar predisposition was reported from the United Kingdom *(UK; McCann et al, 2007)*. The author is unaware of further studies so that it remains unclear

Figure 1 - Burmese Cat.
An Australian study and a study from the UK report that Burmese cats have a genetic predisposition to develop diabetes mellitus (Rand et al, 1997; McCann et al, 2007). *However, global breed predispositions are still disputed.*

(Courtesy of: Prof. C. Reusch, Vetsuisse-Faculty University of Zurich)

Figure 2 - Obese (10 kg) 11-year old cat with DM. *The risk of diabetes mellitus is increased in obese cats.*



(Courtesy of: Prof. C. Reusch, Vetsuisse-Faculty University of Zurich).

Figure 3 - Neuropathy in a diabetic cat resulting in plantigrade stance. *A plantigrade stance is a typical clinical sign in indicating diabetic neuropathy.*

whether the reported over representation of Burmese cats in Australia and the UK is a global phenomenon.

2 - Clinical findings

(see also: Nelson, 2005)

Most diabetic cats are older than 7 years of age. The classical symptoms are osmotic polyuria which develops subsequent to hyperglycemia, secondary polydipsia and often polyphagia. A large proportion of diabetic cats are overweight at the time of diagnosis **(Figure 2)**. Loss of body weight, despite hyperphagia, may occur, but cats are usually still overweight at the time of presentation. Diabetic cats are rarely emaciated when they are first presented to veterinarians.

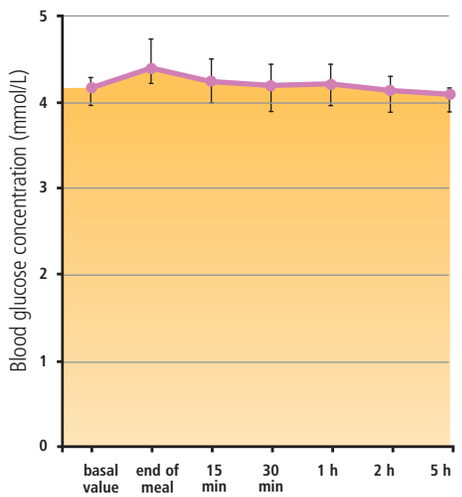
Due to dehydration, some diabetic cats may be lethargic. Diabetic neuropathy can lead to rear limb weakness and plantigrade gait **(Figure 3)**. Rear limb muscle atrophy may be present. Hepatic lipidosis can lead to hepatomegaly. As further complications, diabetic cats may suffer from infection such as stomatitis or cystitis.

3 - Specifics of feline metabolism

► Adaptation to a carnivorous diet

The cat is a true carnivore which distinguishes it clearly from the omnivorous dog. The natural diet of wild felids, e.g. mice, contains approximately 70-80% water. On a dry matter basis (on DMB), it contains about 55-60% of protein, 35% of fat, but less than 10% carbohydrate. This is very different from many commonly used commercial dry cat

FIGURE 4A - LACK OF POSTPRANDIAL HYPERGLYCEMIA IN CATS FED A HIGH PROTEIN DIET (54% PROTEIN AND 8% CARBOHYDRATE ON DMB)



After 24h of fasting, cats were given access to a test meal corresponding to 50% of their normal daily intake. The test meal was offered for 10 minutes during which time all food offered was consumed. The blood glucose concentration in 10 healthy experimental cats just before and after presentation of the test meal is shown.

foods which contain a much higher percentage of carbohydrates, mainly represented by starch from cereals, even if a high digestible dry catfood should not contain more than 40% carbohydrates on DMB. Cats fed a high protein diet (54% on DMB) did not show postprandial hyperglycemia *(Martin & Rand, 1999)* (see also **Figure 4 A & B**), unless relatively high amounts of simple sugars were added **(Figure 4 B)**. This may be one of several reasons why diets high in protein, i.e. near-natural diets, have beneficial effects in controlling nutrient metabolism in diabetic cats (see below).

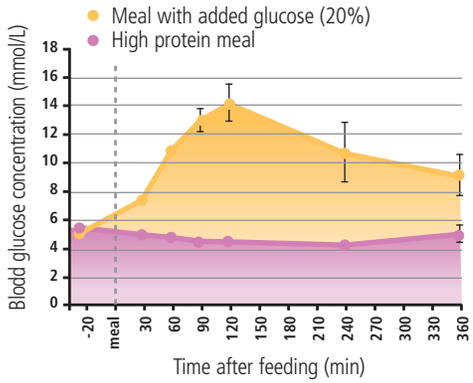
Cats have a generally high demand for essential amino acids. Arginine and taurine are essential in cats. It has been argued that taurine deficiency may be a causal factor contributing to DM. However the potential usefulness of taurine to prevent or reduce diabetic retinopathy or neuropathy (reviewed in *Franconi et al, 2006*) should not be taken as evidence for a causal relationship. Currently no experimental evidence is available that would suggest such a link in cats.

► Intensive gluconeogenesis

In cats, gluconeogenesis from amino acids is not downregulated even if protein intake is deficient *(Rogers et al, 1977)*.

The activity of gluconeogenic enzymes is much higher in cats than in dogs *(Washizu et al, 1998; Washizu et al, 1999; Takeguchi et al, 2005)*. On the other hand, cats seem to be deficient in hepatic glucokinase (GK) function due to low hepatic GK expression or enzymatic activity *(Washizu et al, 1999; Schermerhorn, 2005; Tanaka et al, 2005; but see section on pancreatic glucose sensing in cats via GK)*. However, regulation of GK activity in cats seems to differ from other species because cats have a very low activity in GK regulating protein *(Schermerhorn, 2005)* which in other species would be associated with high GK activity. The activity of other glycolytic key enzymes, including hexokinase which can perhaps partly compensate for low GK activity, is higher in cats than in dogs *(Washizu et al, 1999)*.

FIGURE 4B - INFLUENCE OF THE DIET ON POSTPRANDIAL HYPERGLYCEMIA IN 12 CATS



Postprandial hyperglycemia does not occur when cats are fed a high protein diet (54% protein and 8% carbohydrate on DMB), unless high amounts of glucose are added (20% per weight).

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As a direct effect of a low carbohydrate intake under natural feeding conditions, cats have developed a high capacity for intensive gluconeogenesis from glucogenic amino acids.

4 - Classification of diabetes mellitus

Different terminology has been used to describe the different forms of diabetes mellitus in humans and other species. The following terminology, based on the underlying pathophysiology, will be used throughout this chapter. Primary diabetes mellitus can be subdivided into type 1 diabetes mellitus (1DM) and type 2 diabetes (2DM) **(Table 2)**.

In humans, these were formerly also named juvenile and adult-onset diabetes, respectively. However, due to the massive increase in childhood obesity, up to 50% of diabetic children now suffer from 2DM compared to only 5-10% as observed previously. Therefore, the terms of juvenile or adult-onset diabetes should no longer be used.

Insulin-dependent (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) are purely descriptive terms which define the necessity of a diabetic human or animal to be treated with insulin to achieve metabolic control. The underlying pathophysiology is not reflected in these terms and will therefore not be used here.

The most common type of feline DM is pathophysiologically similar to 2DM in humans (for review, see *Henson & O'Brien, 2006*) and will be described in the following paragraph. Even though

Table 2 - Classification of feline diabetes mellitus

Type of DM			Occurrence in cats	Major defects
Primary DM	Type 1 DM (1DM)		rare	autoimmune mediated destruction of pancreatic beta-cells
	Type 2 DM (2DM)		at least 90% of cases	disturbed beta-cell function insulin resistance pancreatic islet amyloid
Other causes of DM (formerly called secondary DM)	Antagonistic disease	Infection	approx. 10% of cases	insulin resistance
		Pancreatitis, pancreatic tumor		destruction of functional beta-cells
		Acromegaly		insulin antagonistic effect of GH
	Steroid-induced			e.g. cats treated with progesterone derivatives (megestrol acetate)

DM = diabetes mellitus GH = growth hormone

histological changes in pancreatic islets suggestive of a 1DM like syndrome have been described in cats *(Nakayama et al, 1990)*, this seems to be an uncommon finding. Further, cats do not develop autoantibodies against beta-cell antigens or insulin *(Hoenig et al, 2000)*, arguing against an autoimmune-induced form of diabetes typical for 1DM. Finally, it is now recognized that the pathophysiology of 2DM also involves inflammatory, immune-mediated processes *(Donath et al, 2005)*. Therefore, the presence of inflammatory processes does not exclude a 2DM like pathophysiology.

5 - Introduction to feline diabetes mellitus

► Major defects in feline diabetes mellitus

Feline diabetes and human 2DM are pathophysiologically comparable endocrinopathies. When necessary for the understanding of underlying disturbances, reference to data from experimental models, mostly from rodents, will be made in this chapter.

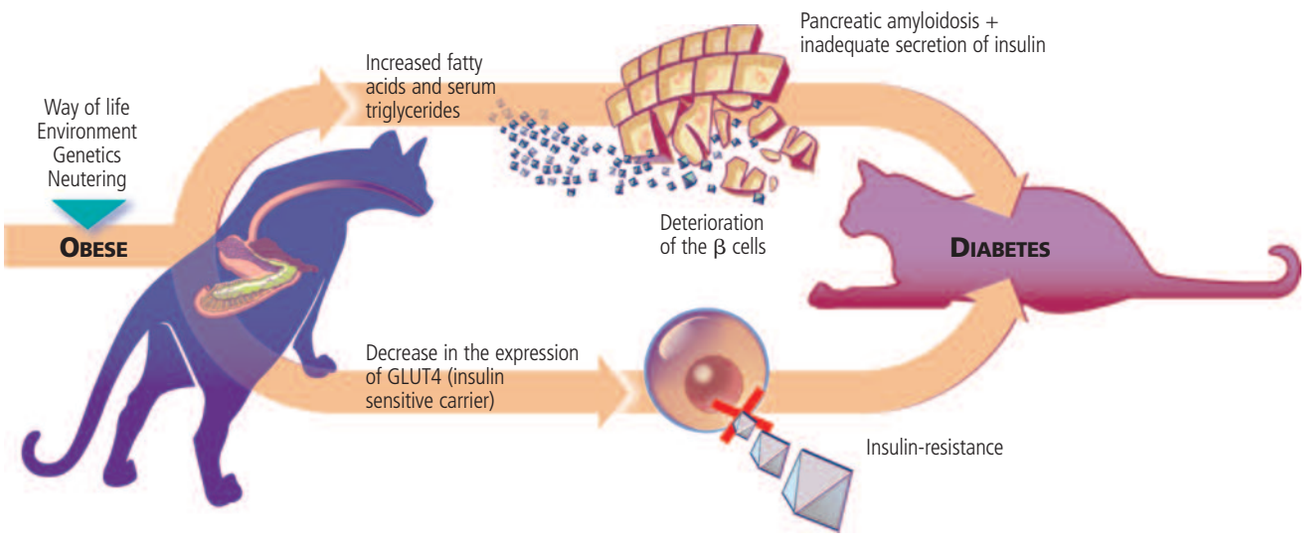
The major defects in diabetic cats and 2DM humans are:
- insulin resistance resulting in disturbed utilization of nutrients in insulin-sensitive tissues.
- disturbed pancreatic beta-cell function, resulting in the abnormal release and lack of insulin and amylin.
- deposition of pancreatic islet amyloid resulting from precipitation of amylin (islet amyloid polypeptide) **(Figure 5).**

Further defects will also be discussed in this paragraph. It is still debated whether the primary defect in 2DM or feline diabetes is disturbed beta-cell function or impaired insulin action. However, at the time of diagnosis both defects are usually present and contribute to the deterioration of the metabolic situation. Due to glucotoxicity, both defects also contribute to the self-perpetuation of the disease that usually can be observed.

► Genetics and feline diabetes mellitus

In human 2DM, genetics determining the predisposition of individuals to the development of 2DM are an area of intensive research. Several mutations and gene polymorphisms have been identified which are linked to an increased risk to develop 2DM in certain diabetic patients (for review, see e.g. *Barroso, 2005; Malecki, 2005*). However, it is clear that the massive increase in the occurrence of human 2DM is not the result of a major change in the genetic background but rather the result of life style changes such as abundance of food and lack of physical activity that make us more vulnerable to the development of obesity and subsequently 2DM. Hence, a previously beneficial genetic background may have deleterious effects in today's life.

FIGURE 5 - MAJOR PHYSIOLOGICAL DISTURBANCES IN FELINE DIABETES MELLITUS

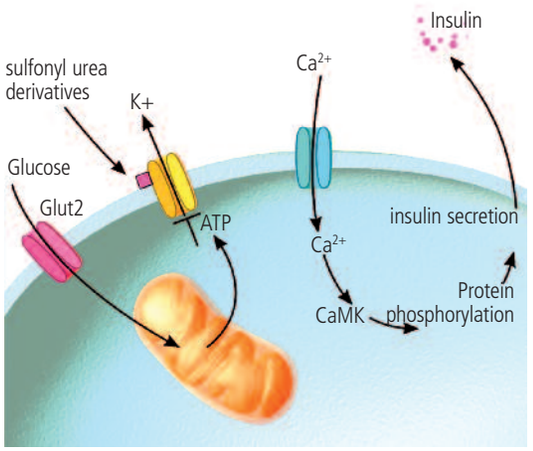


Studies on a possible role of genetic factors in the development of feline diabetes are far less advanced than in humans. Some cats may have an underlying predisposition for glucose intolerance because it was found that baseline insulin levels were higher while first phase insulin response and insulin sensitivity were lower in cats that developed a more severe reduction in insulin sensitivity when gaining body weight *(Appleton et al, 2001b)*. Similar findings were reported by *Wilkins et al (2004)*. Further, at least some studies suggest a breed disposition for the development of feline DM with Burmese cats being at higher risk *(Rand et al, 1997)*. Despite these indications for a possible role of genetic factors, nothing is known about the mode of inheritance and about the nature of the genes that could possibly be affected.

6 - Physiological aspects of nutrient handling

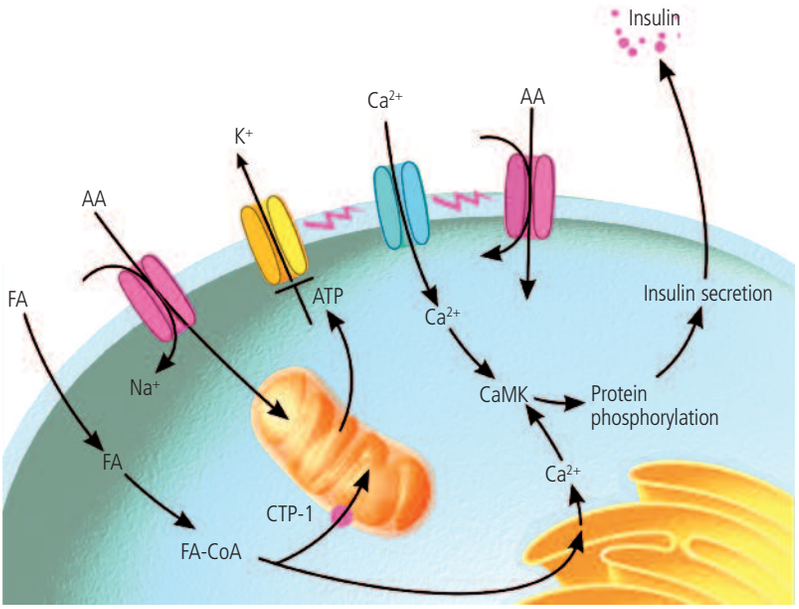
Before discussing details of the pathophysiology of feline diabetes, a few aspects of the physiological role of the key hormonal players will be briefly summarized. In healthy animals, pancreatic insulin secretion is controlled mainly by nutrients **(Figures 6 & 7)**. Insulin action in target tissues is mediated by the insulin receptor. Binding of insulin to its receptor activates the receptor intrinsic tyrosine kinase which then triggers rapid effects (e.g., translocation of the insulin-sensitive glucose transporter GLUT4 and modification of the activity of metabolic enzymes) and delayed effects relying on influences on gene transcription. The latter are mediated by the transcription factor peroxisome proliferator-activated receptor γ (PPARγ). This transcription factor is targeted by the antidiabetic drugs thiazolidinediones which increase insulin sensitivity.

FIGURE 6 - REGULATION OF INSULIN SECRETION BY GLUCOSE IN PANCREATIC BETA-CELLS



Glucose is taken up by the beta-cells via the GLUT2 glucose transporter and subjected to metabolism via glycolysis and the Krebs cycle in mitochondria. Adenosine triphosphate (ATP) leads to closure of ATP-sensitive K+ channels which are also the target structures for sulfonylurea drugs. The resulting depolarization opens voltage-sensitive Ca^{2+} channels, Ca^{2+} influx leads to activation of Ca^{2+} dependent kinases (CaMK) and finally secretion of insulin.

FIGURE 7 - REGULATION OF INSULIN SECRETION BY AMINO ACIDS AND FATTY ACIDS IN PANCREATIC BETA-CELLS



Metabolism of amino acids (AA) and fatty acids (FA) results in the formation of ATP, similar to glucose metabolism ***(see Figure 6)****. Alternatively, some amino acids, e.g. arginine, cause direct depolarization (electrogenic transport) of the beta-cell membrane and subsequent Ca^{2+} influx. Activated fatty acids (FA-CoA) can also release Ca^{2+} from intracellular Ca^{2+} stores.*
CPT-1: carnitine palmitoyl transferase-1

► Pancreatic glucose sensing in cats

Cats given intravenous or peroral glucose loads exhibit a strong increase in insulin secretion. Similarly, intravenous administration of amino acids, such as arginine, increases insulin secretion in cats. Under natural feeding conditions, nutrient induced insulin release seems to be very efficient because postprandial hyperglycemia is absent in cats fed a high protein diet **(Figure 4)**. However, the relative contribution of amino acids versus glucose in respect to the meal induced increase in circulating insulin levels is less clear. In recent years, the nutrient sensing machinery in the feline pancreas has been partly elucidated *(Schermerhorn, 2006)*. Despite the low activity of hepatic glucokinase (GK), pancreatic GK is present in cats and its activity seems to be comparable to other species. GK is one of the main components of the glucose sensing mechanism *(Schuit et al, 2001)*. Other essential components such as subunits of ATP-sensitive K+ channels **(Figures 6 & 7)**, Kir6.2 and SUR1, have also been characterized in cats *(Schermerhorn, 2006)*.

► Potentiation of nutrient-stimulated insulin secretion by incretins

Nutrient-stimulated insulin secretion is potentiated by incretin hormones, the most important being glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP; formerly known as gastric inhibitory polypeptide). Incretins are defined as hormones that are released in response to nutrients and that potentiate nutrient-induced pancreatic insulin secretion. Due to incretin action, a given glucose load triggers a more pronounced insulin response when administered orally than parenterally (for review: *Drucker, 2001*).

In humans and laboratory rodents, GLP-1 is secreted in response to meal ingestion with blood levels rising postprandially. Part of GLP-1 secretion is due to a direct effect of luminal glucose on the ileal L-cells through a glucose sensing mechanism. It is believed, however, that nutrients also indirectly trigger the release of ileal GLP-1 because plasma GLP-1 levels rise within minutes after meal onset, i.e. long before any ingested nutrient might reach the ileum *(Drucker, 2001)*. GLP-1's potent insulinotropic effect is glucose-dependent and disappears at plasma glucose levels below approximately 4.5 mmol/l (80 mg/dL). Therefore, GLP-1 usually does not induce hypoglycemia. GLP-1 acts via a potentiation of glucose-induced insulin release, most likely by an interaction at the ATP-dependent K+-channel (see above; **Figure 6**), but also through effects directly involving the secretion of insulin granula.

GLP-1 also seems to stimulate insulin biosynthesis and the synthesis of the glucose sensing machinery, mainly the GLUT2 glucose transporter and glucokinase. Finally, GLP-1 also exerts trophic effects on beta-cells and its precursors, thereby stimulating beta-cell differentiation and proliferation. This is accompanied by an inhibition of beta-cell apoptosis which seems to play a major role in the development of human 2DM *(Donath et al, 2005)* and most likely feline DM.

Similar to amylin, GLP-1 has been shown to diminish glucagon release. This effect is glucose-dependent in that GLP-1 inhibits glucagon release at euglycemic or hyperglycemic levels but not at hypoglycemic levels when glucagon's effect to defeat hypoglycemia is necessary and important.

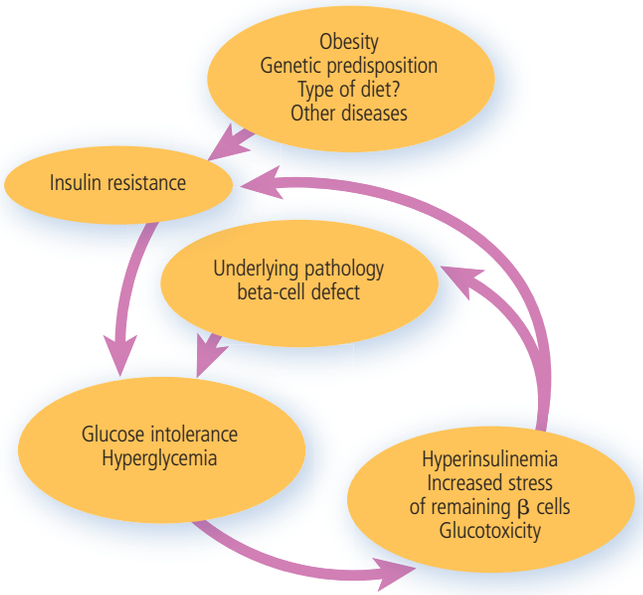
► Pancreatic amylin

Pancreatic beta-cells are also the major source for amylin which is co-synthesized and co-secreted with insulin in response to appropriate stimuli *(Lutz & Rand, 1996)*. The lack of amylin and its metabolic effects may play a role in the development of human 2DM and feline DM. These effects are unrelated to the propensity of human and feline amylin to form amyloid deposits which is another important contributing factor to feline DM (see below; *O'Brien, 2002*). At least three hormonal effects of amylin are of physiological relevance and contribute to the regulation of nutrient metabolism:

- inhibition of food intake *(Lutz, 2005)*
- modulation of pancreatic glucagon release by reducing excessive postprandial hyperglycemia (*Edelman & Weyer, 2002*)
- regulation of gastric emptying (*Edelman & Weyer, 2002*).

It should be mentioned that none of these effects has so far been confirmed in cats but their physiological relevance has clearly been shown in both humans and rodents. However, a preliminary study in healthy cats has shown that amylin may reduce circulating glucagon levels in cats (*Furrer et al, 2005*) (see also below and **Figure 16**). In humans, the amylin analogue pramlintide (Symlin^{R}) is now an approved adjunct treatment to insulin for diabetic patients for its effects to reduce glucagon secretion and to inhibit gastric emptying.

FIGURE 8 - THE VICIOUS CIRCLE OF INSULIN RESISTANCE, DEFECT IN BETA-CELL FUNCTION AND GLUCOTOXICITY, THAT EVENTUALLY LEADS TO BETA-CELL EXHAUSTION AND OVERT DM



Insulin resistance, which can be caused by obesity or genetic predisposition, and possibly beta-cell defects, that cause reduced insulin secretory capacity, lead to glucose intolerance and subsequently hyperglycemia. This causes an increased secretory demand on the remaining beta-cells. Further, glucotoxicity progressively disturbs beta-cell function and promotes insulin resistance. Eventually, the pancreatic beta-cells will fail to produce sufficient amounts of insulin leading to overt DM.

7 - Pathophysiology of feline diabetes mellitus

► Insulin resistance in feline diabetes mellitus

One of the two major metabolic hallmarks of human 2DM and feline DM, next to disturbed pancreatic beta-cell function, is insulin resistance. Insulin resistance, or lower than normal insulin sensitivity, is characterized by a reduced response of insulin target tissues to a given amount of insulin. This can be assessed via insulin-sensitive glucose uptake which is markedly reduced in insulin resistant individuals. While oversecretion of insulin may compensate at least partly for insulin resistance, measurable glucose intolerance or overt hyperglycemia will develop once hyperinsulinemia cannot be sustained, or when maintained stress on beta-cells leads to their exhaustion **(Figure 8)**.

> Tests to assess insulin sensitivity

The classical clinical tests to assess insulin sensitivity and secretion are the intravenous glucose tolerance test (IVGTT; *O'Brien et al, 1985; Appleton et al, 2001a,b*) or the insulin sensitivity test (IST; *Feldhahn et al, 1999; Appleton et al, 2001a,b*). In the IVGTT, the increase in blood glucose and insulin concentrations are measured following an intravenous glucose bolus. Reported upper limits of the normal range for glucose half-life in plasma (glucose T1/2) in healthy cats are approximately 75-80 min *(Lutz and Rand, 1996; Appleton et al, 2001a,b)*. In the IST, the glucose-lowering effect of insulin is assessed directly *(Appleton et al, 2001a,b)*.

Glucose intolerant "pre-diabetic" and diabetic cats typically present with higher glucose concentrations in IVGTTs and with glucose T1/2 that is prolonged. Fasting insulin levels seem to be more variable because they have been reported to be elevated in some studies *(e.g., Nelson et al, 1990)* but not in others *(e.g., Lutz & Rand, 1996)*.

> Mechanisms for insulin resistance

Impaired glucose tolerance in diabetic cats is the result of a reduced insulin response *(O'Brien et al, 1985)* and reduced insulin sensitivity. Insulin sensitivity in diabetic cats is approximately 6 times lower than in healthy cats *(Feldhahn et al, 1999)*. The exact underlying mechanisms for insulin resistance in human 2DM and in feline DM are still unknown *(Reaven, 2005; Reusch et al, 2006b)*. Similar to humans, the major cause of insulin resistance in cats is obesity and physical inactivity. Insulin sensitivity in obese cats is markedly reduced compared to lean control animals (see below).

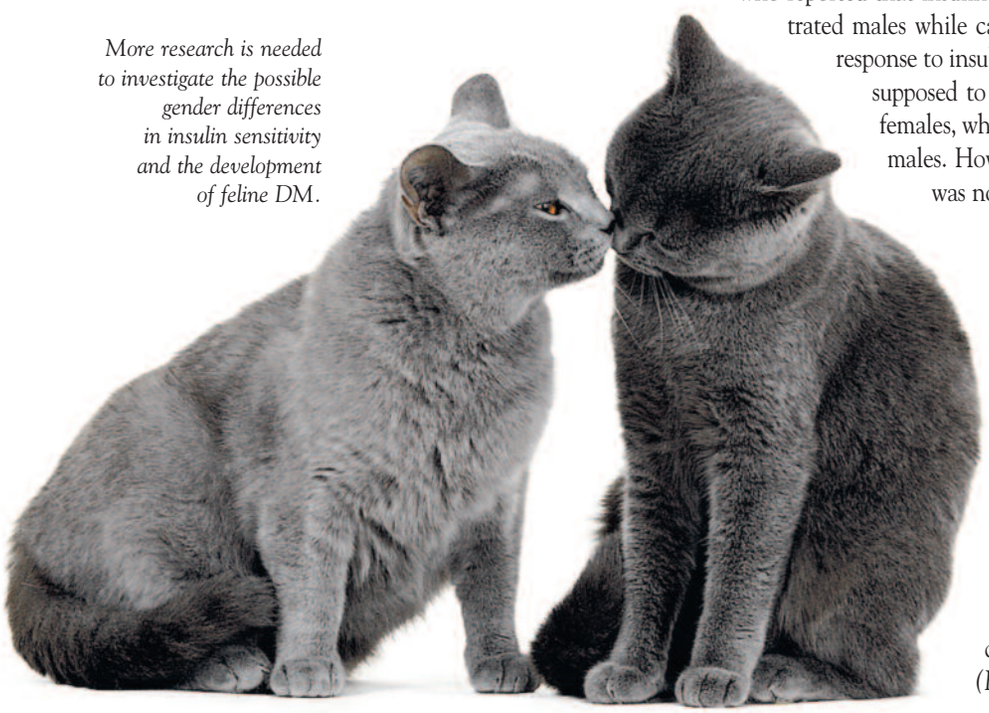
> Factors contributing to insulin resistance

Genetic causes of receptor or post-receptor defects have not been analyzed in detail in cats, but some molecular tools have become available lately that will allow us to study some of the underlying mechanisms of peripheral insulin resistance in more detail. Most attention has been drawn to glucose transporters in insulin-sensitive tissues and to metabolically active cytokines released from adipose tissue *(e.g., Brennan et al, 2004; Hoenig et al, 2007a; Zini et al, 2006)*.

Whether there is a systemic **difference in insulin sensitivity between male and female cats** is less clear. On the one hand, it has been reported that male cats have lower insulin sensitivity and higher baseline insulin concentrations than female cats *(Appleton et al, 2001a; Rand & Marshall, 2005)*. The latter study was performed in lean animals which were fed a diet relatively high in carbohydrate. However, all animals, males and females, were castrated at the time of study. Therefore, it is unlikely that direct effects of sexual hormones can explain the difference in insulin sensitivity. Either early effects of sexual hormones, acting before the time of castration, or indirect effects of sexual hormones may account for these differences.

On the other hand, **obesity** is well recognized as the main risk factor to induce insulin resistance, and relative body weight (BW) gain after castration appears to occur more rapidly in females than in males *(Martin & Siliart, 2005)*. This somehow contrasts to a study by Hoenig et al *(2007b)* who reported that insulin leads to increased glucose oxidation in obese castrated males while castrated females maintain greater fat oxidation in response to insulin. This metabolic gender difference was therefore supposed to favor more rapid fat accumulation in males than females, which may explain the greater risk of DM in neutered males. However, the same authors also reported that gender was not an independent risk factor in a study comparing glucose kinetics parameters between lean and obese cats *(Hoenig et al, 2007a,b)*.

More research is needed to investigate the possible gender differences in insulin sensitivity and the development of feline DM.



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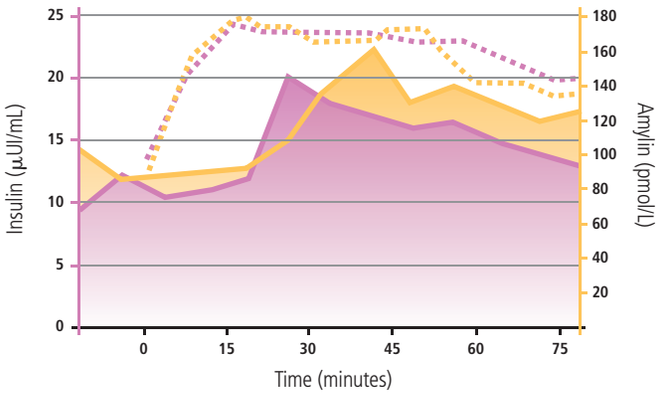
Other causes of insulin resistance include insulin antagonistic hormones, e.g. **glucocorticosteroids and progestins**, which directly counteract insulin action. Further, at least in other species, glucocorticosteroids increase food intake and may therefore contribute to the development of obesity. Presumably, they have similar effects in cats. Hyperthyroidism and growth hormone excess (acromegaly) have also been shown to reduce glucose tolerance, possibly due to the induction of peripheral insulin resistance *(Hoenig & Ferguson, 1989; Feldman & Nelson, 2004)*.

FIGURE 9 - PLASMA AMYLIN AND PLASMA INSULIN CONCENTRATIONS IN CATS WITH NORMAL AND DISTURBED GLUCOSE TOLERANCE



Glucose (1 g/kg BW) was infused intravenously and the plasma concentrations of amylin and insulin were determined by radioimmunoassay. Despite unchanged baseline amylin and insulin concentrations, the overall beta-cell secretory capacity is clearly reduced in cats with disturbed glucose tolerance. Glucose tolerant cats had glucose T1/2 below 80 min. Glucose intolerant cats had glucose T1/2 above 80 min. (See also **Figure 22***).*

► Disturbed pancreatic beta-cell function

The second major hallmark of feline diabetes is disturbed beta-cell function. Typical defects are a markedly reduced or missing first phase insulin secretion and a delayed onset of second phase insulin release which mainly relies on insulin synthesis. Even though the baseline insulin concentration may be unchanged, the overall insulin secretory capacity is clearly reduced in diabetic cats **(Figure 9)**. In most cases, the underlying defect of disturbed beta-cell function at the molecular level is completely unknown.

Because insulin and amylin are usually cosecreted, similar defects also refer to amylin secretion **(Figure 9)**. However, early phases of feline DM seem to be associated with relative hyperamylinemia *(Lutz & Rand, 1996)*. It is currently unknown whether initial hypersecretion of amylin contributes to accelerated deposition of pancreatic islet amyloid (see below) or whether it may rather be regarded as an adaptive response to help control blood glucose due to amylin's metabolic effects such as inhibition of postprandial glucagon secretion (see below).

Once established, deficient insulin secretion leads to overt hyperglycemia. Sustained hyperglycemia then causes progressive disruption of normal beta-cell function. This phenomenon is called glucotoxicity *(Prentki et al, 2002)* and will be discussed below. Further complication results from inflammatory events which are now considered an important feature in the pathophysiological sequence leading to beta-cell insufficiency in 2DM like syndromes (*Donath et al, 2005*; see below).

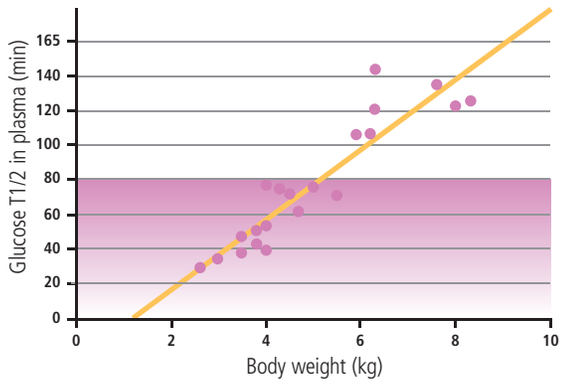
► Obesity and the development of diabetes mellitus

The higher prevalence of feline DM in recent years is most likely caused by the rise in obesity in our cat population. Obesity considerably increases the risk to become diabetic about 4 times compared to lean cats, and at least 60% of obese cats seem to become diabetic over time *(Hoenig, 2006a,b)*. Further, and similar to humans, the degree of overweight seems to be directly linked to the increased risk of developing DM. In studies by Scarlett and coworkers

FIGURE 10 - BODY CONDITION SCORING IN CATS

Scoring	Characteristics
Emaciated: 1 	- Ribs, spine, pelvic bones easily visible (short hair) - Obvious loss of muscle mass - No palpable fat on rib cage
Thin: 2 	- Ribs, spine, pelvic bones visible - Obvious abdominal tuck (waist) - Minimal abdominal fat
Ideal: 3 	- Ribs, spine not visible, but easly palpable - Obvious abdominal tuck (waist) - Few abdominal fat
Overweight: 4 	- Ribs, spine not easly palpated - Abdominal tuck (waist) absent - Obvious abdominal distention
Obese: 5 	- Massive thoracic, spinal and abdominal fat deposits - Massive abdominal distention

Figure 11 - Association between glucose tolerance (assessed by glucose half-life in an IVGTT) and body weight in clinically healthy cats



The upper limit of normal was a glucose T1/2 of less than 80 min. Glucose T1/2 was significantly higher in overweight compared to normal weight cats (Lutz & Rand, 1995).

(Scarlett et al, 1994; Scarlett & Donoghue, 1998), overweight cats were 2.2 times as likely, and obese cats were 6 times as likely to be diabetic than optimal weight cats. Different scoring systems have been described but the most common scoring systems used are the 5-point system **(Figure 10)** (where a BCS of 3 is considered ideal) or the 9-point system (where a BCS of 5 is considered ideal); (see Obesity chapter).Therefore, any increase in body weight above normal should be avoided to reduce the risk of cats to develop DM *(Scarlett & Donoghue, 1998)*.

Once obesity is established, the heat production and hence the energy requirement, is reduced in obese cats when corrected for metabolic BW *(Hoenig et al, 2006c; 2007a,b)*. This will help to perpetuate obesity unless food intake is rigorously adjusted. In another study *(Nguyen et al, 2004a,b)*, it was reported that total energy expenditure is unchanged in neutered or intact cats of different BW if values are corrected for metabolic BW or for lean body mass. However, *Nguyen et al* (2004a,b) used a different technique to determine total energy expenditure than *Hoenig et al* (2007b) which may explain the different outcome.

> Obesity and insulin resistance

A number of studies have shown that obese cats face a high risk of developing DM because they have a higher baseline insulin concentration, show an abnormal insulin secretion pattern in IVGTT and euglycemic hyperinsulinemic clamp studies, and are insulin resistant *(Biourge et al, 1997; Scarlett & Donoghue, 1998; Appleton et al, 2001b; Hoenig et al, 2002; 2007b)*. Depending on the experimental technique and the degree of obesity, insulin sensitivity was reported to be reduced by 50 to over 80%. Figure 11 shows one example of how glucose tolerance in cats is affected by body weight (see also **Figure 13**). A cat was considered having abnormal glucose tolerance when glucose half-life was above 80 min in an IVGTT *(Lutz & Rand, 1995)*.

Insulin resistance seems to be associated with a decreased expression in the insulin-sensitive glucose transporter GLUT4, while the expression of GLUT1, which mediates insulin-independent glucose transport, is unaltered *(Brennan et al, 2004)*. This effect occurs early in the development of obesity, before overt glucose intolerance is observed. Interestingly, at basal insulin levels glucose utilization seems to be normal in obese cats. However, in a stimulated state (e.g. by IVGTT), not only insulin sensitivity but also glucose effectiveness, that is, the ability of glucose to promote its own utilization at baseline insulin levels, was reduced by approximately 50% *(Appleton et al, 2001b; Hoenig et al, 2006c; 2007a,b)*.

> Obesity and lipid metabolism

Obese cats have higher baseline concentrations of non-esterified fatty acids (NEFA) than lean cats. This may reflect in part a general change from glucose to fat metabolism in skeletal muscle of obese cats. Lower activity of lipoprotein lipase in body fat combined with higher activity of lipoprotein lipase and of hormone-sensitive lipase in the muscle in obese cats may favor the redistribution of fatty acids from adipose tissue to skeletal muscle *(Hoenig et al, 2006b; 2007b)*. The lipid accumulation in skeletal muscle seen in obese cats could then result in a lower insulin sensitivity because changes in lipid metabolism lead to altered insulin signaling and affect GLUT4 expression *(Wilkins et al, 2004; Brennan et al, 2004)*. In obese cats, both intramyocellular and extramyocellular lipids increase. Whether and how elevated intramyocellular lipids affect GLUT4 expression, and hence insulin sensitivity directly remains to be study. All in all, general obesity clearly favors the development of insulin resistance in muscle *(Wilkins et al, 2004)*.

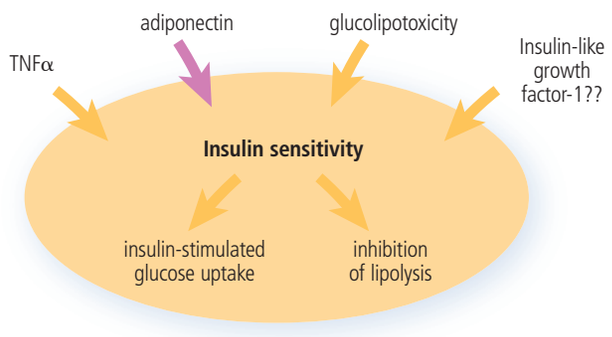
The link between obesity and the changes in metabolic handling of nutrients in adipose and skeletal muscle tissue may be represented by differential expression of tumor necrosis factor-alpha (TNFα). TNFα reduces lipoprotein lipase, and a study has shown that TNFα is upregulated in adipocytes, but downregulated in skeletal muscle of obese cats *(Hoenig et al, 2006b)*.

TNFα is one of the numerous hormones and cytokines that are released by adipose tissue and that are now considered of pivotal importance for regulating nutrient handling (for review, see *Lazar, 2005*). All endocrine factors released from adipose tissue are collectively called adipokines. TNFα in particular is not only produced by adipocytes, but also by macrophages. In fact, obesity is considered a low grade inflammatory disease of adipose tissue. Many cytokines released from adipose tissue induce peripheral insulin resistance. For example, TNFα, which is among the best investigated, interferes with insulin signalling and causes insulin resistance.

Adiponectin is the only adipokine known which is inversely related to the amount of body adiposity (for review, see *Ahima, 2005*). Adiponectin improves insulin sensitivity by increasing fatty acid oxidation, reducing hepatic gluconeogenesis, and by inhibiting inflammatory responses. Because its concentration is reduced in obesity, it combines with increased release of TNFα to promote insulin resistance. However, it has to be pointed out that none of these effects have been investigated in detail in cats (see also **Figure 12**). It was also claimed that elevated levels of insulin-like growth factor-1 (IGF-1) may constitute the link between obesity and insulin resistance *(Leray et al, 2006)*. However, this has never been shown in cats and the data in other species are also conflicting. *Reusch et al* (2006a) have shown that diabetic cats have lower IGF-1 levels which increase in response to insulin treatment.

Despite many similarities between human 2DM and feline DM, it should be highlighted that there may also be some distinct differences. One of them being that in cats, insulin suppresses the serum concentration of NEFA's more in obese than in lean cats. This appears to be due to an increased sensitivity to insulin-induced fatty acid uptake *(Hoenig et al, 2003)*. Further, obese cats seem to accumulate similar amounts of subcutaneous and visceral fat. This may be of importance because in humans, visceral fat in particular has been associated with the metabolic derangements of obesity.

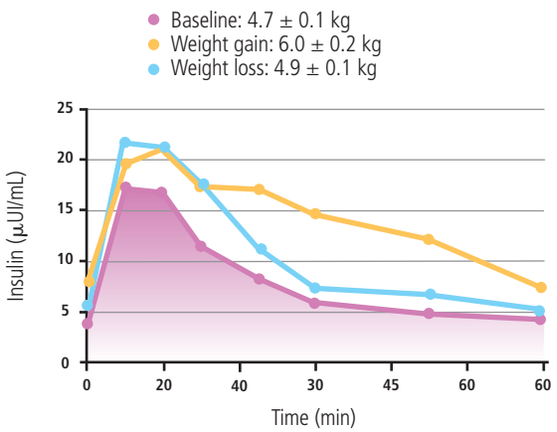
FIGURE 12 - INSULIN RESISTANCE



Tumor necrosis factor-alpha and glucolipotoxicity reduce insulin sensitivity in insulin target tissues (Rossetti et al, 1990; Hoenig et al, 2006), *resulting in reduced insulin-stimulated glucose uptake and decreased inhibition of lipolysis. Adiponectin increases insulin sensitivity* (Ahima, 2005). *Insulin-like growth factor-1 has been hypothesized to reduce insulin sensitivity, but data are conflicting* (Leray et al, 2006; Reusch et al, 2006).

FIGURE 13 - THE EFFECT OF BODY WEIGHT GAIN AND RECOVERY TO NORMAL BODY WEIGHT ON PLASMA INSULIN LEVELS

(Biourge et al, 1997)



Cats were tested with an IVGTT. 0.5 g/kg glucose was injected at t=0 min

> Reversibility of insulin resistance

Regarding the possible treatment outcome for diabetic cats, it is important to note that insulin resistance induced by obesity in cats is reversible after the correction of body weight **(Figure 13)** (*Biourge et al, 1997*). Hence, if diabetic cats are obese, lowering their body weight to normal should always be part of the therapy. In the course of the above mentioned study *(Biourge et al, 1997)*, cats were also exposed to a poorly palatable diet which resulted in a voluntary decrease in food intake. The ensuing rapid body weight loss led to a deterioration of glucose tolerance and severely depressed insulin secretion. This was, however, temporary. Presumably, insulin resistance was caused by an adaptation to nutrient deprivation and a shift from carbohydrate to fat catabolism. This may result in elevated levels of triglycerides and free fatty acids. Hence, these are increased in obesity, but also during massive caloric restriction and must be considered a normal metabolic adaptation (see also *Banks et al, 2006*).

GLUCOTOXICITY AND LIPOTOXICITY

The concept of glucotoxicity, or better glucolipotoxicity, is not novel *(Rossetti et al, 1990)* but research over the last few years has yielded good progress in the understanding of underlying causes and mechanisms. Glucotoxicity and lipotoxicity refer to a defect in stimulus-secretion coupling which ultimately leads to beta-cell failure. Both phenomena occur relatively rapidly so that hyperglycemia sustained for only a few days downregulates the glucose transport system, and an elevation of free fatty acids for 24 hours reduces insulin secretion.

Even though the phenomenon of increased body weight in neutered cats has been known for a long time, more in-depth studies on underlying causes have only recently been performed. The increase in body weight, and hence the decrease in insulin sensitivity, in cats after neutering appears to result from both an increase in food intake and a decrease in energy requirement *(Root et al, 1996; Biourge et al, 1997; Fettman et al, 1997; Harper et al, 2001; Hoenig & Ferguson, 2002; Kanchuk et al, 2002; Kanchuk et al, 2003)*. The latter effect, however, has been disputed because it was not consistently observed in male cats *(Kanchuk et al, 2003)*. The different outcome of studies may be due to procedural differences. *Kanchuk et al* (2003), determined energy expenditure as expressed per lean body mass. This was done on the understanding that BW gain in overfed cats results mainly from an increase in adipose tissue mass which is metabolically relative inactive (*Kanchuk et al, 2003*; see also *Martin et al, 2001*). In any case, neutered cats have a much higher risk of becoming obese.

► General concepts of glucotoxicity, lipotoxicity, and glucolipotoxicity

Glucose sensing in the feline pancreas seems to be similar to other species. Via the pathways outlined in **Figure 6 & 7**, glucose and free fatty acids (or NEFA) normally increase insulin secretion. Glucose also promotes normal expansion of beta-cell mass, and the two mechanisms, glucose stimulation and uptake via GLUT2, and glucose-induced cell proliferation seem to be directly linked through distinct intracellular signaling pathways (reviewed in *Prentki & Nolan*, 2006). The effect of glucose on beta-cell proliferation is further stimulated by incretins such as GLP-1 and free fatty acids. Hence, GLP-1 protects beta-cells from apoptosis and promotes beta-cell growth.

As reviewed by *Prentki et al* (2002), glucose concentrations below 10 mmol/L (180 mg/dL) normally are not toxic to the pancreatic beta-cells. This refers to physiological postprandial hyperglycemia which triggers beta-cell proliferation *(Donath et al, 2005)*. Similarly, physiologically elevated fatty acid concentrations alone are not toxic, at least when malonyl-CoA, which is a side product of glucose metabolism in beta-cells and which inhibits uptake of fatty acids in mitochondria for subsequent beta-oxidation, is low. Fatty acids increase insulin secretion via increases in Ca^{2+} and diacylglycerol **(Figure 7)**. Problems only arise when hyperglycemia and elevated fatty acids occur simultaneously and for prolonged periods. While insulin secretion initially is increased via glucose and long chain fatty acid-CoA **(Figures 6 & 7)**, a marked elevation of glucose, and activated fatty acids and further lipid signalling molecules reduce insulin secretion and promote apoptosis. These effects are called glucotoxicity and lipotoxicity, respectively. Because lipotoxicity is most apparent under prevailing hyperglycemia, the term glucolipotoxicity has been coined *(Prentki & Nolan, 2006)*.

It has to be made clear that only few aspects of gluco- and lipotoxicity have been studied in cats so far. Nonetheless, the author believes that due to the many similarities between rodent models of 2DM and especially human 2DM and feline DM *(Henson & O'Brien, 2006)*, many aspects discussed in the following section are probably also valid for cats (see below).

The reduction in beta-cell mass caused by chronic hyperglycemia and glucotoxicity results from an imbalance between beta-cell neogenesis and proliferation, and beta-cell apoptosis *(Donath et al, 2005)*. During chronic hyperglycemia and hyperlipidemia, glucose, saturated fatty acids and triglycerides accumulate in beta-cells, triggering the release of cytokines. All these factors reduce insulin secretion and favor beta-cell apoptosis. At the cellular level, glucotoxicity is associated with mitochondrial dysfunction which, due to enhanced oxidative glucose metabolism, may be linked to increased oxidative stress in pancreatic beta-cells *(Prentki & Nolan, 2006)*. Reactive oxygen species can be "detoxified", but this happens at the expense of ATP and hence lower insulin secretion **(Figures 6 & 7)**.

Dysfunctional lipid metabolism, triglyceride and free fatty acid cycling also contribute to beta-cell failure. This results in the accumulation of long chain fatty acid-CoA which directly influences

the ATP-sensitive K channel that is involved in glucose-stimulated insulin release. Further, elevated intracellular malonyl-CoA levels reduce the uptake of fatty acids into mitochondria and thereby shift fat metabolism from fatty acid oxidation to fatty acid esterification and lipid accumulation. This results in a lower production of intracellular ATP which is important for stimulus-secretion coupling *(Prentki & Nolan, 2006)*.

In recent years, evidence has also accumulated that glucotoxic and lipotoxic events are directly linked to islet inflammation. Among other factors, interleukin 1-beta (IL-1beta) has been identified as one of the key molecules *(Donath et al, 2005)*. Even though IL-1beta upregulation has now been reported in several animal models of 2DM, further studies are clearly required to investigate the link between hyperglycemia and inflammation *(Prentki & Nolan, 2006)*. The author is not aware of any such studies having been performed in cats to date.

► Gluco- and lipotoxicity in cats

In their paper entitled *Experimental diabetes produced by the administration of glucose*, Dohan and Lukens (1948) described the effect of sustained hyperglycemia on the islets of Langerhans. They report that cats developed degranulation of beta-cells followed by degeneration of islets. Many cats developed overt diabetes mellitus, at that time characterized by massive glucosuria.

> Glucotoxicity

Glucotoxicity clearly contributes to beta-cell failure in cats but it is reversible if hyperglycemia resolves. However if maintained, permanent loss of beta-cells may ensue. In healthy cats, sustained hyperglycemia of about 30 mmol/L (540 mg/dL) induced by chronic glucose infusion almost completely shut down insulin secretion three to seven days after the start of infusion. Pancreatic histology revealed massive changes in beta-cell morphology. Pancreatic beta-cells showed vacuolation, glycogen deposition, loss of insulin staining and pyknosis. However, even profound histological changes appeared to be reversible upon early resolution of hyperglycemia *(Rand & Marshall, 2005)*. The author's unpublished studies also clearly show that hyperglycemia of about 25 mmol/L (450 mg/dL) for only 10 days is sufficient to cause a massive decrease in the insulin secretory capacity of pancreatic beta-cells in healthy cats.

© Y. Lamceau/RC/European shorthair

Interestingly, the first report on glucotoxicity in cats by was published in 1948.

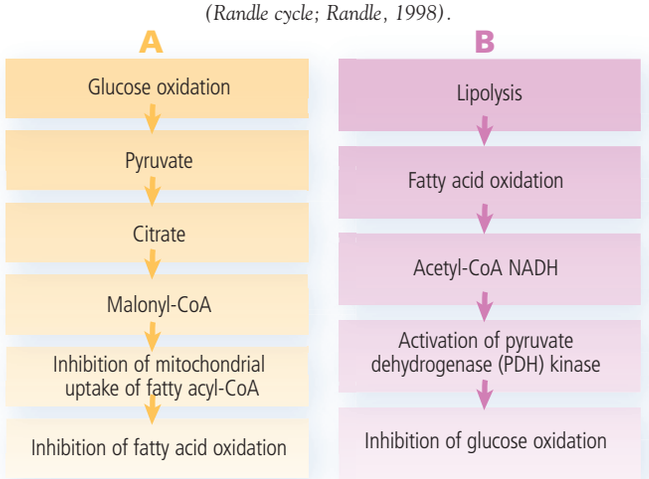
> Lipotoxicity

Lipotoxicity has not been investigated in detail in cats. However, *Hoenig (2002)* hypothesized that lipotoxicity might also play a pathogenic role in the diabetic cat. As first described in the glucose fatty acid cycle (Randle cycle; *Randle, 1998*), glucose inhibits fatty acid oxidation, and vice versa **(Figure 14)**. Because NEFA concentrations are elevated in obese cats and because obese cats are most prone to developing diabetes mellitus, it is plausible to suggest that NEFA reduces glucose metabolism in beta-cells. However glucose metabolism is a necessary component in glucose-stimulated insulin release. Hence, glucose-stimulated insulin release would be decreased. A study by the same group has shown that saturated fatty acids in particular seem to be detrimental to glucose control in cats while polyunsaturated fatty acids (3-PUFA) may have beneficial effects *(Wilkins et al, 2004)*.

Similar cellular mechanisms as just described for the pancreatic beta-cell also seem to play a role in glucolipotoxicity in insulin target tissues. This has been investigated

FIGURE 14 - SIMPLIFIED CONCEPT OF THE GLUCOSE FATTY ACID CYCLE

(Randle cycle; Randle, 1998).



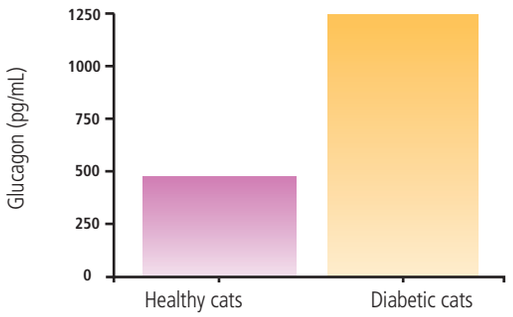
Glucose supply promotes glucose oxidation, glucose and lipid storage and inhibits fatty acid oxidation (A). Fatty acid oxidation impairs glucose oxidation (B) and may promote glucose storage in the form of glycogen if glycogen reserves are depleted.

in less detail but as mentioned earlier, intramyocellular lipid accumulation in skeletal muscle cells reduces their insulin sensitivity (*Wilkins et al, 2004*; see also *Hoenig, 2002*). Hence, elevated glucose levels and perturbed lipid metabolism in diabetic cats not only lead to beta-cell failure but may also reduce insulin sensitivity in insulin-target tissues.

All in all, gluco- and lipotoxicity seem to be phenomena which contribute to the progressive deterioration of metabolic control in diabetic cats, both via an effect on pancreatic beta-cells and via an effect on insulin-sensitive target tissue. This clearly underlines the pivotal importance of glucose lowering strategies to curtail this progressive deterioration. Hence, early reversal of hyperglycemia, preferentially by aggressive insulin treatment, reverses glucolipotoxicity, and this will help to achieve diabetic remission in a large number of diabetic cats (see also paragraph on transient diabetes; *Nelson et al, 1999*).

FIGURE 15 - BASELINE HYPERGLUCAGONEMIA IN DIABETIC CATS AFTER 12H OF FASTING

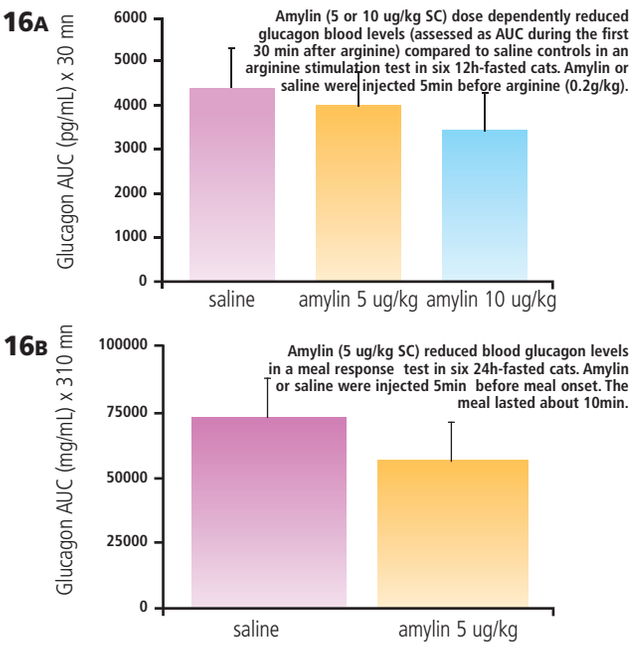
(Tschuor et al, 2006)



Median values of 7 healthy and 10 diabetic cats are shown.

FIGURE 16 - AMYLIN SLIGHTLY REDUCES MEASURED GLUCAGON BLOOD LEVELS IN AN ARGININE STIMULATION TEST (AST; FIGURE 16A) AND A MEAL RESPONSE TEST (MRT; FIGURE 16B)

(Furrer et al, 2005)



AUC = area under the curve, n = 6.
The effects approached significance.

► Amylin as a circulating hormone in the development of feline diabetes mellitus

As discussed, amylin is a normal secretory product of pancreatic beta-cells in all species. Amylin is co-synthesized and co-secreted in parallel with insulin in response to appropriate stimuli *(Lutz & Rand, 1996)*. Hence, changes in plasma insulin levels are usually associated with corresponding changes in plasma amylin levels. In human 2DM and in feline DM, the hormonal situation changes over the course of the disease. Early phases of feline 2DM or mild forms of the disease are often characterized by (compensatory) hyperinsulinemia and absolute or relative hyperamylinemia *(O'Brien et al, 1991; Lutz & Rand, 1996)*. Early hyperamylinemia may favor the deposition of feline amylin as pancreatic amyloid (see below). Progressive beta-cell failure in more severe forms and late stages of feline DM, however, leads to overt hypoinsulinemia and hypoamylinemia *(Johnson et al, 1989; Ludvik et al, 1991)*. Most clinical cases of feline DM are probably presented to veterinarians at that stage.

The regulation of nutrient metabolism by amylin involves modulation of pancreatic glucagon release, the regulation of gastric emptying (for review: *Edelman & Weyer, 2002*), and an inhibition of food intake *(Lutz, 2005)*. Hence, the lack of amylin in DM results in oversecretion of glucagon, accelerated gastric emptying and overeating. At least in humans and rodents, amylin has been shown to decrease excessive postprandial hyperglucagonemia observed in DM *(Fineman et al, 2002)* and to normalize gastric emptying. Hyperglucagonemia is also present in diabetic cats (**Figure 15**; *Tschuor et al, 2006*), but it is unknown at present whether this is due to the lack of amylin in these animals. However, preliminary studies in healthy cats show a trend for an effect of amylin to reduce glucagon output (**Figure 16**; *Furrer et al, 2005*). Similar studies in diabetic cats have not been performed yet. Further, it has not been investigated in detail whether, similar to humans or rodents, gastric emptying in diabetic cats is accelerated. Hence, it is unknown if presuming that such defect were present, this would be due to amylin deficiency.

In summary, there is reason to believe that the lack of amylin in diabetic cats contributes to metabolic dysregulation. The most prominent effect in this regard is the lack of amylin's suppression

of prandial glucagon secretion. Amylin replacement is now a common form of therapy in human DM but is so far unknown in the treatment of diabetic cats.

► Pancreatic glucagon as a circulating hormone in the development of feline diabetes mellitus

Pancreatic glucagon as a pathogenic factor in the development of DM has been neglected for many years due to the overwhelming importance that was given to insulin deficiency as the critical factor. Notwithstanding, deficient suppression of glucagon secretion, especially in the immediate postprandial period, seems to be a major contributor to postprandial hyperglycemia **(Figure 15)** *(O'Brien et al, 1985; Furrer et al, 2005; Tschuor et al, 2006)*. Diabetic hyperglucagonemia seems to be directly linked to amylin deficiency and hence disinhibition of glucagon release. This may also be true for the cat **(Figure 16)** *(Furrer et al, 2005)*. To what extent reduced insulin suppression of glucagon release also contributes to the phenomenon in cats, remains to be determined.

► Pancreatic amyloidosis

The most common and consistent morphological feature is islet amyloidosis **(Figure 17)** *(Yano et al, 1981; O'Brien et al, 1985; Johnson et al, 1986; Johnson et al, 1989; Lutz et al, 1994; Lutz & Rand, 1997)*. Amyloid deposition is found in a large proportion of overtly diabetic cats and cats with impaired glucose tolerance, a state also referred to as pre-diabetic *(Johnson et al, 1986; Westermark et al, 1987; Lutz & Rand, 1995)*. Islet amyloidosis is thought to play an important role in the pathogenesis of 2DM and feline DM because it contributes to progressive beta-cell loss which is typically observed over the course of the disease *(Höppener et al, 2002)*.

Pancreatic amyloid deposits consist mainly of amylin, hence amylin's other name islet amyloid polypeptide, or IAPP *(Westermark et al, 1987)*. Pancreatic amylin has the propensity to precipitate as amyloid deposits only in a small number of species such as humans, non-human primates and cats *(Johnson et al, 1989; Westermark et al, 1987)*, and only these species naturally develop a 2DM like syndrome. A necessary precondition is a certain amino acid sequence in the middle part of the amylin molecule in humans and cats (but not rats) that is unrelated to amylin's hormonal action, but predisposes amylin to form insoluble fibrillar aggregates. A second prerequisite appears to be hypersecretion of amylin leading to high local amylin concentrations in pancreatic islets *(Cooper, 1994)*. Especially during early islet amyloid formation, soluble amylin fibril oligomers contribute to beta-cell toxicity and subsequent beta-cell loss *(Höppener et al, 2002; Butler et al, 2003; Konarkowska et al, 2006; Matveyenko & Butler, 2006)*. A third and only poorly defined factor in the development of islet amyloidosis seems to be some malfunction of pancreatic beta-cells leading to aberrant processing of amylin *(Ma et al, 1998)*.

As mentioned, early phases of feline DM are characterized by hyperamylinemia *(O'Brien et al, 1991; Lutz & Rand, 1996)*. This may favor the deposition of feline amylin as pancreatic amyloid. Progressive beta-cell failure in late stages of feline DM leads to low circulating amylin levels *(Johnson et al, 1989; Ludvik et al, 1991; Cooper 1994)*.

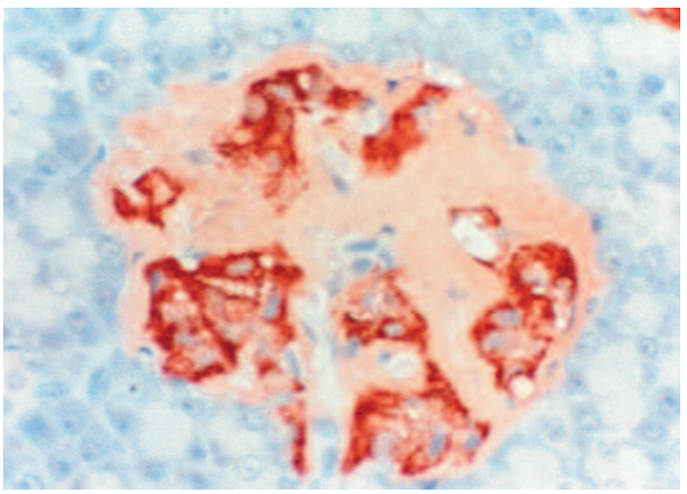


Figure 17A - Pancreatic islet of a cat with massive deposition of islet amyloid *which consists mainly of precipitates of the beta-cell hormone amylin.*

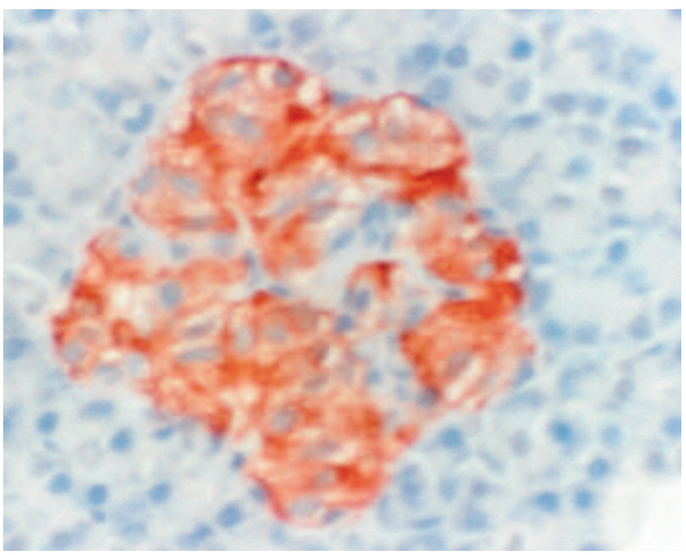
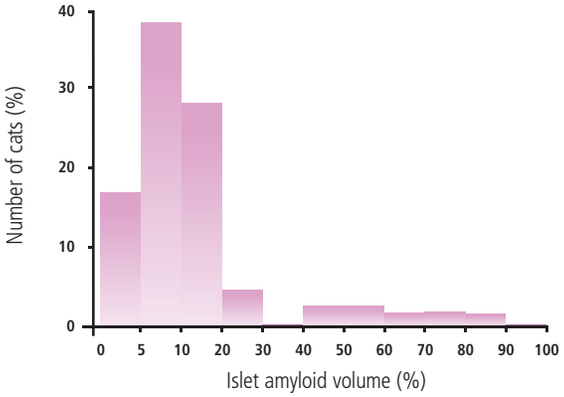


Figure 17 B - The pancreatic islet of a healthy control cat *is shown for comparison. Immunohistochemical stain for amylin. Intact beta-cells stain in red, islet amyloid stains in pink.*

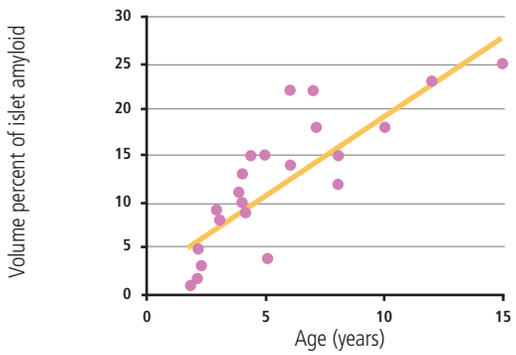
FIGURE 18 - FREQUENCY OF ISLET AMYLOID DEPOSITION IN 84 CLINICALLY HEALTHY CATS



Some cats have large amyloid deposits without developing clinical signs of DM (Lutz et al, 1994). *Volume percent of islet amyloid is referred to the total islet volume (=100%).*

FIGURE 19 - ISLET AMYLOID DEPOSITION INCREASES WITH AGE

(Lutz et al, 1994)



Young clinically healthy cats have no or only minor detectable deposition of pancreatic amyloid.

► Quantitative aspects of islet amyloid in cats

Being the most prominent histological finding in diabetic cats, it was very interesting to note that islet amyloid deposition also occurs in non-diabetic, healthy cats. Some of these cats appeared to develop relatively large amounts of islet amyloid without obvious clinical signs (**Figure 18**) *(Lutz et al, 1994)*. The prevalence of pancreatic amyloid increased with age (**Figure 19**), hence a finding similar to the general observation of an increased prevalence of feline diabetes in older animals. Most important, however, diabetic cats had markedly larger deposits of pancreatic amyloid than healthy cats, and the extent of amyloid deposition seemed to be directly related to the severity of clinical signs in feline DM *(O'Brien et al, 1985; Johnson et al, 1989; Lutz et al, 1994)*. This is also reflected in the association between the amount of pancreatic islet amyloid and the occurrence of glucose intolerance as assessed via glucose half-life in plasma in an IVGTT (**Figure 20**).

Unfortunately, even though pancreatic islet amyloid is an important factor in the pathophysiology of feline DM, it cannot be assessed under *in vivo* conditions. Therefore, it is currently not a helpful prognostic marker for the development of the disease.

Studies in transgenic rodents have clearly pointed to an important role of amylin-derived amyloid in the development and progression of 2DM. Small molecular weight, soluble amylin oligomers in species with an amyloidogenic amino acid sequence, are causative for beta-cell apoptosis (for review: see *Muff et al, 2004*). Nonetheless, the primary events leading to the formation of these cytotoxic oligomers in 2DM remain to be resolved.

► The link between hyperglycemia and the formation of islet amyloid

Now that the major pathogenetic factors (gluco-lipotoxicity and amylin-derived islet amyloid) contributing to progressive beta-cell failure in diabetic cats have been reviewed, it should be noted that it is as yet completely unknown whether and how there may be a link between these factors. However, it seems possible that changes in the intracellular milieu induced by elevated glucose or fatty acid levels (intracellular stress) may create conditions that promote the formation and precipitation of islet amyloid fibrils. The most toxic form to beta-cells are small molecular oligomers of amylin fibrils which are most likely formed early in the disease process. Hence, any therapy aimed at reducing blood glucose levels, and subsequently at reducing the secretory stress on pancreatic beta-cells, as early as possible in the disease process may favor diabetic remission as seen in transient DM (see below).

► Reduced insulin sensitivity in diseased cats

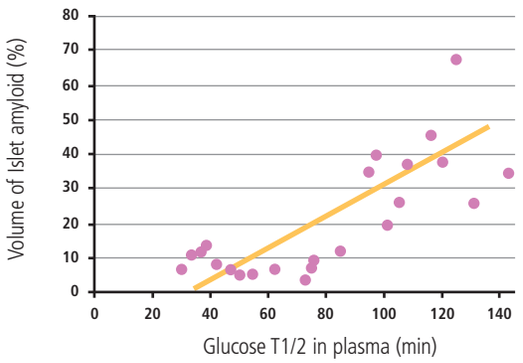
Similar to humans, glucose homeostasis seems to be frequently impaired in cats suffering from various diseases including severe inflammation, malignant neoplasia, sepsis, viral infection, end-stage renal disease, and chronic heart failure. As an underlying cause, a combination of augmented synthesis of pro-inflammatory cytokines and the presence of insulin counter-regulatory hormones has been hypothesized. This has been substantiated in cats with congestive heart failure which have elevated levels of TNFα *(Meurs et al, 2002)*.

Further, stomatitis, pulmonary lesions *(Mexas et al, 2006)*, and urinary tract infections *(Jin & Lin, 2005)* seem to be more frequent in diabetic cats. Seriously ill cats may show profound stress-induced hyperglycemia. They do not always suffer from concomitant hyperinsulinemia which would be indicative of insulin resistance *(Chan et al, 2006)*.

The exact mechanisms linking disturbed glucose homeostasis and various illnesses in cats are still largely unknown. Various cytokines are most likely involved. A recent preliminary study has shown that a 10-day infusion of lipopolysaccharide, which is a cell wall component of Gram negative bacteria and which causes the release of various cytokines, leads to impaired glucose tolerance *(unpublished)*. It could also be speculated that these disorders are associated with reduced levels of the adipocyte hormone adiponectin which appears to be an important factor in regulating insulin sensitivity in insulin target tissues *(Hoenig et al, 2007a)*. Apart from effects of cytokines on insulin-sensitive tissues, various cytokines directly reduce pancreatic endocrine secretion.

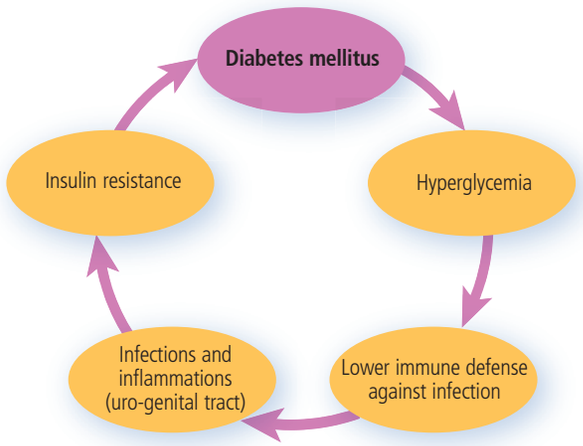
FIGURE 20 - THE AMOUNT OF PANCREATIC ISLET AMYLOID IS POSITIVELY CORRELATED TO GLUCOSE T1/2 AS DETERMINED IN AN IVGTT

(Lutz et al, 1994)



Finally, it should also be recognized that one is faced with a typical chicken and the egg conundrum. On one hand, hyperglycemia in DM reduces the body defense against infection, for example, in the urogenital tract *(e.g., Lederer et al, 2003; Bailiff et al, 2006)*. On the other hand, infection and inflammatory disorders, perhaps through TNFα, are associated with insulin resistance which may ultimately lead to DM **(Figure 21)**.

FIGURE 21 - SELF-PERPETUATION OF DIABETES MELLITUS

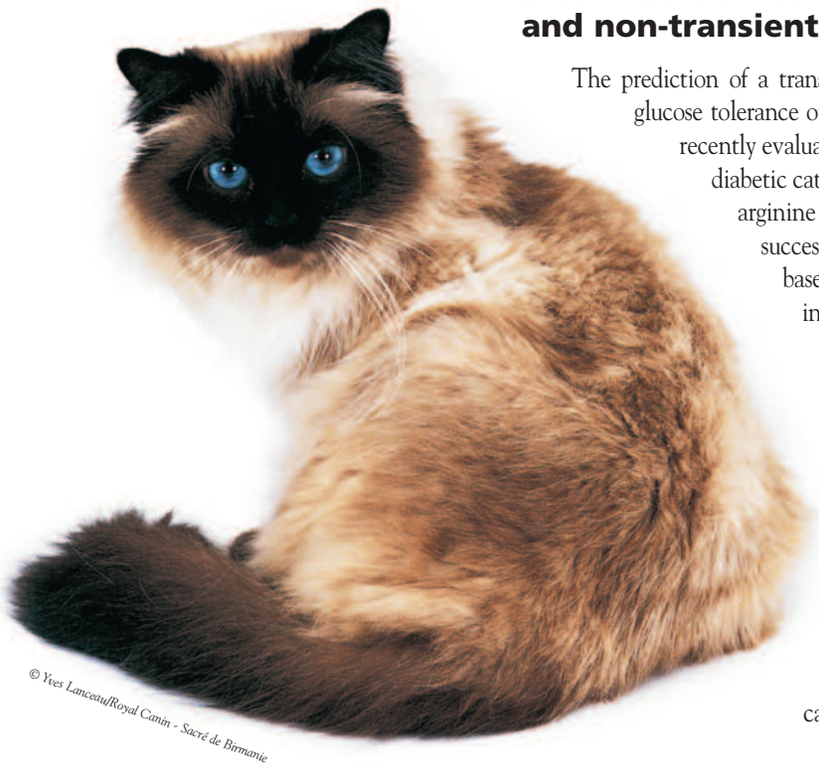


8 - Transient diabetes

Transient DM occurs relatively frequently in diabetic cats. Historically, approximately 20% of diabetic cats were reported to fall into this category *(Nelson et al, 1999; Nelson, 2005)*. However, the proportion of transiently diabetic cats seems to have increased recently (see below). Transiently diabetic cats go into spontaneous remission, that is, clinical symptoms such as polyuria and polydipsia resolve, blood glucose levels normalize and glucosuria disappears. This usually happens within one to four months after the initation of therapy *(Nelson et al, 1999)*. At that time, specific antidiabetic glucose-lowering therapy can be discontinued. Once DM resolves, the glucose induced insulin secretion is normalized. Nevertheless, beta-cell density is still decreased and islet pathology is present. Therefore, most of these cases correspond to a subclinical phase of DM *(Nelson et al, 1999)*.

► Conditions for diabetic remission

The conditions that need to be fulfilled for diabetic remission to occur are not yet completely clear. Obviously, an adequate number of functional beta-cells still needs to be present *(Nelson et al, 1999)*. One important factor seems to be the early resolution of hyperglycemia and hence the disappearance, or at least reduction, of glucotoxicity. Intensive glucose-lowering therapy, perhaps supported by an appropriate diet (see below), can terminate the vicious circle of chronic hyperglycemia leading to an impairment of pancreatic beta-cell function and decreased insulin sensitivity. Because glucotoxicity is initially reversible, it seems plausible that the earlier glucose-lowering therapy is initiated in diabetic cats, the higher the likelihood for diabetic cats to go into remission. However, hard scientific data to support this idea are lacking.



Monitoring for the reversal of subclinical to clinical DM can easily be performed by monitoring glucosuria with a dipstick. Simply place the urine dipstick in a freshly spoiled litter mixed with a small volume of water.

► Differences between transient and non-transient diabetic cats?

The prediction of a transient disease course in diabetic cats, e.g. via intravenous glucose tolerance or glucagon stimulation tests, has proven difficult. We have recently evaluated the possibility to prospectively predict the likelihood of diabetic cats going into remission based on their insulin response in an arginine stimulation test (AST; *Tschuor et al, 2006*). This test had successfully been used in human type 2 diabetics. As expected, the baseline glucose concentration was significantly higher, and the insulin response was significantly lower in the diabetic compared to healthy cats. Baseline glucagon and the glucagon response to arginine was significantly higher in diabetic cats. Despite clear differences between diabetic and healthy cats, no significant difference for any of the parameters (glucose, insulin, glucagon) were detected between transient and non-transient diabetic cats. Therefore, the AST seems unable to prospectively differentiate between a transient and a non-transient course of DM in cats (*Tschuor et al, 2006)* (see below and **Figure 25**). Another recent study investigated whether IGF-1 levels may help to predict transient DM in cats. This idea, however, had to be rejected *(Alt et al, 2007)*.

In diabetic cats that go into remission, recurrence of clinically overt DM is always possible. Islet pathology is usually present in transiently diabetic cats. Therefore, the susceptibility to revert to overt DM is probably higher than in previously healthy cats. This may be caused by additional stressors such as insulin-antagonistic drugs (e.g. glucocorticoids, megestrol acetate) or obesity. It is usually impossible to predict if or when clinical signs will recur, underlying the necessity to monitor cats in diabetic remission carefully for recurrence. In some cases, cats have been reported to revert from subclinical to clinical DM more than 3 years after the first resolution of symptoms *(Nelson et al, 1999)*.

► Evolution of the remission rate of diabetic cats

The proportion of transiently diabetic cats seemed to have increased over the last years, reaching 70% in some studies. This may be related to the recent recommendation to feed diabetic cats a diet relatively high in protein and low in carbohydrate, respectively. Whether the improvement of the metabolic situation depends on the high protein content (49-57% DMB in studies by *Frank et al, 2001; Mazzaferro et al, 2003*), the low carbohydrate (18% in the study by *Bennett et al, 2006*), or both, may require further investigation (see also below). We have also confirmed that the remission rate of diabetic cats is higher than previously reported when the cats were fed a high-protein diet (approx. 54% protein, 8% carbohydrate DMB; *Tschuor et al, 2006*). In our study, approximately 50% of insulin-treated cats went into remission within 4 weeks of intensive therapy. Interestingly, remission occurred before considerable weight loss was observed.

9 - Long-term consequences of diabetic hyperglycemia

Chronic hyperglycemia has deleterious effects on insulin-producing pancreatic beta-cells and on insulin target tissues (glucotoxicity; see above). But long-term hyperglycemia also seems to be the major factor contributing to other complications frequently seen in diabetic cats. These are diabetic neuropathy, nephropathy and retinopathy. The two main underlying mechanisms are glycation of proteins and osmotic damage due to the accumulation of sugar alcohols.

► Glycation of proteins and accumulation of sugar alcohols

An early pathologic change of DM is increased unspecific, non-enzymatic glycosylation (or glycation) of proteins, which cause abnormal aggregation of collagen fibrils and the production of superoxide radicals. This results in damage to the connective tissue and basal membranes. Further, osmotic cell damage seems to occur due to the accumulation of the sugar alcohol sorbitol which is not freely permeable to the cell membrane. Sorbitol is generated from glucose through aldose reductase activity. While only small amounts of sorbitol are generated under normal conditions, hyperglycemia can lead to the accumulation of considerable amounts of sorbitol by an "overflow" mechanism when normal glucose utilization via hexokinase is saturated.

► Diabetic neuropathy, retinopathy and cataract

The exact prevalence of diabetic neuropathy, nephropathy and retinopathy in cats is unknown. Diabetic neuropathy leads to hindlimb weakness and a typical plantigrade stance **(Figure 3)**. The pathology seems to share many similarities with human diabetic neuropathy *(Mizisin et al, 2007)*.

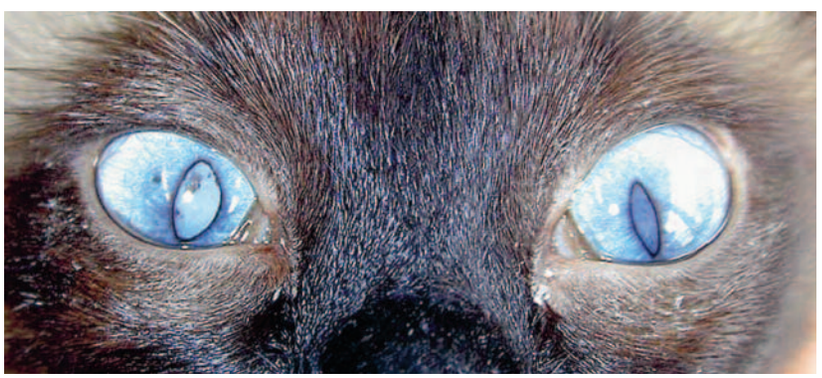
Interestingly, if intensive glucose-lowering therapy is initiated rapidly after diagnosis, at least some of these changes seem to be reversible and gait normalizes. Even though diabetic nephropathy and retinopathy also occur in cats, diabetic retinopathy is only rarely observed in clinical practice. Experimentally induced hyperglycemia has been shown to lead to retinal changes only after several years of duration, and these changes could only be detected using specific diagnostic techniques *(personal communication; Dr. M. Richter, Division of Ophthalmology, Vetsuisse Faculty, University of Zurich)*.

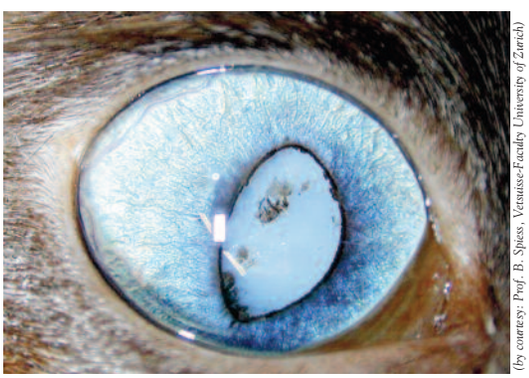
Similarly, and in contrast to dogs, diabetic cataracts are also very rare in diabetic cats **(Figure 22)**. It has been suggested that the generation of sorbitol in older diabetic cats was much lower than in dogs and young cats because of the lower aldose reductase activity in old cats *(Richter et al, 2002)*. Excess sorbitol is responsible for the damage to the lens. Even though DM is very infrequent in young cats, young diabetic cats often present typical lens opacity as in diabetic dogs, probably because of their high aldose reductase activity *(Richter et al, 2002)*. A recent study challenged the view of a generally low occurrence of diabetic cataracts in cats *(Williams & Heath, 2006)*. This study showed that lens opacities occur much more frequently than previously suggested. In addition, these opacities occurred at a much younger age in diabetic than in non-diabetic cats.

10 - Diagnosis of feline diabetes mellitus

Diagnosis of feline DM should always include an assessment of the key clinical features that typically occur in uncomplicated forms of diabetes, i.e. polyuria, polydipsia, polyphagia, loss of body weight. Obviously, the presence of one or all features, although indicative, is not sufficient for establishing the diagnosis. Therefore, laboratory parameters need to be assessed.

Figure 22 *- Cataract in a diabetic cat.*





(by courtesy: Prof. B. Spiess, Vetsuisse-Faculty University of Zurich)

FIGURE 23 - SERUM FRUCTOSAMINE CONCENTRATIONS IN NORMOGLYCEMIC AND HYPERGLYCEMIC CATS WITH STRESS-INDUCED OR CHRONIC DIABETIC HYPERGLYCEMIA

(From: Prof. C. Reusch, Vetsuisse-Faculty University of Zurich)

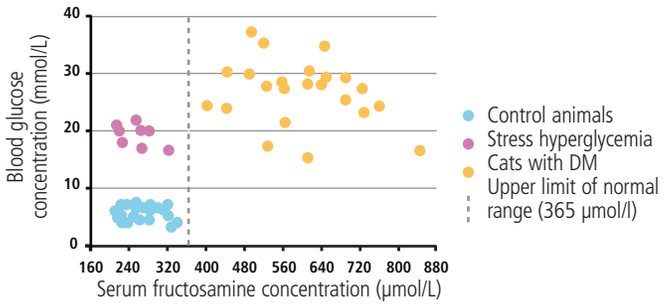


TABLE 3 - COMPARISON OF FRUCTOSAMINE AND GLYCATED HEMOGLOBIN FOR THE ASSESSMENT OF SUSTAINED HYPERGLYCEMIA

	Fructosamine	Glycated hemoglobin
Common characteristics	- Derive from irreversible, non-enzymatic and unspecific binding of glucose to amino acid residues. - Directly proportional to the average blood glucose concentration over time. - Depend on the average turnover rate of the respective protein which is shorter for serum proteins than for hemoglobin.	
Respective characteristics	- Fructosamine refers to the sum of glycated serum proteins which can be measured by colorimetric assays. - A marker for the average glycemia over the last 10-14 days. - Affected by changes in serum protein levels.	- Glycated hemoglobin is a glycosylation product of hemoglobin and glucose. It is measured by chromatography. - Indicative for the average blood glucose level over the previous 4-8 weeks. - Affected by the hemoglobin concentration.

► Fasting hyperglycemia

Fasting hyperglycemia is one of the key symptoms in diabetic cats, but fasting hyperglycemia alone is not reliable due to the phenomenon of stress hyperglycemia **(Figure 23)**. Cats are much more prone to stress-induced hyperglycemia than dogs. Blood glucose levels in stressed cats often exceed 20 mmol/L (360 mg/dL) *(Laluha et al, 2004)*. Therefore, stress-induced hyperglycemia has to be excluded before initiating insulin therapy (see below). Similar to fasting blood glucose, glucosuria may be misleading. While glucosuria is present in diabetic cats and is normally absent in healthy cats, stress-induced hyperglycemia can occur to such an extent that spill over of glucose into the urine is not uncommon.

► Plasma insulin

Diabetic cats are not able to secrete enough insulin to maintain blood glucose levels in the normal range. This deficiency, however, might be referred to as relative, i.e. the plasma insulin level may seem normal but for the level of glycemia, these cats are hypoinsulinemic. Having said this, it is clear that the determination of fasting insulin levels is usually not helpful, unless there is massive absolute hypoinsulinemia. Further, insulin levels are not measured routinely due to the high cost involved, and the limited availability of species specific insulin assays.

It was proposed that proinsulin, or the insulin: proinsulin ratio, respectively, may be a helpful tool to diagnose DM in cats. In humans, elevated fasting levels of proinsulin seem to be indicative of beta-cell damage and proinsulin may serve as an early marker for beta-cell dysfunction. The amino acid sequence of feline proinsulin has been published. Therefore it is possible that assays may become available to assist in the early diagnosis of feline DM *(Hoenig et al, 2006a)*. Interestingly, pro-insulin secretion appears to be elevated in obese cats.

► Fructosamine and glycated hemoglobin

As mentioned, neither fasting blood or urine glucose levels are reliable markers for feline DM. As such, fructosamine and glycated (glycosylated) hemoglobin are now two frequently used markers for the long-term assessment of glycemia in the diagnosis and the monitoring of feline DM **(Tables 3 & 4).** Both products derive from irreversible, non-enzymatic and unspecific binding of glucose to amino acid residues.

- **Fructosamine** refers to the sum of glycated serum proteins which can be measured by colorimetric assays.
- **Glycated hemoglobin**, especially the fraction of glycated hemoglobin A1c (HbA1c), is a glycosylation product of hemoglobin and glucose. It is measured by chromatography. Glycated hemoglobin is only rarely used as a diagnostic marker in cats.

The level of fructosamine and glycated hemoglobin is directly proportional to the average blood glucose concentration over time. Both also depend on the average turnover rate of the respective

protein which is shorter for serum proteins than for hemoglobin. Therefore, the serum fructosamine concentration is a marker for the average glycemia over the last 10-14 days while the concentration of glycated hemoglobin is indicative for the average blood glucose level over the previous four to eight weeks. The levels of fructosamine and glycated hemoglobin are also affected by changes in serum protein levels and the hemoglobin concentration, respectively. These have to be taken into account when interpreting laboratory data *(Nelson, 2005)*.

TABLE 4 - INTERPRETATION OF SERUM FRUCTOSAMINE AND GLYCATED HEMOGLOBIN LEVELS IN DIABETIC CATS
(adapted from Nelson, 2005)

Monitoring of diabetic cats	Fructosamine (µmol/L)	Glycated hemoglobin (%)
normal values	190-365 µmol/L (mean 240)	0.9 - 2.5% (mean 1.7)
excellent glycemic control	350 - 400	1.0 - 2.0
good control	400 - 450	2.0 - 2.5
fair control	450 - 500	2.5 - 3.0
poor control	> 500	> 3.0
sustained hypoglycemia	< 300	< 1.0

Normal values differ slightly between different laboratories.

Fructosamine is used more frequently in clinical practice because it can be easily and rapidly measured. Since the original report about fructosamine as an indicator of blood glucose levels in diabetic cats *(Kaneko et al, 1992)*, numerous subsequent publications supported the usefulness of fructosamine as an easy-to-use and reliable marker for the assessment of chronic hyperglycemia (e.g., *Reusch et al, 1993; Lutz et al, 1995; Crenshaw et al, 1996; Thoresen & Bredal, 1996; Plier et al, 1998; Elliott et al, 1999; Reusch & Haberer, 2001)*. Normal values show some variation between different laboratories but are all in the same order of magnitude **(Table 4)**. Compared to blood glucose levels, one of the major advantages of the assessment of serum fructosamine is that its level is unaffected by short-term, stress induced hyperglycemia which can clearly be distinguished from diabetic hyperglycemia **(Figure 23)**.

► Other tests

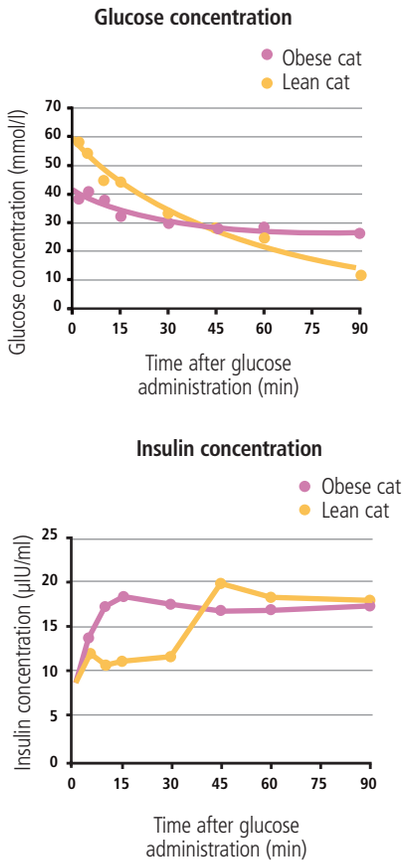
Even though not routinely performed in clinical practice, more elaborate tests are available to assess glucose metabolism in cats. Most commonly used are:
- the intravenous glucose tolerance test (IVGTT) *(O'Brien et al, 1985; Link & Rand, 1998; Appleton et al, 2001a,b)*
- the arginine stimulation test (AST) *(Kitamura et al, 1999)*
- the glucagon stimulation test (GST)

Less common are insulin sensitivity tests (IST) *(Feldhahn et al, 1999; Appleton et al, 2001a,b)*, while the euglycemic hyperinsulinemic clamp *(Petrus et al, 1998)* and the hyperglycemic glucose clamp *(Slingerland et al, 2007)* are only used for research purposes. In the euglycemic hyperinsulinemic clamp, a constant dose of insulin is infused and glucose metabolism parameters are derived from the amount of glucose that has to be infused to maintain blood glucose levels in the normal range. In the hyperglycemic glucose clamp, the blood glucose concentration is clamped to a fixed value and glucose metabolism parameters are derived from glucose and insulin levels throughout the clamp period.

With the IVGTT, glucose tolerance is assessed by calculating glucose half-life in plasma (glucose T1/2; upper limit of normal: approximately 75-80 min) *(Lutz & Rand, 1996; Appleton et al, 2001a)*. Insulin sensitivity and the insulin secretory pattern, indicative of beta-cell function, can also be estimated **(Figures 9 & 24)**. Even though IVGTT are mostly used under standardized conditions, a study suggested that uniform and reliable reference values for the IVGTT cannot be established *(Hoenig et al, 2002)*. Environmental factors like diet, housing, husbandry, and laboratory equipment, substantially influence the results. Therefore, the pattern of response to IV glucose injection should be evaluated rather than absolute concentrations of glucose or insulin *(Hoenig et al, 2002)*. In the same study, it was proposed that glucose should be injected at a dose of at least 0.8 g/kg (a dose of 1 g/kg is used routinely) because lower doses which have been used in some studies (e.g., *Nelson et al, 1990*) may not enable the full assessment of the insulin response in cats of different body weight and body condition.

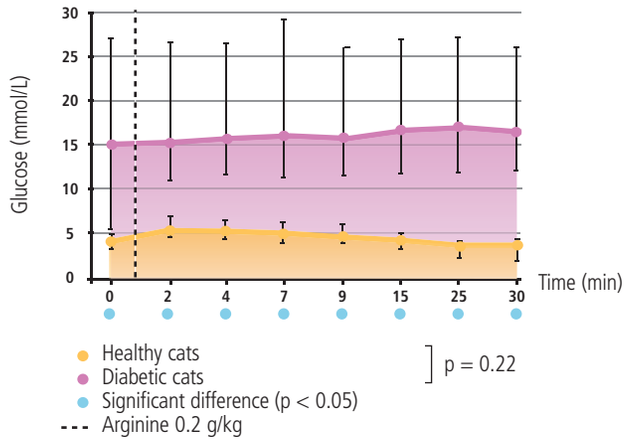
The AST, which triggers the release of both insulin and glucagon, has been used less often in diagnosing feline DM. Differentiation between healthy and diabetic cats is easily possible using this test, but permanently diabetic cats cannot be distinguished from cats going into diabetic remission (transient diabetes; **Figure 25**; *Tschuor et al, 2006*).

FIGURE 24 - GLUCOSE TOLERANCE TEST

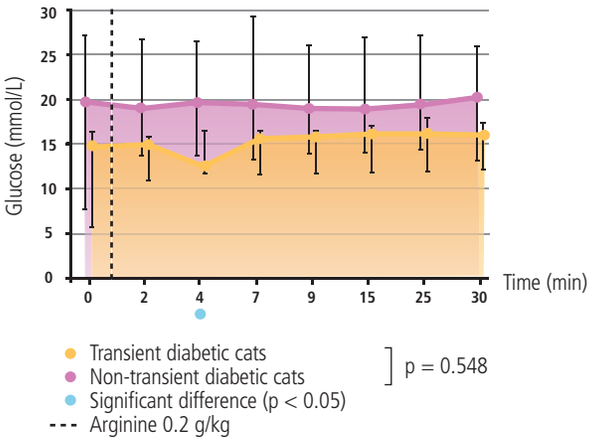


Glucose tolerance test in a lean cat (BW 3.5 kg) with normal glucose tolerance (glucose T1/2 37 min) and an obese cat (BW 6.5 kg) with abnormal glucose tolerance (glucose T1/2 125 min). Glucose (1 g/kg BW) was injected at t=0 min.

FIGURE 25 - ARGININE STIMULATION TEST



In an arginine stimulation test (arginine injection at t=0 min; 0.2 g/kg BW), blood glucose concentration in healthy cats is significantly lower than in diabetic cats.



However, this test can not differentiate between permanently and transiently diabetic cats (Tschuor et al, 2006).

11 - Treatment strategies

► Key issues in treating diabetic cats

Treatment beyond the disappearance of clinical signs (polyuria, polydipsia), which has traditionally been considered sufficient for treating diabetic cats, offers additional benefits. The benefits are linked to the possibility of spontaneous remission of feline DM, i.e. the transition into a subclinical form of DM. Remission of DM is thought to be mainly due to the disappearance of glucotoxicity once hyperglycemia is controlled. The key issues in treating diabetic cats must focus on lowering the blood glucose level into a range of 5-15 mmol/L (90-270 mg/dl).

Another key issue is that glucose lowering therapy should be initiated as soon as possible after the diagnosis of DM has been established. Early initiation of therapy is warranted because glucotoxic changes in pancreatic islets are at first reversible, but with time will become irreversible *(Prentki & Nolan, 2006)*. Although it has not been unequivocally demonstrated, it is the author's clinical impression that early intervention leads to a higher percentage of diabetic cats that go into remission.

Overall, the recommendation is to treat early and intensively. Today, this is typically coupled with dietary intervention, especially the use of high-protein (> 50% protein DMB), low-carbohydrate (< 15% DMB) diets (see below).

► Insulin as a glucose lowering drug

Insulin therapy is by far the most effective means to achieve good glycemic control in diabetic cats. Feline insulin is not available for therapy, but insulin of animal origin (bovine or porcine), human recombinant insulin and a synthetic analogue of human insulin have been used for the treatment of diabetic cats *(Goossens et al, 1998; Marshall & Rand, 2002; Weaver et al, 2006)*. The different types of insulin that are currently used are summarized in **Table 5**.

The exact treatment schedules for diabetic cats can be found in textbooks of veterinary internal medicine, e.g. *Nelson* (2005). Except for the treatment of an acute diabetic crisis (e.g. acute diabetic ketoacidosis), when regular crystalline insulin may be administered intramuscularly or intravenously, insulin is normally injected subcutaneously. Most diabetic cats will need insulin injections BID because of the short duration of action of insulin preparations in that species compared to humans.

Table 5 - Types of insulin commonly used for the treatment of diabetic cats

Type of insulin	Route of administration	Onset of effect	Maximum effect	Duration of effect
Regular crystalline	IV IM SC	immediate 10 - 30 min 10 - 30 min	0.5 - 2 h 1 - 4 h 1 - 5 h	1 - 4 h 3 - 8 h 4 - 10 h
NPH (neutral protamine Hagedorn)	SC	0.5 - 2 h	2 - 8 h	4 - 12 h
Lente	SC	0.5 - 2 h	2 - 10 h	6 - 18 h
Ultralente	SC	0.5 - 8 h	4 - 16 h	6 - 24 h
PZI (protamine zinc insulin)	SC	0.5 - 4 h	4 - 14 h	6 - 20 h
Commonly used insulin preparations				
Caninsulin® (intermediate insulin; porcine)	SC	1 - 2 h	4 - 6 h	8 - 12 h
Lantus® (long acting; human insulin analogue, glargine)	SC		16 h	24 h

The use of these agents in cats can be restricted according to the licence applicable in each country.

The only registered insulin preparation for dogs and cats in some countries is lente porcine insulin consisting of 30% amorphous and 70% crystalline Zn-insulin (e.g., Caninsulin^{R}). Insulin therapy typically is initiated with BID injections of this intermediate-type insulin. Dosing in cats typically starts at 1-2 U/cat. Recommendations for dose adjustments vary with the type of insulin used. This usually requires serial blood curves which can be either produced at home (home monitoring) or under clinical settings.

A new preparation of human synthetic insulin is now also used in diabetic cats *(Marshall & Rand, 2002; Marshall & Rand, 2004; Weaver et al, 2006; Rand, 2006)*. Glargine insulin is an insulin analogue which is released slowly from subcutaneous depots. It is used in humans to provide a constant, peakless baseline insulin supply. In humans, glargine is often combined with meal associated injections of short acting insulins.

In cats, glargine is thought to result in better glycemic control over an entire 24h-period. In the study by *Weaver et al* (2006), glargine was shown to provide good glycemic control in cats even if only administered SID. Obviously, this would constitute an important advantage for cat owners, but most cats will require BID injections.

► Other forms of therapy

Because feline DM is a type of DM corresponding to human type 2 DM, forms of therapy other than insulin have been tested. It should however be clearly stated that by far the best outcome of diabetic therapy is obtained with insulin, complemented by an appropriate diet (see below).

The use of sulfonylurea derivates, which stimulate pancreatic beta-cell secretion **(Figure 6)** and may improve peripheral insulin sensitivity, is probably the most advanced non-insulin form of therapy. The sulfonylurea of choice is glipizide *(Nelson et al, 1993; Feldman et al, 1997)*. Considering the outcome of various studies, it seems safe to state that at best only 25% of diabetic cats will respond to glipizide treatment. Secondary failures to treat diabetics with sulfonylureas are not uncommon because sulfonylureas not only stimulate insulin but also amylin secretion *(Hoenig et al, 2002)*. The high local amylin concentrations and progressive deposition of pancreatic islet amyloid may be a long-term detrimental sequelae of treatment with these drugs *(Hoenig et al, 2002)*.

Another class of orally available antidiabetic drugs are the thiazolidinediones (glitazones) which are ligands of PPARγ. Glitazones therefore increase insulin sensitivity of insulin target tissues. Darglitazone, one member of this group of compounds, increased insulin sensitivity in obese cats

(Hoenig et al, 2003). The usefulness of these drugs in the routine treatment of feline DM, however, remains largely unknown.

Metformin improves insulin sensitivity mainly via inhibition of hepatic gluconeogenesis and glycogenolysis. Even though metformin can have beneficial metabolic effects in diabetic cats, its use for routine treatment was largely questioned: only few of the treated cats improved after treatment. Metformin does not seem to offer any advantage over conventional treatment *(Nelson et al, 2004)*.

Postprandial hyperglycemia is one key feature of DM. Therefore, slowing down postprandial intestinal glucose absorption appears as a viable alternative in diabetic therapy. The competitive inhibitor of pancreatic amylase and glucosidases in the intestinal brush border membrane, acarbose, has been proposed for this purpose *(Nelson, 2005)*. Even though acarbose may slow gastrointestinal glucose absorption, the recommendation of feeding diabetic cats with a high protein diet seems to largely outweigh the benefit of using acarbose.

► Future therapeutic options

The metabolic effects of amylin and GLP-1 have been described previously in this chapter. Beneficial effects of both amylin and GLP-1 are an inhibition of gastric emptying and of postprandial glucagon release (for amylin, see **Figure 16**). Not all of these effects have been investigated in cats so far. The amylin analogue pramlintide (Symlin^{R}), which is combined with insulin, and the GLP-1 agonist exendin-4 (Byetta^{R}) are now in clinical use for the treatment of human diabetics. Neither drug has been tested in diabetic cats so far and whether these treatments would constitute considerable advantages over current treatment options with insulin is not clear.

Chemical compounds that activate glucokinase have been considered interesting targets for diabetic therapy *(Schermerhorn, 2006)*. Clinical usefulness of these drugs is unlikely in the foreseeable future.

12 - Dietary aspects in the treatment of feline diabetes mellitus

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One of the main goals in diabetic therapy and prevention is to maintain optimal body condition.

The optimal diet for feeding the diabetic cat may not yet be known. However, the concept of the most beneficial diet in feline diabetes has seen some major changes over the last few years. Certainly the major step to better glycemic control was the introduction and recommendation of diets high (⩾ 45 % of calories) in protein and low (⩽ 20 % of calories) in carbohydrate.

Retrospectively, it seems obvious to feed cats a high protein diet which closely resembles their natural diet. Nonetheless, recognition that this may be particularly useful for the diabetic cat has revolutionized diabetic therapy. The traditional high (⩾ 30 % of calories) carbohydrate (mainly starch), high (⩾ 50 g total dietary fiber (TDF)/ 1000 kcal) fiber diet, which probably was adopted indiscriminately from the recommended diet in diabetic dogs or humans, is no longer recommended for cats. This mainly refers to the carbohydrate content of diets.

► General goals for feeding the diabetic cat

(see also: Biourge, 2005)

Because feline DM is a lifestyle disease similar to human type 2 DM, one of the main goals in diabetic therapy and prevention is to maintain optimal body condition. As will be discussed below, high protein

diets are of particular benefit in feeding diabetic cats. However, the use of these specific diets is most effective when combined with aggressive glucose lowering therapy. For this, insulin therapy is the most useful. This will help to control for glucotoxicity (see above). The best results have been obtained with twice daily insulin injections. Without insulin therapy (or other glucose lowering therapies), it is extremely unlikely that one will be able to successfully treat diabetic cats, at least in the initial phase of treatment. With the combination of insulin and diet, however, there is a good chance for diabetic remission which may allow discontinuation of insulin administration. To achieve good metabolic control and to avoid the risk of insulin-induced hypoglycemia, consistency in timing and in the diet's caloric content is also important.

The three main goals in the nutritional management of diabetic cats are:
1. to control excess body weight.
2. to reduce postprandial hyperglycemia.
3. to stimulate endogenous insulin secretion.

► Prevent or correct obesity

Obesity is directly linked with insulin resistance which predisposes cats to develop overt diabetes mellitus *(Scarlett et al, 1994; Scarlett & Donoghue, 1998)*. Prevention of obesity must therefore be one of the main goals when feeding cats.

PRINCIPLES IN THE FORMULATION OF DIETS FOR DIABETIC CATS

The ideal diet for the diabetic cat should be:
- moderate in energy (< 4,000 kcal/kg DMB)
- moderate in fat (< 30% of the calories)
- rich in protein (>45% of the calories)

Veterinarians should clearly council cat owners to restrict feeding immediately after neutering. Diets with low energy density, i.e. with a restricted amount of fat should be used. Dry diets that are high in fat (≥ 40 % of calories), especially if fed free choice in neutered cats, have been linked to weight gain and the development of obesity in numerous studies (e.g., *Scarlett et al, 1994; Scarlett & Donoghue, 1998)*. To the contrary, feeding a moderate fat (25% of calories), moderate carbohydrate diet (35% of calories) reduced weight gain following neutering compared to a high fat (> 40 % of calories) dry diet *(Nguyen et al, 2004b)*.

Weight loss is encouraged if the cat is fed a high protein diet (45% protein; 25% carbohydrates on DM) rather than a diet richer in carbohydrates (28% protein, 38% carbohydrates) *(Hoenig et al, 2007a)*. Restricting caloric intake to the actual needs is important, even if cats are fed diets that closely resemble their natural diet because, at least in the short term, high protein diets do not lead to a significant amount of weight loss if fed ad libitum. However, during restricted feeding, when cats loose body weight, high protein diets may have an additional beneficial effect of favoring the loss of body fat over lean body mass *(Mazzaferro et al, 2003; Hoenig et al, 2007a)*.

A moderate increase in dietary fiber (25-30 g/1000 kcal) might be of interest to moderate the energy density of the diet and to reduce the concentration of fat and carbohydrates. The amount of food offered has to be adjusted to the body composition *(Nguyen et al, 2004a,b)*. On average, this translates into a daily energy requirement of approximately 45-55 kcal/kg of body weight. Because most of our pet cats are neutered and have a sedentary lifestyle, feeding highly palatable, energy rich diets should be reduced. It should be made clear to the owner that any increase in body weight above normal increases the risk of cats to develop DM and should therefore be avoided *(Scarlett & Donoghue, 1998)*. Once established, obesity is the major risk factor for the development of feline DM because of decreased insulin sensitivity *(Biourge et al, 1997; Appleton et al, 2001b)*. Obese cats with insulin resistance have a disturbed insulin secretory pattern even before glucose tolerance is affected *(Hoenig, 2002)*.

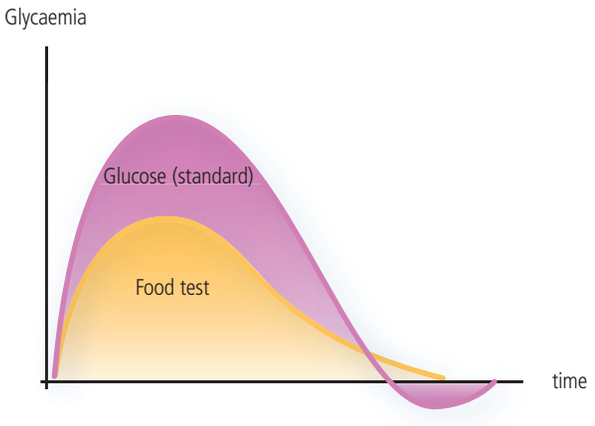
► Minimize postprandial glucose excursions

Apart from body weight alone, however, there may also be an additional influence of diet. High carbohydrate (50% of calories) intake will promote postprandial glycemia, especially if the carbohydrate source has a high glycemic index **(Figure 26)**. Hyperglycemia will stimulate pancreatic beta-cells to secrete more insulin. This stress might become overwhelming on the pancreas of overweight cats in which insulin resistance is present. However, there are no studies to date to show that high carbohydrate diets are directly linked to the development of insulin resistance or overt DM.

FIGURE 26 - WHAT IS THE GLYCEMIC INDEX?

Measuring method in man:
- 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
- Glycemic 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.



Diabetic cats fed a high protein diet (protein 57%; carbohydrate 8% DMB) achieve better metabolic control than cats fed a high carbohydrate diet (protein 40%, carbohydrate 24%; *Frank et al, 2001)*. The use of high protein diets also helps to reduce postprandial hyperglycemia **(Figure 4)** (63% protein DMB, 8% carbohydrate in the study by *Kettelhut et al*, 1980; 54% and 8% in the study by *Tschuor et al, 2006)*.

Not only the high protein and low carbohydrate content are of importance, but also the source of carbohydrate. Carbohydrates in diets for diabetic cats were recommended to be complex with a low glycemic index (i.e. barley, corn). Rice, which has a higher glycemic index than corn, resulted in a more pronounced increase of postprandial glucose and insulin levels *(Rand et al, 2004)*.

It is unknown at present if this aspect is still relevant considering the low amount of carbohydrates in today's typical diabetic diets. The glycemic index in high carbohydrate diets for diabetic cats would have played a more considerable role than in diets following today's recommendations. Neither the specific role of the glycemic index in low carbohydrate diets nor the effect of mixed carbohydrate sources have so far been investigated.

► Stimulate endogenous insulin secretion

The third goal can also be achieved by high protein diets because the response of pancreatic beta-cells to amino acids in diabetic cats is usually maintained for longer periods than their response to glucose *(Kitamura et al, 1999)*. Arginine has a strong effect on pancreatic insulin secretion.

► Use of high protein diets in the treatment of feline diabetes mellitus

Introduction of high protein diets to feed diabetic cats has been a major step forward in improving therapy in feline DM. Several studies have shown that high protein diets improve the metabolic situation in diabetic and obese cats.

- *Hoenig* (2006a,b) reported that insulin sensitivity of fat metabolism was not normalized in obese cats after body weight loss when the cats were fed a high carbohydrate diet but a high protein diet (45% DMB) improves insulin sensitivity in obese cats. Diabetic cats were not tested in this study.

- The use of a high protein (57% DMB and 50% of calories) low carbohydrate (8% DMB and 13% of calories), canned diet *(Frank et al, 2001)* showed a clear beneficial effect over a higher carbohydrate (24% DMB and 23% of calories), high fiber (56 g TDF/1000 kcal) diet. In diabetic cats fed the high protein diet, the insulin dose could be reduced by up to 50%, and completely withdrawn in 3 of 9 cats *(Frank et al, 2001; Bennett et al, 2006)*.

- In our own experience *(Tschuor et al, 2006)*, the use of a high protein (54% DMB) low carbohydrate (8%), canned diet led to a much higher rate of diabetic remission (50-70%) than previously observed. Interestingly, this occurred even before any marked body weight loss was apparent. Therefore, even though high protein diets have been reported to make weight loss easier in cats *(Szabo et al, 2000; Michel et al, 2005)*, this does not seem to be required for the beneficial effects observed in diabetic individuals.

► Use of high protein diets in the prevention of feline diabetes mellitus

It has been hypothesized that feline pancreatic beta-cells may not be well adapted to high dietary carbohydrate loads and that high carbohydrate diets may be detrimental in cats. Nonetheless, the long-term consequences of overfeeding healthy cats with carbohydrates in respect to their contribution to the development of feline diabetes is currently unknown. One report mentions that insulin sensitivity is decreased and that hyperinsulinemia prevails in cats fed a high carbohydrate diet compared to cats fed a high protein diet *(Hoenig, 2002)*. On the other hand, another study did not reveal any effect of a high protein (approx. 57% DMB protein 22% DMB carbohydrate) versus a medium protein (32% DMB protein, 49% DMB carbohydrate) diet on insulin concentration and insulin sensitivity during an IVGTT or an arginine stimulation test in normal weight cats *(Leray et al, 2006)*. More detailed experiments on a possible direct influence of high protein versus high carbohydrate diets to the development of insulin resistance, beta-cell failure and eventually DM in cats are clearly warranted.

The underlying mechanisms that could explain the positive effects of high protein, low carbohydrate diets are not clear. It has been suggested that the positive effect of these diets may be linked to a decrease in IGF-1 levels (*Leray et al, 2006*; but see *Alt et al, 2007* reporting low IGF-1 levels in diabetic cats that normalize upon insulin treatment). Interestingly, in the study by Leray and colleagues no effect of a high protein (50% protein calories) dry diet on insulin sensitivity was observed in normal weight cats *(Leray et al, 2006)*. This was different from findings in other species. Therefore, it is unknown whether feeding cats with high protein diets is an effective means to prevent the development of diabetes mellitus. Clearly, this question remains unanswered at present.

► Dietary carbohydrate and fiber content in the diet of the diabetic cat

The traditional diet for the diabetic cat contained relatively high (≥ 30 % of calories) amounts of carbohydrate and of dietary fiber (≥50 g TDF/1000 kcal). Dietary fiber is considered beneficial because it slows gastric emptying, gastrointestinal glucose absorption, increases insulin sensitivity and improves the control of nutrient metabolism by releasing gut hormones *(Nelson et al, 2000)*. Viscous soluble fibers were considered of most value because they slow the transport of glucose to the surface of the gastrointestinal mucosa *(Nelson, 2005)*.

A study compared the outcome on the diabetic management of two canned diets with a protein content of approximately 40% of energy, one containing low amounts of carbohydrate (12% of energy) and dietary fiber (0.1g/100kcal), and one containing moderate amounts of carbohydrate (26% of energy) and high amounts of fiber (approximately 5 g/100 kcal) *(Bennett et al, 2006)*. The rate of diabetic remission was higher in the former diet (> 60% versus approx. 40%). Hence, a low content of carbohydrate clearly seems to be beneficial, and seems to outweigh the relatively low fiber content in this diet.

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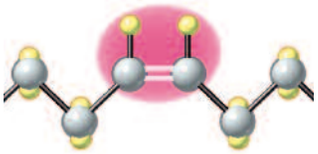
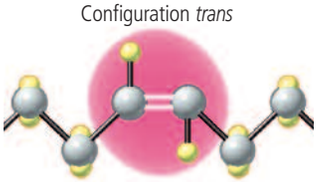
Psyllium seeds have been traditionally used in weight loss diets. Mucilage is able to absorb a great deal of water in the stomach, forming a voluminous gel. This slows down gastric emptying.

TRANS- AND CIS-CONFIGURATION OF FATTY ACIDS

Configuration *cis*



Configuration *trans*



In the trans-configuration, the hydrogen atoms are on the opposite sides of the double bond.

A study by *Nelson et al* (2000) compared two diets with similar amounts of protein (44% of dry matter), one containing a high amount (13% DMB), and one containing a low amount of fiber (2% DMB). The high fiber diet was beneficial. However, it also contained markedly less carbohydrate (27 versus 38% DMB) and slightly more protein. All factors combined might therefore have been responsible for the beneficial effect.

Overall, there is good evidence that the optimal diet for a diabetic cat should have a high protein and low carbohydrate content. Under these conditions, a high fiber content may be of slightly less importance than previously thought. However, by slowing gastrointestinal transit, dietary fiber still has its place in diets for diabetic cats. Further, a high fiber content leads to overall caloric dilution of the diet which clearly may help to control body weight in cats.

► The role of specific fatty acids

The role of different types of fatty acids in obese cats has also been evaluated. One diet was enriched in omega-3 polyunsaturated fatty acids (n-3 PUFA; total fat content 20.1% on DMB; 9.6% of fat consisting of n-3 PUFA), the control diet contained reduced amounts of n-3 PUFA (total fat content 19.8%; 1.5% of n-3 PUFA). The diet high in n-3 PUFA was shown to improve the long-term control of glycemia and lower plasma insulin levels *(Wilkins et al, 2004)*. In contrast, saturated fatty acids were considered to have detrimental effects on glucose control. The proposed underlying mechanism of omega 3-PUFA's role in metabolism may include an activation or increased expression of PPAR-gamma, and thus an increase in insulin sensitivity.

► Trace elements and antioxidants

The trace element **chromium** has been considered an essential cofactor for insulin action. The exact mechanism of chromium action to increase insulin sensitivity is unknown. However, the data are conflicting and far from conclusive. At present, there is no clear evidence to recommend the use of chromium. To the author's knowledge, the effect of chromium in diabetic cats has not been tested. Compared to other treatment options, chromium's beneficial effect appears negligible.

Vanadium, another trace element, seems to have comparable effects to chromium yet may act through different mechanisms. Only preliminary results are available which suggest that vanadium may have some beneficial effects in diabetic cats. The recommended dose was 0.2 mg/kg per day, administered via food or water *(Nelson, 2005)*.

Glucotoxicity induced by chronic hyperglycemia contributes to progressive beta-cell damage and insulin resistance. In part, this is due to increased intracellular oxidative stress. Whether widespread use of antioxidants may help to reduce these effects, has, to the authors' knowledge, not been investigated in well-controlled studies in cats. However, these compounds are considered safe based on the current scientific data. One may therefore consider fortifying diets with antioxidants.

TRANS-FATTY ACIDS

Patricia A. Schenck, DVM, PhD

Trans-fatty acids (TFA) are a specific type of unsaturated fat. Naturally occurring unsaturated fatty acids are mostly in the cis-configuration. In TFA, the spatial configuration is different because the hydrogen atoms are on the opposite sides of the double bond. TFA are found naturally in ruminant meats and dairy products. They are created by microbial transformation of cis-unsaturated fatty acids in the forestomachs. High levels of TFA, however, are also created during industrial hydrogenation or deodorization mainly of plant oils. The concentration of TFA in ruminant fats is approximately 5 to 8 g/100g fat, whereas the TFA of partially hydrogenated vegetable oils averages 45g TFA/100g oil.

TFA and human nutrition

Recently, public interest has focused on the potential health risks associated with TFA intake in humans. Dietary TFA have been suggested to increase insulin resistance in humans, increasing the risk for the development of type 2 diabetes mellitus. Therefore, the replacement of TFA with polyunsaturated fat was postulated to markedly reduce the risk for the development of diabetes. Because of these potential health risks, some government agencies require the clear labeling of TFA contents in human foods, and some countries such as Denmark restrict the sale of processed oils containing high levels of TFA (e.g., more than 2% TFA in Denmark). In the United States, TFA have to be itemized separately in the Nutrition Facts label of food products.

Not all TFA are equal

It is very important to stress that not all TFA are equal. The negative effects of some TFA that are mainly created during industrial processing of vegetable fat have to be clearly separated from effects of other TFA that are created by microbial fermentation in the ruminants' forestomachs. At least some of the latter TFA, e.g. the C-18 trans-vaccen acid, may rather have beneficial health effects. Trans-vaccen acid can be metabolized to conjugated linoleic acid which has been shown to have antidiabetic effects and anti-cancerogenic effects in animal experiments.

TFA in cat and dog food

Currently, there is no reason to believe that pet food containing TFA derived from ruminant sources has any deleterious effects on animal health. To my knowledge, no studies evaluating the effects of TFA in pets have been reported at this time nor have the different effects of TFA derived from ruminant sources versus industrially processed vegetable oils been looked at in cats or dogs.

13 - High protein diet and renal function

The question about the long-term effect of high protein diets on renal function has been raised. However, it should be stressed that there is no indication that the long term feeding of diets high in protein causes a deterioration of kidney function in normal cats or in cats with early kidney disease *(Finco et al, 1998)*. Obviously, high protein diets are contraindicated for cats with uremia, and nephropathy is a relatively common finding in diabetic cats *(Nelson, 2005)*. To the author's knowledge, however, no study has investigated this question in detail.

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In our experience, most cats readily accept the currently available diets that are high in protein and low in carbohydrate. Cats like these diets, and many cats are rather polyphagic in the initial stages of treatment.

In cases where impaired renal function and azotemia occur concurrently in diabetic cats, the use of diets with reduced amounts of protein may be warranted to minimize the risk of a uremic crisis. In these cases, one may envisage the combination of such a diet with drugs like acarbose, which limits gastrointestinal carbohydrate absorption. However, hard data to support this idea are lacking.

Despite a clear improvement in the management of diabetic cats since the introduction of diets high in protein and low in carbohydrate, many questions remain to be answered.

- Is protein or carbohydrate the key factor, i.e. is it the high protein or the low carbohydrate content that is most important?
- Do some particular amino acids such as arginine, have beneficial effects? Hence, would different sources of protein play a role *(Leray et al, 2006)*?
- What are the long term consequences of feeding these diets for the risk of diabetic ketosis or diabetic nephropathy? At present, there is no indication that the long term feeding of diets high in protein leads to a deterioration of kidney function in normal cats or in cats with early kidney disease *(Finco et al, 1998)*.
- What are the long term consequences of feeding high protein diets on body weight and body composition?

14 - Practical recommendations to feed the diabetic cat

► Format of the food

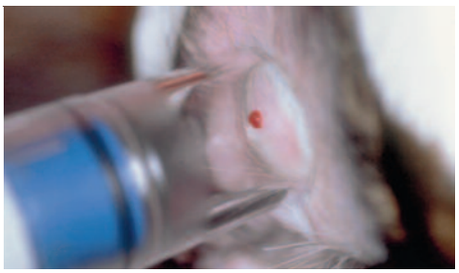
Today, special diets for diabetic cats are available both as canned or dry food. Extrusion technology has been improved to such a degree where dry diets with high protein and low carbohydrate content have become available. Clearly, there is no indication whether a canned versus a dry diet offers a major advantage as long as the composition of the diet with a high protein and low carbohydrate content is controlled.

► Method of feeding

Most diabetic cats can best be fed twice a day, with insulin being injected just before or after meals. Obviously, this feeding regimen does not correspond to the natural feeding rhythm in cats which, when fed ad libitum, may consume up to 15 small meals throughout the day. Nevertheless, especially with the use of high protein diets, postprandial glucose levels increase only slightly compared to high carbohydrate diets *(Kettelhut et al, 1980; Kienzle, 1994; Martin & Rand, 1999)*. Therefore, the timing of insulin injection relative to offering food, may seem less important. This was confirmed in an unpublished study indicating that the timing of insulin injection, which was supposed to be optimized for insulin action to occur (45 minutes before meal versus at the onset of the meal), had little effect on metabolic control *(Alt, 2006)*. Hence, the composition of the diet is much more important than the timing of meals. It needs to be stressed, however, that food must be available once insulin action occurs to prevent life-threatening hypoglycemia.

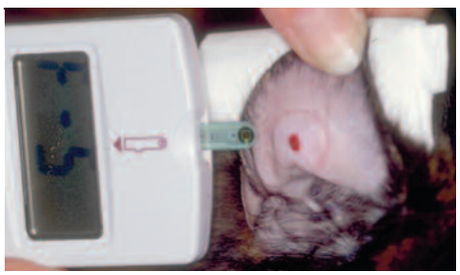
Courtesy of Prof. C. Reusch, Vetsuisse-Faculty University of Zurich).

Figure 27 - Home monitoring of blood glucose concentration in cats.



Courtesy of Prof. C. Reusch, Vetsuisse-Faculty University of Zurich).

Capillary blood obtained from the cat's ear.



Courtesy of Prof. C. Reusch, Vetsuisse-Faculty University of Zurich).

Glucose is easily checked with portable glucometers.

► Medical checks

Caution must be taken to avoid hypoglycemia when insulin-treated diabetic cats are shifted to a high protein, low carbohydrate diet.

This point also stresses that throughout therapy, diabetic cats should be regularly monitored. This can be achieved by home monitoring for the blood glucose level with portable glucometers **(Figure 27)** *(Reusch et al, 2006b)* coupled with regular laboratory determination of serum fructosamine concentrations. Owners should also be aware of the possible clinical signs associated with hypo- or hyperglycemia. Throughout therapy, but also when insulin therapy is no longer necessary (transient diabetes mellitus), owners can easily check their cats for the recurrence of glucosuria using glucose sticks in fresh cat litter that is mixed with a small volume of water. This will provide at least some information to consider adjustment in the insulin regimen.

Remission of diabetes mellitus is possible in many cats if the blood glucose concentration can be controlled with insulin therapy combined with a high protein diet. Therefore, many cats may not need lifelong insulin therapy. Insulin is discontinued with acquisition of glycemic control. It is recommended to maintain the high protein diet during remission. In addition, the cat should be regularly reevaluated to monitor for recurrence of clinical signs of diabetes mellitus. If or when the diabetes returns, specific treatment must be immediately reinstated.

Conclusion

Feline DM is a frequent metabolic disorder and its prevalence has increased over the last 30 years. This is most likely linked to the obesity problem in our pet population, especially in cats. However, at the same time treatment has become much more successful and the fatality rate in diabetes mellitus decreased tremendously over the last 10-20 years. Considering the major underlying pathophysiological disorder, i.e. the lack of insulin and insulin action, most diabetic cats have traditionally been treated with insulin. Insulin is still the treatment of choice because it is best suited to control metabolism and to help reduce glucolipotoxicity. This may result in complete resolution of clinical signs. Over the last few years, it has become very clear that insulin therapy should be supported by switching the diet of diabetic cats to a high protein (> 50%) low carbohydrate (<15%) diet. The remission rate has increased markedly since the introduction of these diets in the treatment regimen. Overall, feline DM clearly is a disease that can and should be treated.

Frequently asked questions about dietetic treatment of feline diabetes mellitus

Q	A
What is the most effective way to treat diabetic cats?	Experience over the last few years clearly favors intensive insulin therapy (mostly BID), combined with feeding a high protein diet, low carbohydrate diet.
Do diabetic cats have postprandial hyperglycemia?	This seems to depend largely on the composition of the diet. Cats fed high protein diets that are now recommended for diabetic cats show no or only a slight postprandial increase in glycemia. The higher the carbohydrate content of a diet, the stronger the postprandial hyperglycemia will be.
What is the effect of different diets on average blood glucose levels?	In general, it is much easier to maintain near-normal glycemia in insulin-treated, diabetic cats when they are fed a high-protein, low-carbohydrate diet. Postprandial hyperglycemia is almost absent, and the average blood glucose level is reduced.
How long before or after insulin injection should a diabetic cat be fed?	If meal-fed, diabetic cats can be injected just after feeding but no clear recommendation can be given. A study compared feeding immediately after injection or 45 min after injection. No major differences on metabolic control were observed.
What feeding paradigm is best for diabetic cats?	If maintenance of body weight is not a problem, it appears possible to feed diabetic cats ad libitum. If obesity is of concern, restricted feeding requires that food is not available ad libitum. In this situation, two meals per day, just followed by insulin injection, may be most appropriate.
What do you do if a diabetic cat does not eat after the insulin injection?	In an emergency situation, when a diabetic cat has received its full dose of insulin and does not eat, the cat should be offered rapidly absorbable carbohydrates, e.g. honey, to prevent life-threatening hypoglycemia. If a diabetic cat suddenly refuses to eat the diet, another formulation should be tested, preferably also with a high protein content. Such an emergency situation can be prevented if insulin is injected only after the cat has eaten the meal. Obviously, this may be difficult for some owners for practical or time reasons.
Can the diet for a diabetic cat be varied from day to day?	Ideally, diabetic cats should be fed with high protein diets throughout the remainder of their lives, even if diabetic remission occurs. Anecdotal reports indicate that hyperglycemia will reappear within a few days when switching a cat in diabetic remission to a high carbohydrate diet. Therefore, given the metabolic situation in cats and the specific benefit of high protein, low carbohydrate diets in diabetic cats, it appears safe to recommend the long term use of these diets, even after resolution of clinical signs.
Does physical activity play a role in therapy?	It may be very difficult to control physical activity in cats. However, it is recommended to keep physical activity at a relatively constant level so that energy intake and energy expenditure are well matched to the treatment regime with insulin and diet.
Should the diet for diabetic cats contain high levels of dietary fibers?	Traditionally, high fiber diets were recommended for diabetic cats. However, the high fiber content does not seem to be the most important factor. High protein low carbohydrate diets seem to be very effective. It is currently not completely clear if high protein high fiber diets would offer an additional benefit. In any case, however, the lower caloric density in high fiber diets will render the control of body weight easier.
What should be done to achieve ideal body weight in diabetic cats?	Most diabetic cats are obese. Therefore, treatment should also aim at reducing body weight to normal levels. A decrease of 1.5% of body weight per week appears to be safe (see Obesity chapter).When fed high protein diets, cats loose mainly body fat and maintain lean body mass.
Can diabetes mellitus be prevented?	The risk for becoming diabetic increases dramatically in overweight cats. Therefore, preventing obesity seems to be the most important factor to lower the risk of developing the disease. This is true in particular for neutered cats, because neutered cats eat more and need less energy. Neutered cats are three to four times more likely to become obese, and obese cats are four times more likely to become diabetic.

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Focus on:

Arginine

For cats, arginine is an essential amino acid used in the synthesis of many proteins. It also plays a role in essential functions:

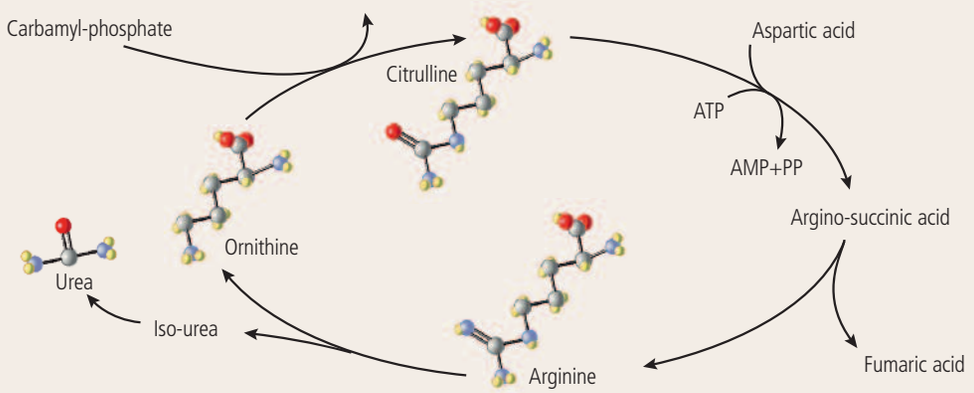
- as a mandatory intermediary in the synthesis of urea
- as a precursor in the synthesis of nitric oxide and biogenic amines
- as a stimulator of secretion of several hormones, such as insulin, glucagon and gastrin.

Consequences of arginine deficiency

While a kitten's growth obviously depends on adequate intake of arginine through the food, it should not be forgotten that adult cats are extremely sensitive to even a short-term deficiency of arginine. When it receives a food that contains a high amino acid content but no arginine, signs of ammonia intoxication appear within 1-3 hours: ptyalism, vomiting, ataxia, hyperesthesia and nervous problems *(Morris and Rogers, 1978)*. In some conditions, the intoxication can be lethal.

The cat's strong dependence on arginine can be explained by its excellent adaptation to a carnivorous diet. Arginine is abundant in animal protein. On the other hand, while ornithine and citrulline are possible arginine precursors in other mammals, the conversion rate is too low in cats to cover arginine requirements.

SYNTHESIS OF UREA



Cats require arginine for the synthesis of urea.

Recommended arginine intakes in cats

For adult cats, the NRC (2006) recommends an intake of < 0.77% DM (ME is around 4,000 kcal/kg) or 1.93 g/1000 kcal. The arginine should be raised in proportion to the protein content (+ 0.02 g of arginine by g of protein above the minimum level of 20%).

Arginine, a promoter of insulin secretion

In cats, amino acids and especially arginine greatly stimulate the secretion of insulin by the pancreas *(Curry et al, 1982)*. Arginine acts by producing direct depolarization of the membranes of the ß cells in the pancreas and induces a flow of calcium ions.

This secretion of insulin is also stimulated in the presence of glucotoxicity.

In the event of chronic hyperglycemia, the secretion of insulin in response to arginine is normal or increased, while the secretion of insulin in response to glucose is decreased *(Kitamura et al, 1999)*.

These observations may explain the benefit of very high protein diets for diabetic cats. A high arginine diet (>7 g/1000 kcal) helps stimulate insulin secretion and promotes the remission of the disease.

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Diabetes mellitus is most often observed in mature cats, peaking around 10-12 years.

Risk factors for diabetes mellitus in cats

Endocrine diseases are increasingly the new frontier of feline medicine. Together with hyperthyroidism, diabetes mellitus is one of the most common endocrinopathies in cats. For the last few years, the number of obese subjects in the cat population has been on the increase, as has the incidence of diabetes mellitus.

Obesity

This is the principle risk factor. It is responsible for the reduction in peripheral sensitivity to insulin. Compensatory hyperinsulinemia can then lead to the exhaustion of ß cells in the pancreas.

Age

The disease is most common in mature individuals with insulin resistance (error in the peripheral action of insulin) and insufficient insulin secretion. A peak is observed around 10-12 years.

Sex

Males appear to be at greater risk of diabetes (in association with obesity)

Drugs

Glucocorticoids and synthesized progestagens reduce insulin sensitivity.

Endocrine disease

E.g. acromegaly and hyperadrenocorticism, which are uncommon in cats.

Clinical signs

Diabetes mellitus is a heterogeneous disease characterized by pronounced hyperglycemia following an insulin secretion and/or action anomaly. By analogy with observations in humans, most cats appear to suffer from type 2 diabetes.

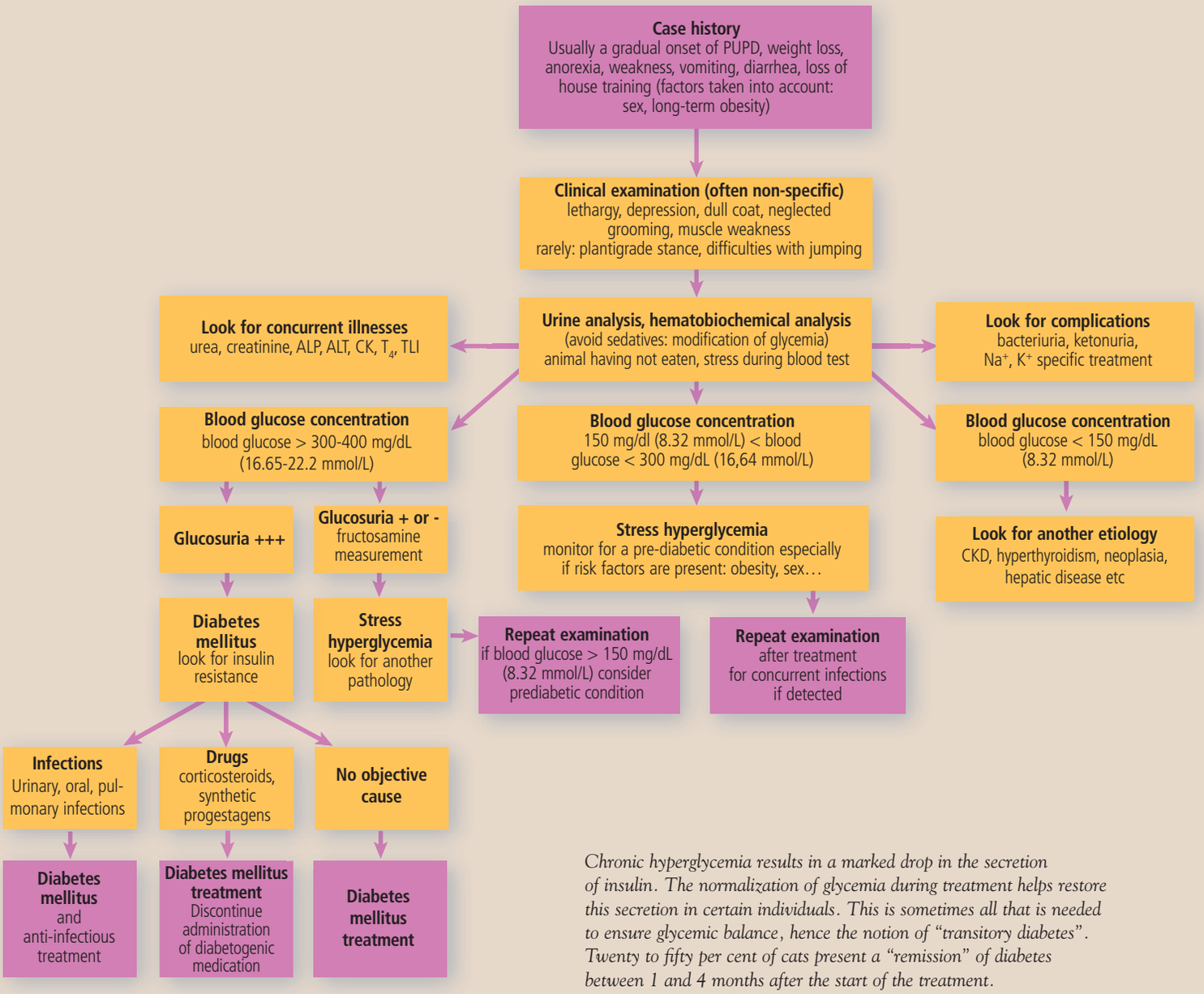
The most common symptoms observed by owners are:

- polydipsia
- weight loss over several weeks
- anorexia
- fatigue, lethargy
- vomiting
- polyphagia

Poor personal hygiene and locomotor problems (e.g. difficulty jumping) may sometimes cause owners to consult a veterinarian. All these signs are often mild and develop very slowly.

Decision-making algorithm when diabetes mellitus is suspected in a cat

(Dr. Dominique Péchereau)



Chronic hyperglycemia results in a marked drop in the secretion of insulin. The normalization of glycemia during treatment helps restore this secretion in certain individuals. This is sometimes all that is needed to ensure glycemic balance, hence the notion of "transitory diabetes". Twenty to fifty per cent of cats present a "remission" of diabetes between 1 and 4 months after the start of the treatment. For this reason, and with a view to sparing the pancreatic function as far as possible, insulin is the preferred initial treatment.

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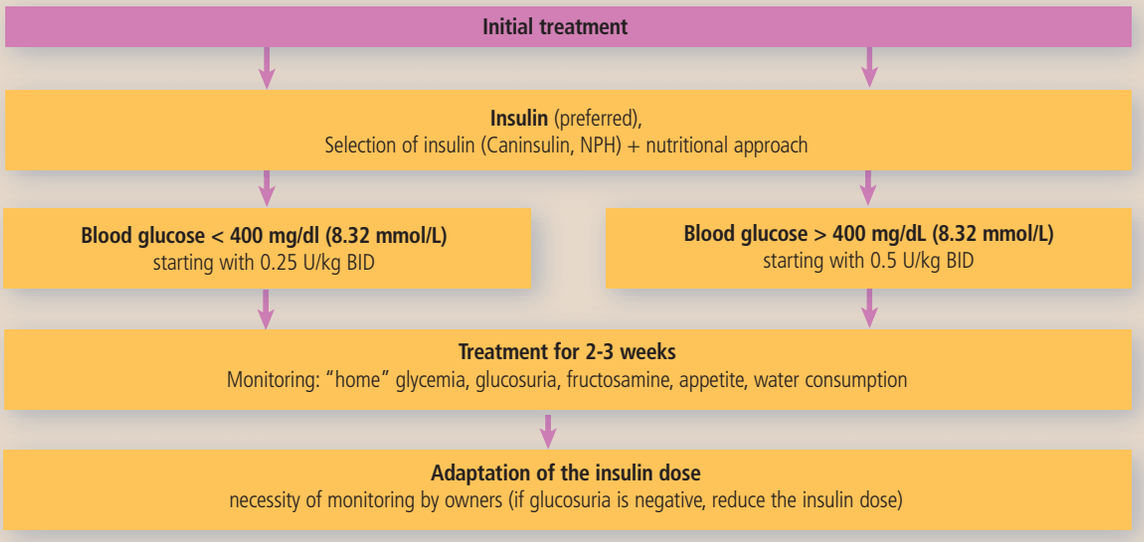

Frequency of insulin therapy

Give preference to two daily insulin injections, while checking the activity of the selected insulin.

- Never start with more than 0.5 U/kg, twice per day (at least the first two weeks).
- Always make sure the owner is properly instructed to ensure the efficacy of the treatment. Practice the injection, emphasize the necessity of consistency with the dose, draw attention to the injection site and signs to be monitored (especially those connected to hypoglycemia).

Treatment follow-up

Blood glucose concentration

Owners should monitor the blood glucose concentration using a "glucometer". The aim is to maintain the blood glucose between 120 and 160 mg/dl (6.66 and 8.88 mmol/L). If it falls below 120 mg/dl (6.66 mmol/L), the insulin dose should be reduced.

Monitor water consumption

Monitoring water consumption is a very reliable parameter for indicating the degree of glycemic control.

Regularly check glucosuria

It is important that owners know how to use and interpret a urine strip test. The renal glucose threshold in cats is between 200 and 270 mg/dl (11.1 and 14.99 mmol/L) of glycemia. Regularly monitoring the urine for glucosuria will provide an indication of when to reduce the insulin dose in cases of transient diabetes mellitus. If the glucosuria remains negative over several consecutive samples, the insulin dose maybe reduced.

Measurement of fructosamine and glycosylated hemoglobin

The analysis of these parameters simplifies the control by the owner. Fructosamine must be kept below 500 µmol/L and glycosylated hemoglobin below 3%.

Dietary rules

Control excess weight

Obesity is a major risk factor with respect to insulin resistance, so it is vital to select a food with a moderate energy and fat content, and a high protein content to promote an ideal body condition and maintain the lean mass. The supplementation of L-carnitine is also recommended to facilitate the use of fatty acids and so weight loss.

Minimize stimulation of ß cells by glucose

High protein diets (> 45 % of dry matter (DM)) with a moderate starch content (< 20% DM) from a source with a low glycemic index helps limit post-prandial hyperglycemia peaks. These types of diet combat insulin resistance. The presence of psyllium, a soluble fiber that slows down gastric emptying and regulates digestive transit, also helps slow down glucose assimilation.

Stimulate endogenous secretion of insulin

Several amino acids, especially arginine, promote endogenous secretion of insulin in cats. This is an additional argument in favor of using high protein diets in the event of diabetes mellitus in cats.

By following the nutritional rules, you can reduce the insulin dose or even achieve remission of the disease.


Hyperlipidemia

Patricia A. SCHENCK
DMV, PhD

Diagnostic approach to the hyperlipidemic cat and dietary treatment

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ABBREVIATIONS USED IN THIS CHAPTER

ACAT: acyl-coenzyme A cholesterol acyltransferase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
CETP: cholesteryl ester transfer protein
DHA: docosahexaenoic acid
EPA: eicosapentaenoic acid
HDL: high density lipoproteins
HMGCoA reductase: 3-hydroxy-3-methylglutaryl coenzyme A reductase
IDL: intermediate density lipoproteins
LCAT: lecithin cholesterol acyltransferase
LDH: lactate deshydrogenase
LDL: low density lipoproteins
LPL: lipoprotein lipase
ME: metabolizable energy
VLDL: very low density lipoproteins

Diagnostic approach to the hyperlipidemic cat and dietary treatment

Patricia A. 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 abnormally high lipid concentration in serum or plasma. Normally hyperlipidemia occurs after ingesting a meal, especially a meal high in fat, but fasting hyperlipidemia is indicative of abnormal lipid metabolism. (The term lipemia, the presence of lipids in serum or plasma, is often incorrectly used to describe an abnormal excess concentration of 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 abnormally high concentration of circulating cholesterol or triglyceride. They both may occur alone or in combination with hyperlipoproteinemia.***

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. Salts of bile acids are secreted by the liver and enter the small intestine via the bile, and most secreted salts exist as conjugates with taurine in cats. 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 hydrolysed by pancreatic cholesterol esterase. Free cholesterol passively diffuses across the intestinal mucosal cell wall *(Westergaard & Dietschy, 1976)*. Within the intestinal cell, free cholesterol is re-esterified with fatty acids, and is 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 hydrolysed by pancreatic lipase to monoglycerides, diglycerides, and free fatty acids **(Figure 1)**. 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. 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 by way of the thoracic duct.

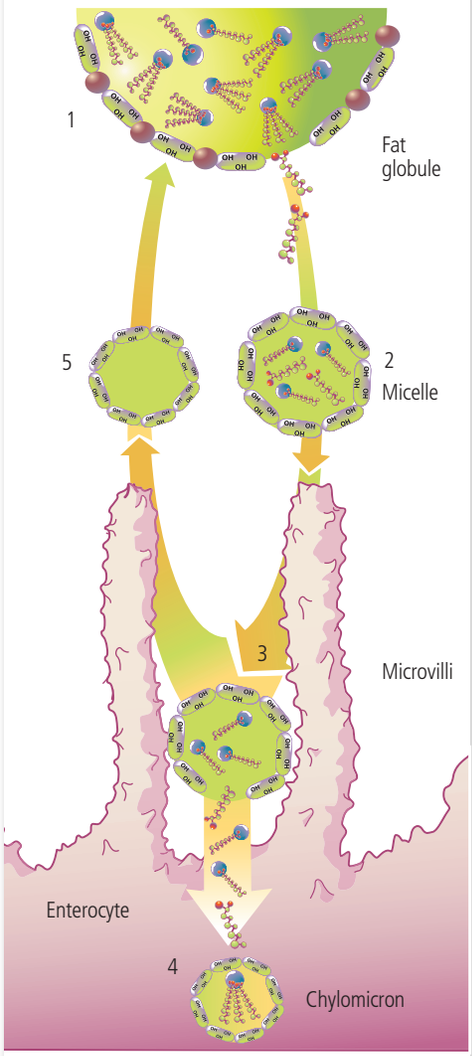
► Cholesterol synthesis

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 & Dietschy, 1981)*. In humans, approximately 1 g cholesterol per day is synthesized within the body from acetyl CoA, and 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 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 & Weisgraber, 1974)*. Lipoproteins in humans have been well characterized *(Alaupovic et al, 1968; Assmann, 1982; Shepherd & Packard, 1989)*, but direct correlations cannot be made to the feline due to many differences in lipoprotein characteristics *(Mahley et al, 1974; Mahley & Weisgraber, 1974)*.

FIGURE 1 - DIGESTION AND ABSORPTION OF LIPIDS
(From Gogny, 1994)



1- Fat globules: lipases act on the surface of the emulsion

2- Micelle: transport form for fatty acids

3- Fat release to the enterocytes

4- Triglycerides resynthesis and incorporation in chylomicrons

5- Absorption of biliary salts in the ileum

biliary salts
lipase and colipase
free fatty acids
monoglyceride
diglyceride
triglyceride

Lipoproteins are micellar particles with a hydrophobic core containing triglycerides and cholesteryl esters, and an amphipathic outer surface containing phospholipid, 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 (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. Cats 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

► Chylomicrons

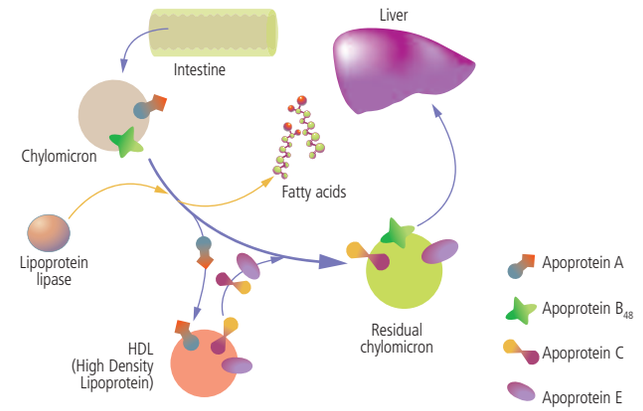
Chylomicrons are the largest of the lipoproteins with the lowest density **(Table 2)**. Chylomicrons have a high triglyceride content, low protein content and remain at the origin on lipoprotein electrophoresis *(Bauer, 1996)*. Chylomicrons contain different types of apoproteins. In the peripheral circulation, chylomicrons contribute apoprotein A to HDL in exchange for apoprotein C and E **(Figure 2)**, increasing their protein content *(Capurso, 1987)*. A chylomicron remnant is formed.

Lipoprotein lipase (LPL) activated by apoprotein C-II of chylomicrons hydrolyzes the triglyceride present in chylomicrons, creating a phos-

TABLE 2 - FELINE LIPOPROTEIN CHARACTERISTICS

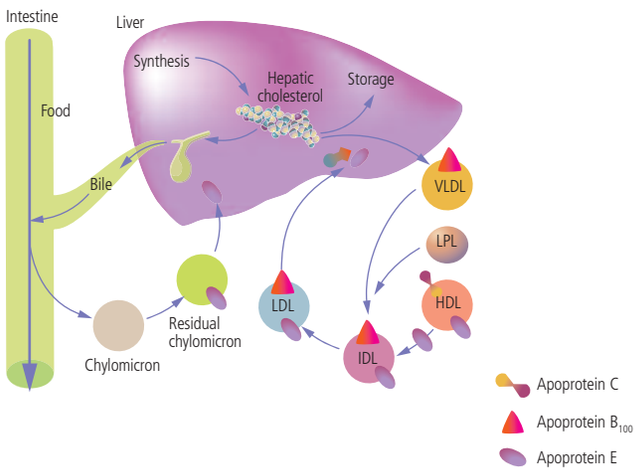
			APPROXIMATE COMPOSITION (%)					
Lipoproteins	**Hydrated density g/mL**	**Electrophoretic mobility**	**Triglycerides**	**Cholesteryl ester**	**Free cholesterol**	**Proteins**	**Phospholipids**	**Major apoproteins**
Chylomicrons	0.960	Origin	**90**	2	1	2	6	B_{48}
VLDL	< 1.006	β (pre-β)	**60**	13	7	5	15	B_{100}, E, C
LDL	1.030 – 1.043	β	10	**38**	8	22	22	B_{100}
HDL - HDL2 - HDL3	- 1.063 – 1.100 1.100 – 1.210	- α1 α1	4 - -	16 - -	6 - -	50 - -	25 - -	- E, A-1, C A, C

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.

pholipid-rich particle. Lipoprotein lipase is associated with endothelial cell surfaces, interacting with membrane associated heparan sulfate *(Nilsson-Ehle et al, 1980)*. Chylomicron remnant formation is necessary for hepatic clearance of chylomicrons *(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)*.

► Very low density lipoproteins (VLDL)

VLDL are synthesized by hepatocytes **(Figure 3)**, and are a major transporter of triglyceride *(Mills & Taylaur, 1971)*. VLDL are smaller and heavier than chylomicrons, have a density of < 1.006 g/mL, and contain apoproteins B100, E, and C. VLDL binds to LPL, and LPL 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)*. Feline VLDL exhibits pre-β migration on lipoprotein electrophoresis, which is similar to human VLDL.

► Low density lipoproteins (LDL)

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 & Brown, 1984)*. Feline

LDL exhibits β migration on lipoprotein electrophoresis, have a density of 1.030 - 1.043 g/mL, and contain apoprotein B100.

► High density lipoproteins (HDL)

HDL are the smallest and heaviest of the lipoproteins, with the greatest quantity of protein and least quantity of triglyceride of any of the lipoproteins. Cats have approximately 5 times more HDL than LDL unlike humans, but similar to the canine. Feline HDL is divided into 2 subclasses based on composition and density:

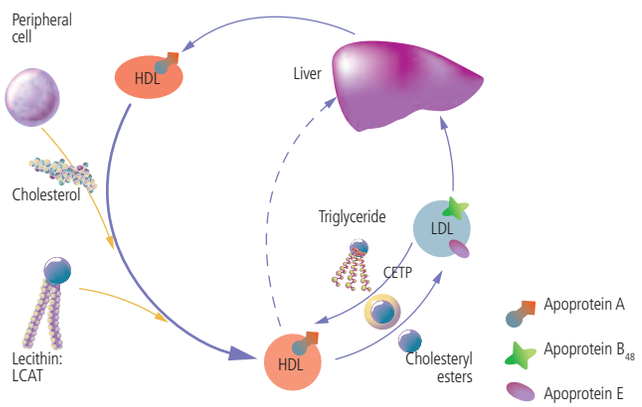
- HDL2 has a density of 1.063 – 1.100 g/mL, and contains apoproteins E, A-1, and C.
- HDL3 is smaller than HDL2 with a density of 1.100 – 1.210 g/mL, and contains apoproteins A and C.

Both HDL2 and HDL3 exhibit α1-migration on lipoprotein electrophoresis *(Demacker et al, 1987)*.

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)*. This mechanism for returning peripheral cholesterol to the liver has been termed reverse cholesterol transport. Cats however have low levels of CETP *(Guyard-Dangremont et al, 1998)*, and 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 cat, reverse cholesterol transport is completed via HDL uptake by the liver. The cat is a "HDL mammal" since most of the circulating cholesterol is carried by HDL and cannot be transferred to LDL as in humans (a "LDL mammal").

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.

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 6)**. The presumption that the cat was fasted should be verified, to ensure that all access to food has been withheld. Once fasting hyperlipidemia has been confirmed, the causes of hyperlipidemia secondary to other disorders should be ruled out. If no secondary disorder resulting in hyperlipidemia is evident, then a primary hyperlipidemia should be considered.

► Serum turbidity

Visual evaluation of the degree of serum turbidity can provide an estimation of serum triglyceride concentration:

- normal, clear serum: typical triglyceride concentration < 200 mg/dL (2.3 mmol/L)
- hazy serum: triglyceride concentration around 300 mg/dL (3.4 mmol/L)
- opacity of the serum: triglyceride concentration approaches 600 mg/dL (6.8 mmol/L)
- serum with the appearance of skim milk: triglyceride concentration is usually around 1000 mg/dL (11.3 mmol/L)
- serum with the appearance of whole milk: triglyceride concentration as high as 2500 (28.2 mmol/L) to 4000 mg/dL (45.2 mmol/L)

► Refrigeration test

To ascertain the lipoprotein classes that may be present in excess, a simple refrigeration test can be performed **(Figure 7)**. 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 the chylomicron layer is clear, then only

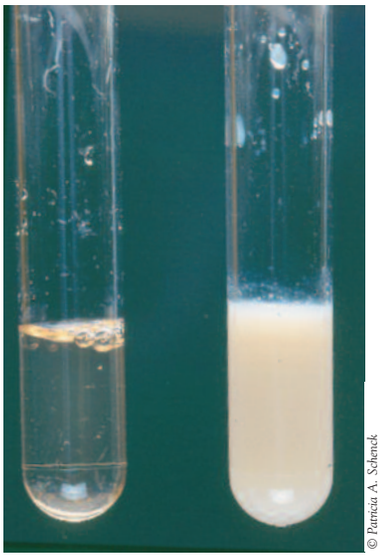


Figure 5 - The appearance of normal and hyperlipidemic serum. *Normal serum should be clear, with no evidence of turbidity (left tube). Fasting serum that is turbid indicates the presence of excess lipid in the serum (right tube).*

Figure 7 - Refrigeration test of hyperlipidemic serum. *On the left, a fasting serum sample 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).*

FIGURE 6 - ALGORITHM TO DETERMINE THE CAUSE OF HYPERLIPIDEMIA

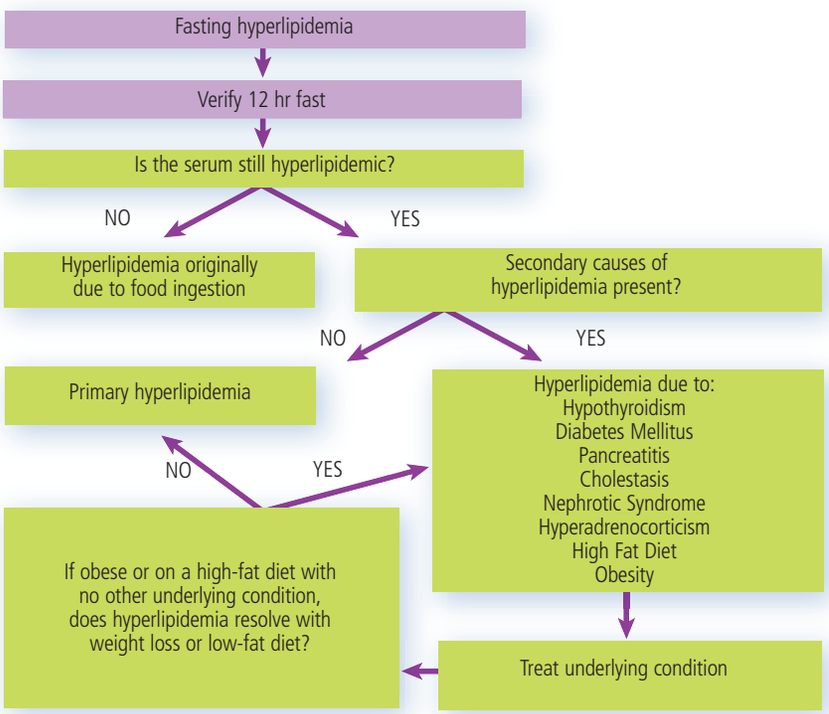
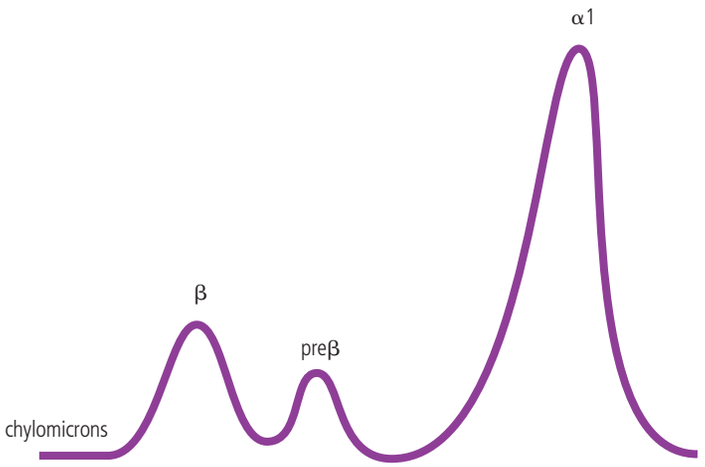


FIGURE 8 - DENSITOMETRIC TRACING OF A LIPOPROTEIN ELECTROPHORETOGRAM FROM A NORMAL CAT.



The peaks from left to right represent the relative concentrations of β-migrating lipoproteins (LDL), preβ-migrating lipoproteins (VLDL), and α1-migrating lipoproteins (HDL2/HDL3). Note the predominance of α1-migrating lipoproteins in the normal cat (a HDL mammal). A small percentage of chylomicrons may be present in normal cats; chylomicrons will exhibit a small peak at the origin if present.

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.

► 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 feline lipoprotein characteristics (i.e. not a human laboratory), since differences exist between humans and cats in electrophoretic pattern. Lipoprotein electrophoresis is not quantitative, but is useful to identify an excess in a particular lipoprotein class.

► 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. Thus ultracentrifugation 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
- if cholesterol is present at a concentration of greater than 700 mg/dL, the measured triglyceride concentration may be falsely lowered *(Shephard & Whiting, 1990)*
- hypertriglyceridemia may result in a falsely lower cholesterol concentration *(Cobbaert & Tricarico, 1993)*
- pentobarbital may falsely increase triglyceride measurement *(Hata et al, 1978)*, but phenobarbitone has no effect on cholesterol concentration *(Foster et al, 2000)*.

Depending on the 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 α1-antitrypsin concentration may also be falsely increased *(Bossuyt & Blanckaert, 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 & Solter, 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 10mg/dL will not interfere with phenobarbital measurement *(Baer & Paulson, 1987)*.

3 - Causes of hyperlipidemia

Hyperlipidemia may be the result of lipid abnormalities secondary to other conditions, or may be a primary disorder of lipid metabolism **(Table 3)**. In the cat, recognized primary disorders include inherited hyperchylomicronemia, and idiopathic hypercholesterolemia. Conditions that can result in secondary hyperlipidemia include hypothyroidism, pancreatitis, diabetes mellitus, nephrotic syndrome, hyperadrenocorticism, cholestasis, obesity or the feeding of very high fat diets.

TABLE 3 - CAUSES OF HYPERLIPIDEMIA IN THE CAT

Postprandial
Primary Inherited hyperchylomicronemia Idiopathic hypercholesterolemia
Secondary Hypothyroidism Pancreatitis Diabetes Mellitus Nephrotic Syndrome Hyperadrenocorticism Cholestasis Obesity "High fat" diets

► Hypothyroidism

Naturally occurring hypothyroidism is rare in cats, and may be congenital or acquired. Iatrogenically-induced hypothyroidism is more common in the cat, arising from treatment for hyperthyroidism. Increases in both serum cholesterol and triglyceride concentrations have been associated with canine hypothyroidism *(Boretti et al, 2003; Rogers et al, 1975)*, and cholesterol elevations are usually moderate *(Jaggy et al, 1994)*. Both serum cholesterol and triglyceride concentrations return to normal with adequate thyroid replacement therapy *(Rogers et al, 1975)*. Changes in lipoproteins have not been evaluated in hypothyroid cats.

In humans with hypothyroidism, mRNA for LDL receptors is decreased resulting in decreased cholesterol and chylomicron clearance *(Kovanen, 1987)*. Lipoprotein lipase activity may be altered *(Hansson et al, 1983; Pykalisto et al, 1976)*, and there is decreased excretion of cholesterol into bile *(Gebhard & Prigge, 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)*.

Naturally occurring atherosclerosis has been noted in dogs with hypothyroidism *(Manning, 1979)*, but has not been observed in the cat.

► Pancreatitis

In humans, there is evidence that pancreatitis is associated with decreased LPL activity *(Hazzard et al, 1984)*. This decreased activity of LPL may result in increased triglyceride concentrations with slower clearance of chylomicrons. Two dogs with pancreatitis also exhibited a moderate decrease in LPL activity, which returned to normal with treatment and resolution of the pancreatitis *(Schenck, unpublished observations)*.

In cats, pancreatitis usually results in hyperlipidemia with elevations in serum cholesterol *(Hill & Van Winkle, 1993)* and possibly triglyceride concentrations. Pancreatitis can be a cause of hyperlipidemia, or a sequel to hyperlipidemia. Little is known regarding lipoprotein abnormalities in the cat with pancreatitis.

► Diabetes mellitus

In diabetes mellitus, elevations of both serum triglyceride and cholesterol concentrations are typically observed *(Rogers et al, 1975)*. Lipoproteins have not been characterized in the diabetic cat, but abnormalities have been well characterized in humans.

In humans with diabetes mellitus, LPL 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 six-fold, indicating an increase in whole-body cholesterol synthesis, and HMGCoA reductase activity is increased in both the liver and intestine *(Feingold et al, 1994; Kwong et al, 1991)*. 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

Since cats and humans both typically exhibit Type 2 diabetes mellitus characterized by insulin resistance, it is likely that there are lipoprotein similarities.

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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)*, but this has not yet been noted in the diabetic cat.

► Nephrotic syndrome

Lipoprotein abnormalities have not been characterized in cats with nephrotic syndrome. Cats with nephrotic syndrome may exhibit mild elevations in serum cholesterol and triglyceride.

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 & Liang, 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 *(Chmielewski et al, 2003; Szolkiewicz et al, 2002)*, and the increased cholesterol does not up-regulate LDL receptors *(Liang & Vaziri, 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 & Vaziri, 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 LPL *(Shearer & Kaysen, 2001)*, and proteinuria may also be associated with the urinary loss of heparan sulfate, an important cofactor for LPL *(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

Hyperadrenocorticism is uncommon in the cat. In cats with hyperadrenocorticism, hypercholesterolemia may be noted *(Moore et al, 2000)*. Hypercholesterolemia may be more prevalent in cases of pituitary-dependent hyperadrenocorticism than in hyperadrenocorticism caused by adrenal tumors. Many cats with hyperadrenocorticism also have concurrent diabetes mellitus which can also cause an increase in serum cholesterol and other lipid abnormalities. In dogs with hyperadrenocorticism, concentrations of both VLDL and LDL have been noted, but lipoproteins have not been characterized in cats with hyperadrenocorticism.

Lipoprotein lipase activity may be 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.

► Cholestasis

In cats with induced cholestasis, hypercholesterolemia was observed *(Center et al, 1983)*. There may be alterations in the content of lipoproteins *(Danielsson et al, 1977)*, but changes in lipoproteins have not been characterized in cats with cholestasis. Hepatic lipidosis arising from weight

loss may cause cholestasis through accumulation of excess triglyceride in hepatocytes. Hepatic lipidosis results in an increase in triglyceride, VLDL, and LDL *(Blanchard et al, 2004)*. LDL becomes enriched with triglyceride, and HDL is enriched with cholesterol suggesting that VLDL secretion is enhanced and VLDL/LDL catabolism is decreased.

► Obesity

In 10 obese cats, serum concentrations of triglyceride and cholesterol were significantly increased with an increase in triglyceride content of VLDL as compared to lean cats *(Hoenig et al, 2003)*. There was no significant difference in serum non-esterified fatty acids or phospholipids, and ultracentrifugation revealed no differences in density of lipoproteins. Lower LPL activity has been observed in obese cats *(Hoenig et al, 2006)* as has been observed in obese dogs *(Schenck, unpublished data)*. Weight loss decreases serum triglyceride and cholesterol concentrations, with a decrease in LDL and VLDL *(Fettman et al, 1998)*. In another study, obese cats also showed a decreased serum cholesterol concentration, but no decrease in LDL with weight loss *(Dimski et al, 1992)*.

► High fat diets

The feeding of high fat diets may result in hyperlipidemia and moderate elevation in serum triglycerides and cholesterol concentrations *(Ginzinger et al, 1997; Thiess et al, 2004)*. HDL-cholesterol, LDL-cholesterol, and triglyceride concentrations were statistically elevated in cats fed a diet containing 30% fat, 3% cholesterol (as fed) for 2 to 8 months *(Ginzinger et al, 1997)*. Changes in lipoprotein migration on electrophoresis have not been characterized in the cat. It is also unknown at what level of dietary fat that cholesterol and triglyceride changes may be noted in the absence of additional dietary cholesterol.

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. There is one well described heritable primary hyperlipidemia in cats. In humans, many different gene mutations or defects resulting in primary hyperlipidemias have been characterized. It is likely that with further study and characterization, additional defects causing primary hyperlipidemia will be identified in the cat.

An idiopathic familial hyperchylomicronemia was first reported in two cats in New Zealand *(Jones et al, 1983)*. Since that time, inherited hyperchylomicronemia has been reported in cats in a number of countries including the USA *(Bauer & Verlander, 1984; Grieshaber et al, 1991)*, France *(Jones, 1993)*, and the UK *(Watson et al, 1992)*. The fact that many of the cats in these initial studies were related, suggested an inherited condition.

Idiopathic familial hyperchylomicronemia is often recognized in kittens or young cats, and affects a number of different breeds.

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TABLE 4 - PHYSICAL EXAMINATION FINDINGS AND CLINICAL SIGNS ASSOCIATED WITH HYPERLIPIDEMIA IN CATS

Cutaneous xanthomata (most common)
***Lipemia retinalis* (most common)**
Lipid keratopathy
Peripheral nerve paralysis
Horner's syndrome
Tibial nerve paralysis
Radial nerve paralysis
Splenomegaly
Decreased body fat mass
Failure to grow
Weakness (less common)
Lethargy (less common)

Figure 9 - Xanthomata in a hyperlipidemic cat. *Xanthomata are often present in peripheral nerves and can cause a Horner's syndrome.*

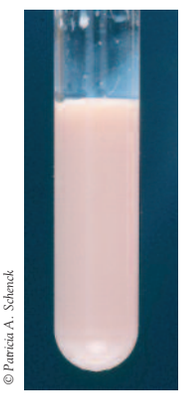


Figure 10 - Blood appearance in case of hyperchylomicronemia. *With inherited hyperchylomicronemia, there are marked elevations in serum triglyceride and cholesterol, and blood will often have a "creamy tomato soup" appearance.*

The most common physical examination findings of inherited hyperchylomicronemia are xanthomata and *lipemia retinalis* **(Table 4)** *(Jones, 1993)*.

Xanthomata are lipid deposits in skin and organs **(Figure 9)**. Xanthomata are often present in peripheral nerves *(Jones et al, 1986)*, and Horner's syndrome, tibial nerve paralysis, and radial nerve paralysis are most common. Xanthomata can also occur in the liver, spleen, lymph nodes, kidney, heart, muscle, and intestines *(Thompson et al, 1989; Johnstone et al, 1990; Grieshaber et al, 1991; Chanut et al, 2005)*. The histopathology of these lesions have been studied, and are characterized by abnormal lipid accumulation in tissues *(Thompson et al, 1989)*.

Lipemia retinalis occurs when hypertriglyceridemia is severe and greater than 15 mmol/L (1364 mg/dl). Lipid keratopathy *(Carrington, 1983)*, lipid in the anterior chamber of the eye *(Brooks, 1989)*, or lipid deposition at the limbus have also been noted in some cats. Weakness, lethargy, and failure to grow have been noted, and affected animals have a higher incidence of being stillborn.

With inherited hyperchylomicronemia, there are marked elevations in serum triglyceride and cholesterol, and blood will often have a 'cream tomato soup' appearance **(Figure 10)**. In one study, the mean cholesterol concentration in 24 cats with inherited hyperchylomicronemia was 6.6 mmol/L (reference range 1.1-5.0 mmol/L) (255 mg/dL; range 42-193 mg/dL), and the mean triglyceride concentration was 10.02 mmol/L (reference range 0.2-0.6 mmol/L) (888 mg/dL; reference range 18-53 mg/dL).

Serum concentration of triglyceride can be extremely elevated in some cats, with triglyceride concentrations reported near 147 mmol/L (13,000 mg/dL) *(Bauer & Verlander, 1984)*. The condition is characterized by a great excess of chylomicrons *(Bauer & Verlander, 1984)*, or by excess chylomicrons with slight increase in VLDL *(Jones et al, 1986)*. This condition most closely resembles Type I hyperlipidemia in humans. Atherosclerosis has not been noted in cats with inherited hyperchylomicronemia despite the lipoprotein abnormalities *(Johnstone et al, 1990)*.

Lipoprotein lipase activity is virtually absent in the inherited hyperchylomicronemia caused by a Gly412Arg missense mutation of the LPL gene of cats. The decrease in LPL activity is not due to a lack of apoprotein C-II which is necessary for LPL activation *(Watson et al, 1992)*. *Peritz et al* (1990) report that the LPL mass is normal in affected cats, but speculate the LPL protein is abnormal and cannot bind to endothelium. However, *Ginzinger et al* (1996) reported an absence of circulating mass of LPL but did find mutant mRNA forms in tissues. A similar defect of LPL has been noted in mink with severe hyperchylomicronemia, normal LPL mass, but no LPL activity *(Christophersen et al, 1997)*.

The cause of hyperchylomicronemia has been shown to be a mutation in the LPL gene *(Ginzinger et al, 1996)*, and both homozygotes and heterozygotes for LPL deficiency have been described *(Ginzinger et al, 1999)*. Homozygotes tend to be more severely affected than heterozygotes, and the severity of hyperchylomicronemia and hypertriglyceridemia is dependent on the magnitude of decrease in LPL activity. In a brother to a severely affected kitten, hypertriglyceridemia was observed but not of the same magnitude as in the severely affected kitten, and LPL activity was decreased but not to the same degree *(Bauer & Verlander, 1984)*.

Adult cats that are homozygous for LPL deficiency have a significantly decreased body fat mass as compared to those that are clinically normal or heterozygotes for LPL deficiency *(Backus et al, 2001)*. Homozygotes born to homozygote dams had a significantly lower body fat mass than homozygotes born to heterozygote dams. Thus the body fat mass depends not only on the lipoprotein status of the cat, but also on the LPL status of the dam.

Another condition that has characteristics similar to inherited hyperchylomicronemia has been observed *(Gunn-Moore et al, 1997)*. Transient hyperlipidemia and anemia has been noted in litters

of kittens with marked increase in chylomicrons and moderate increase in VLDL. After resolution of hyperlipidemia with the feeding of diets containing 9% fat as-fed (approximately 28 g fat/1000 kcal), LPL activity was only mildly lower in affected kittens as compared to normal kittens. These kittens did not exhibit the LPL gene mutation that has been shown in the inherited hyperchylomicronemia that has been well characterized. This suggests the presence of a separate distinct primary hyperlipidemia.

5 - Effects of persistent hyperlipidemia

Long-term effects of hyperlipidemia in cats are unknown. Cats are resistant to the development of atherosclerosis compared to humans, due to differences in lipoprotein metabolism between the species. Experimental atherosclerosis has been induced in cats by feeding a diet containing 30% fat, 3% cholesterol (as fed) for 2 to 8 months *(Ginzinger et al, 1997)*.

► Atherosclerosis

Atherosclerosis is a specific type of arteriosclerosis with deposition of lipid and cholesterol in the arterial tunica intima and tunica media *(Liu et al, 1986)*. It is unclear however, whether cats with inherited hyperchylomicronemia are at increased risk for the development of atherosclerosis. Studies of lipoprotein interactions with arterial walls have shown that large lipoprotein molecules such as chylomicrons and VLDL have a low influx into the intima *(Nordestgaard et al, 1992)*. Thus inherited hyperchylomicronemia may not be associated with premature atherosclerosis *(Ebara et al, 2001)*.

An increased incidence of atherosclerosis has been noted in association with causes of secondary hyperlipidemia in dogs and humans, but has not been reported in cats. This may be due to the low incidence of some causes of secondary hyperlipidemia in the cat, such as hypothyroidism where there has been evidence for associated atherosclerosis in the dog.

► Pancreatitis

There is evidence that persistent hyperlipidemia may lead to pancreatitis *(Dominguez-Munoz et al, 1991)*, and pancreatitis often occurs in humans with inherited hyperchylomicronemia and LPL deficiency. 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 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)*.

► Diabetes mellitus

Persistent hyperlipidemia may also cause diabetes mellitus *(Sane & Taskinen, 1993)*, and diabetes mellitus has been noted as a sequel to inherited hyperchylomicronemia in humans. 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 &*

Corkey, 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)*.

6 - Treatment of hyperlipidemia

Because of the clinical signs associated with primary hyperlipidemia, and the potential risks, hyperlipidemia should be treated aggressively in the cat. The underlying disorder in a secondary hyperlipidemia should be treated, but there is no specific therapeutic regimen for cats with inherited hyperchylomicronemia.

► Fat restricted-diet

The main therapy of primary hyperlipidemia involves feeding a low-fat diet with moderate protein content. Diets low in protein may cause an increase in serum cholesterol concentration (*Hansen et al, 1992)*, and are therefore not recommended unless the presence of other conditions warrant their use. Human patients with inherited hyperchylomicronemia typically must restrict dietary fat intake to less than 15% of calories to control hyperlipidemia.

Feline diets with less than 10% fat (as-fed) or less than 30g fat/1000 kcal are generally adequate. Protein content should be maintained at about 30% as-fed, or greater than 85g protein/1000 kcal. A diet should not be chosen only on the percent fat present in the diet; the diet should be low in fat based on metabolizable energy (ME). Some diets appear low in fat on a percentage basis, but actually provide a higher fat content than expected when the amount of fiber in the diet and metabolizable energy are taken into account. For example, a diet containing 11% fat with an ME of 4000 kcal/kg provides only 27.5 g fat/1000 kcal, whereas a diet containing 9% fat with an ME of 3000 kcal/kg provides 30 g fat/1000 kcal **(Table 5)**. The presence of a blend of fructo-oligosaccharides and beet pulp in the diet may also be desirable, since this blend has been shown to decrease serum triglyceride and cholesterol concentrations in the dog *(Diez et al, 1997)*.

Obesity in association with familial hyperchylomicronemia is uncommon, so it is usually not necessary to restrict caloric intake. If the cat is not obese, the amount of food offered may need to be increased because of the decreased calories provided by the new diet with decreased fat content. Many cats can continue to be fed free-choice. Treats should be restricted since these are most likely not low in fat content.

After feeding a low-fat diet for approximately 4 weeks, the presence of hyperlipidemia should be re-evaluated. Most cats will show at least partial resolution of hyperlipidemia with consumption of low-fat diets. Body condition should be assessed, and if there has been significant weight loss, the patient should receive an increased amount of diet, or possibly be switched to a different diet with higher caloric density.

If after 4 weeks hyperlipidemia is still present, the diet should be continued, and all other sources of food or treats removed. If there has been good owner compliance, then a switch to a different low-fat diet could be considered. The patient should then be reassessed after another one to two months. If hyperlipidemia still persists at that time, drug therapy could be added.

TABLE 5 - INTERPRETATION OF THE FAT CONTENT IN DIETS

	Diet A	Diet B
Amount of fat g/100g diet	11	9
ME kcal/100 g diet	400	300
Fat content	11 g x 1000 kcal/400kcal = 27.5 g fat/1000 kcal	9 g x 1000 kcal/400kcal = 30.0 g fat/1000 kcal

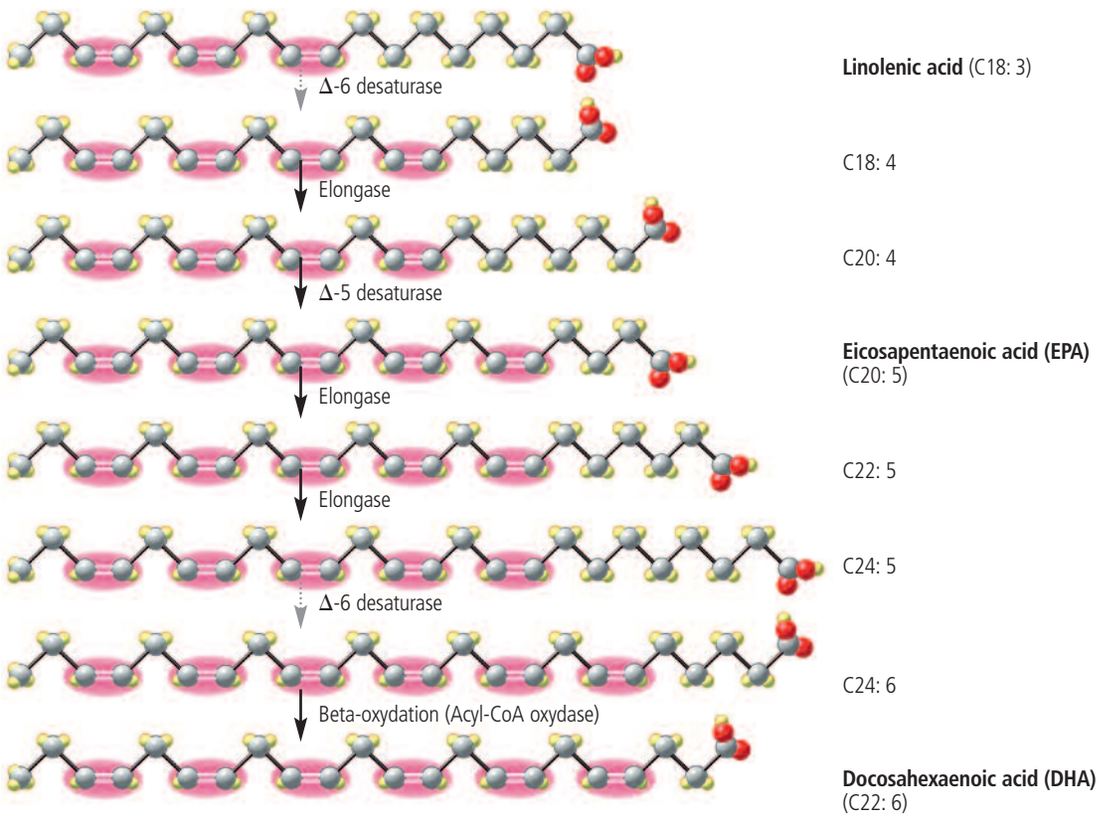
► Omega-3 fatty acid supplementation

Fish oils are rich in omega-3 fatty acids, and have been the supplement of choice in the treatment of dogs with primary hyperlipidemias. However, little is known about the effectiveness of fish oil therapy in cats. Potential doses range from 10 to 200 mg/kg body weight. The fish oil supplement should contain a high percentage of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as these are long-chain omega-3 fatty acids. Products containing a high level of linolenic acid (also an omega-3 fatty acid) will not be as effective, as cats have very low delta-6 desaturase necessary for the conversion of linolenic acid to longer chain omega-3 fatty acids *(Sinclair et al, 1979)* **(Figure 11)**.

The use of fish oil in the treatment of hyperlipidemia has been extensively studied in a number of other species. Fish oil supplement has resulted in a decrease in serum triglyceride and cholesterol in humans *(Okumura et al, 2002)*, rats *(Adan et al, 1999)*, chicks *(Castillo et al, 2000)*, dogs *(Brown et al, 2000)*, and rabbits *(Mortensen et al, 1998)*.

Omega-3 fatty acids act to decrease the synthesis of triglyceride and VLDL in the liver *(Harris et al, 1990; Connor et al, 1993)*, stimulate LPL activity *(Levy et al, 1993)*, decrease the intestinal absorption of lipid *(Thomson et al, 1993)*, and increase cholesterol secretion into bile *(Smit et al, 1991)*. Fish oil also decreases the serum concentration of free fatty acids *(Singer et al, 1990)*, which may be important in the prevention of pancreatitis and diabetes mellitus.

FIGURE 11 - METABOLISM OF LINOLENIC ACID (OMEGA-3)



Delta-6 desaturase activity is crucial for the efficient production of long-chain omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from available linolenic acid. In the feline, delta-6 desaturase activity is significantly reduced (dotted arrows), and thus there is little production of EPA and DHA from linolenic acid.