Unfortunately there are no long-term studies to verify the safety and efficacy of any lipid-lowering agent in cats, and any therapy should be used with caution. One concern with fish oil therapy is the evidence that fish oil increases the concentration of lipoperoxides in LDL *(Puiggros et al, 2002)*. The addition of vitamin E to the fish oil therapy regimen may enhance beneficial effects by increasing glutathione reductase activity and decreasing peroxide levels *(Hsu et al, 2001)*.

► Other therapeutic agents

Other therapeutic agents have been used with variable results.

- Gemfibrozil has been used to stimulate LPL activity and decrease VLDL secretion *(Santamarina-Fojo & Dugi, 1994)*, and in cats is used at a dosage of 7.5 to 10 mg/kg body weight twice daily.
- Niacin therapy has been used, however adverse effects have been noted *(Bauer, 1995)*.
- Garlic extracts have been used to decrease cholesterol in humans *(Steiner et al, 1996)*, but have not been evaluated in cats.
- HMGCoA reductase inhibitors reduce cholesterol synthesis and increase the excretion of LDL from the circulation, but their effectiveness in cats has not been studied.
- Thyroxine therapy can decrease serum total cholesterol in humans *(Brun et al, 1980)*, and is effective in lowering lipid concentrations in hypothyroid dogs, but its use has not been recommended for cats.

The mutation characterizing the LPL deficiency present in humans and cats with hyperchylomicronemia has been identified, and gene transfer therapy has been attempted. Lipoprotein lipase-deficient cats were given an injection of an adenoviral vector containing the human LPL gene, with disappearance of triglyceride-rich lipoproteins up to day 14, at which time antibodies against the human LPL protein were detected *(Liu et al, 2000)*. Concurrent administration of immunosuppressive therapy delayed antibody production, with resolution of hyperlipidemia for three weeks after administration *(Ross et al, 2006)*. Gene replacement therapy for inherited hyperchylomicronemia may become a reality in the future.

Conclusion

There are a number of conditions that can cause hyperlipidemia in the feline. Postprandial hyperlipidemia should always be verified, and secondary causes of hyperlipidemia must be ruled out. A number of the causes of secondary hyperlipidemia are uncommon in the cat (hypothyroidism, hyperadrenocorticism), or are fairly evident based on clinical signs or biochemical profile (diabetes mellitus, pancreatitis). If an underlying cause of hyperlipidemia is present, treatment of the primary disease is usually effective at resolving the secondary hyperlipidemia. Primary causes of hyperlipidemia should be aggressively treated because of the potential complications and clinical signs associated with persistent hyperlipidemia.

Frequently asked questions about feline hyperlipidemia

Q	A
What causes serum to be turbid?	Elevated serum triglyceride carried by lipoproteins causes serum to appear turbid. Opacity is seen when triglyceride concentration approaches 600 mg/dL (6.8 mmol/L). Serum may have the appearance of whole milk when triglyceride concentrations reach 2500 – 4000 mg/dL (28.2-45.2 mmol/L).
What conditions cause hyperlipidemia?	The most common cause is a non-fasted animal. If fasting for greater than 12 hours is confirmed, then primary hyperlipidemia, or secondary hyperlipidemia due to hypothyroidism, pancreatitis, diabetes mellitus, hyperadrenocorticism, cholestasis, or nephrotic syndrome may be present.
Are high fat diets harmful to cats?	Not usually. Lipid metabolism in cats is very different from that in humans. Cats carry most of their cholesterol in HDL, and are very resistant to the development of atherosclerosis. However, if certain diseases such as hypothyroidism or diabetes mellitus are present, high fat diets could result in further lipid abnormalities. In addition, high fat diets for neutered and sedentary cats can contribute to obesity with subsequent health issues.
What causes a "cream layer" to separate in some turbid serum samples?	The "cream layer" which floats to the top of serum is due to the presence of chylomicrons. This is normal in a non-fasted animal, but represents an abnormality if the animal has been fasted for greater than 12 hours.
Do cats develop atherosclerosis?	Contrary to humans, cats rarely develop atherosclerosis due to differences in lipid metabolism. Atherosclerosis could develop in some cats that have a concurrent disease that causes chronic hyperlipidemia.
Should persistent fasting hyperlipidemia be treated?	Yes. If the hyperlipidemia is due to a secondary cause, then treatment of the underlying condition may resolve the hyperlipidemia. There is evidence suggesting that chronic hyperlipidemia may lead to the development of pancreatitis, insulin resistance, diabetes mellitus, or atherosclerosis in some cats.

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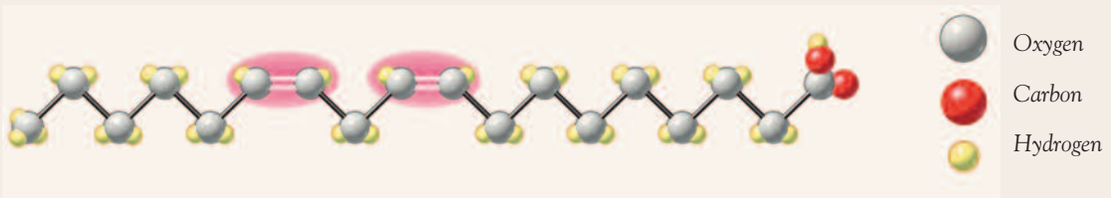
Focus on:

Long-chain omega-3 fatty acids (EPA-DHA)

Omega-3 fatty acids are a separate family of polyunsaturated fatty acids (PUFA). Their precursor is α-linolenic acid (C18:3, n-3), whose chemical structure distinguishes it from linoleic acid (C18:2, n-6), the precursor of the other main family, omega-6 fatty acids.

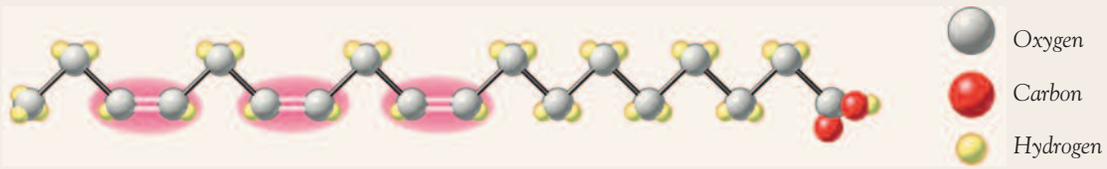
Linoleic acid is an essential fatty acid for cats, which depend on a dietary intake to cover their requirements. With the exception of docosahexaenoic acid (DHA), the omega-3 series of fatty acids are not considered to be essential, as cats can survive with a food that does not contain them. On the other hand, their health may benefit from their introduction in the diet.

LINOLEIC ACID: C18:2 (N-6); OMEGA-6 FATTY ACID PRECURSOR



Omega-6 fatty acids are characterized by the first double bond between the 6th and 7th carbon atom, counting from the omega carbon (the carbon atom located opposite the carboxyl–COOH grouping).

α-LINOLENIC ACID: C18:3 (N-3); OMEGA-3 FATTY ACID PRECURSOR



In the omega-3 fatty acid family, the first double bond is located between the 3rd and 4th carbon atom.

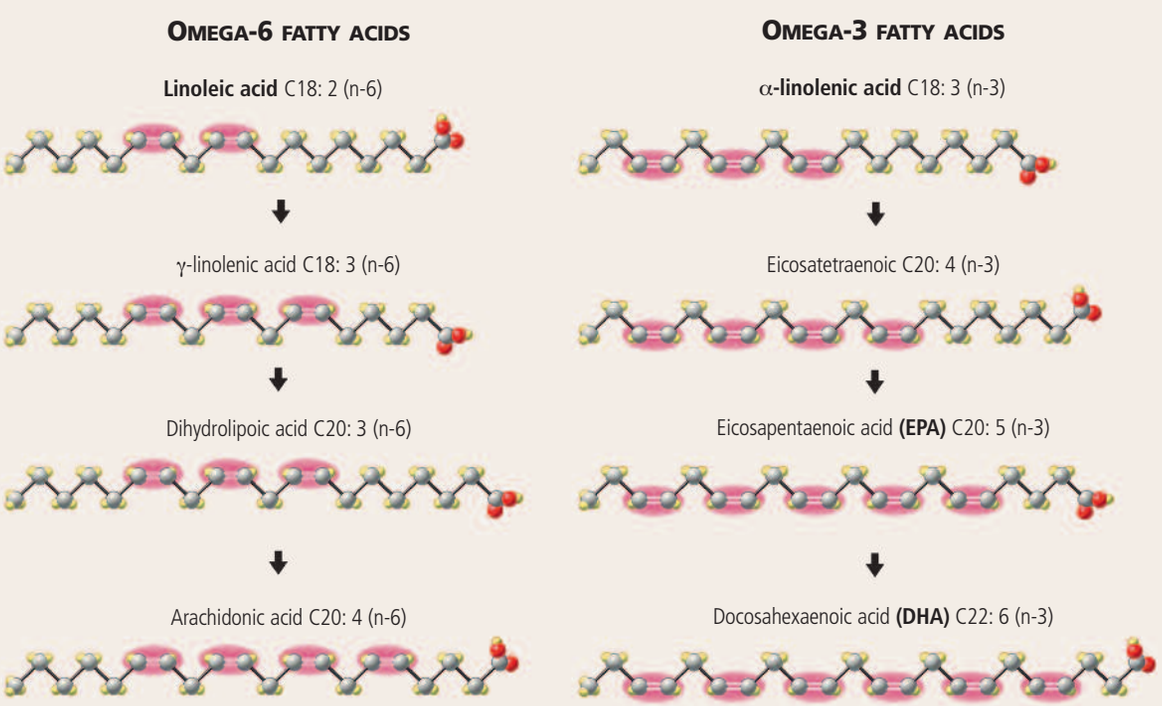
Metabolism of unsaturated fatty acids

The synthesis of long-chain fatty acids is triggered by the action of enzymes in the liver (desaturase and elongase), which add to the carbon atoms and the unsaturated double bonds. These are the same enzymes that act in the synthesis of omega-3 and omega-6 fatty acids, which explains the competition between the two families.

In cats, the enzyme responsible for the first desaturation, Δ6 desaturase, has a very low-level of activity *(Sinclair et al., 1979; Pawlosky et al., 1994)*.

- In the series of omega-6 fatty acids, Δ6 desaturase produces very low quantities of arachidonic acid. In the absence of dietary intake a healthy adult cat may be able to cover its requirements, but gestating queens will produce no or few viable litters and the proportion of cannibalism appears to be higher *(Morris, 2004)*. Arachidonic acid is therefore deemed essential in cats, contrary to dogs.

Hepatic synthesis of long-chain omega-3 and omega-6 fatty acids from their respective precursors



- With respect to omega-3 fatty acids, the yield from α-linolenic acid (omega-3) is very low. Therefore, when EPA-DHA supplementation is recommended, they should be provided preformed in the food.

Sources of omega-3 fatty acids

Some vegetable oils, such as soy oil and especially linseed oil, contain a non-negligible quantity of α-linolenic acid. In contrast, oils sourced from the sea are the only useful sources of EPA and DHA.

PUFA sourced from the sea are synthesized in the chloroplasts of phytoplankton or micro-algae consumed by fish. Higher up the food chain, some fish incorporate omega-3 PUFA and their metabolism transforms them until the fatty acids contain 20-22 carbon atoms. EPA and DHA are especially concentrated in the adipose tissue of fish. Fish oils (especially cold sea fish like salmon, mackerel, anchovy, halibut and herring) can contain more than 30% EPA-DHA.

Comparative content of omega-3 fatty acids of different oils

Omega-3 fatty acids (% DM)	Soy oil	Linseed oil	Fish oil
α-linolenic acid	6	51	<1
EPA + DHA	-	-	17-34

The adaptation of the cat's metabolism to a carnivorous diet is especially expressed by the specific requirements of essential fatty acids, which differ from those of the dog.

Key points
to remember about:

Nutritional management of hyperlipidemia

1 - **Give the cat a low-fat diet**: < 30 g/1000 kcal or less than 10% fat in a 4000 kcal/kg food:

- in the event of obesity, weight loss is indicated to lower the cholesterol concentration;
- when the body condition is optimal the low-fat diet may need to be supplemented with calories compared with a maintenance food to avoid undesirable weight loss.

2 - When the low-fat diet is inadequate to control hyperlipidemia, fish oil (10-200 mg/kg), which is rich in the long chain omega-3 fatty acids EPA and DHA, can reduce serum lipid concentrations.

3 - Adding a large quantity of unsaturated fatty acids (omega-3) increases the risk of oxidation of the lipid membranes. The administration of biological antioxidants (e.g. vitamin E, vitamin C and beta-carotene) can limit the oxidative reactions.

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Dietary therapy for feline chronic kidney disease

ABBREVIATIONS USED IN THIS CHAPTER

ACVIM: American College of Veterinary Internal Medicine
ADH: antidiuretic hormone
ADMA: asymmetric dimethylarginine
ASVNU: American Society for Veterinary Nephrology and Urology
CKD: chronic kidney disease
ECF: extracellular fluid
ESVNU: European Society for Veterinary Nephrology and Urology
GFR: glomerular filtration rate
IRIS: International Renal Interest Society
KDOQI ™: The National Kidney Foundation: Kidney Disease Outcomes Quality Initiative
LDL: low density lipoprotein
MCP-1: monocyte chemotractant protein-1
MW: molecular weight
NRC: National Research Council
PRA: plasma renin activity
PTH: parathyroid hormone
PUFA: polyunsaturated fatty acid
RAAS: renin-angiotensin-aldosterone system
UPC: urine protein to creatinine ratio

Dietary therapy for feline chronic kidney disease

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Jonathan Elliott graduated from Cambridge University Veterinary School in 1985. After completing a year as an Intern in Small Animal Medicine and Surgery at the Veterinary Hospital, University of Pennsylvania, he returned to Cambridge to undertake his PhD studies in the Department of Pharmacology. He completed his PhD in vascular pharmacology in 1989. In 1990 he was appointed to a lectureship in Veterinary Pharmacology at the Royal Veterinary College in London where he is currently Professor of Veterinary Clinical Pharmacology and has developed research interests in feline chronic renal failure and hypertension and equine laminitis. He was appointed Vice Principal for Research in 2004. He is a Diplomate of the European College of Pharmacology and Toxicology and a member of the Veterinary Products Committee, which advises the UK Government on licensing veterinary medicines. Jonathan Elliott was awarded the Pfizer Academic Award in 1998, the BSAVA Amoroso Award in 2001 and the 2006 Pet Plan Scientific Award for his contributions to companion animal medicine, particularly in the areas of equine laminitis and feline chronic kidney disease.

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Kidney disease is extremely prevalent in the aging cat population and is one of the most common medical reasons older cats are seen in veterinary practice. Although good epidemiological data from Europe are lacking, data from the USA suggest that 1 in 3 cats over the age of 12 years have some form of renal insufficiency *(Lulich et al, 1992)****. A study of apparently healthy and biochemically normal cats aged 9 years or older recruited prospectively from primary care practices in central London has demonstrated that, within 12 months, around 1 in 3 cats had biochemical evidence of azotemia (i.e plasma creatinine and/or urea concentrations above upper limits of the reference intervals)*** *(Jepson et al, 2007a)****.***

Introduction

There are a number of well recognized disease processes which damage the kidney in cats and lead to a well defined pathology. In the majority of cats, once the diagnosis of chronic kidney disease (CKD) is made through demonstration of azotemia in association with an inability to produce adequately concentrated urine (see section 2 for further discussion), the underlying disease is often not recognizable, even on renal biopsy. Quite clearly this disease syndrome is not a single entity and a more complete understanding of the pathological processes involved is needed if progress is to be made in the prevention of some forms of CKD in the cat.

Even when azotemia has been detected in cats with clinical evidence suggestive of CKD, progression to the stage where life is not compatible without renal replacement therapy (dialysis or transplantation) is not inevitable in all cases. Progression occurs at different rates in individual cats, emphasizing the heterogeneous nature of chronic kidney disease in the cat. Progress has been made recently on identifying risk factors for progression and evaluating treatments (including diets) in clinical patients against the gold standard of survival.

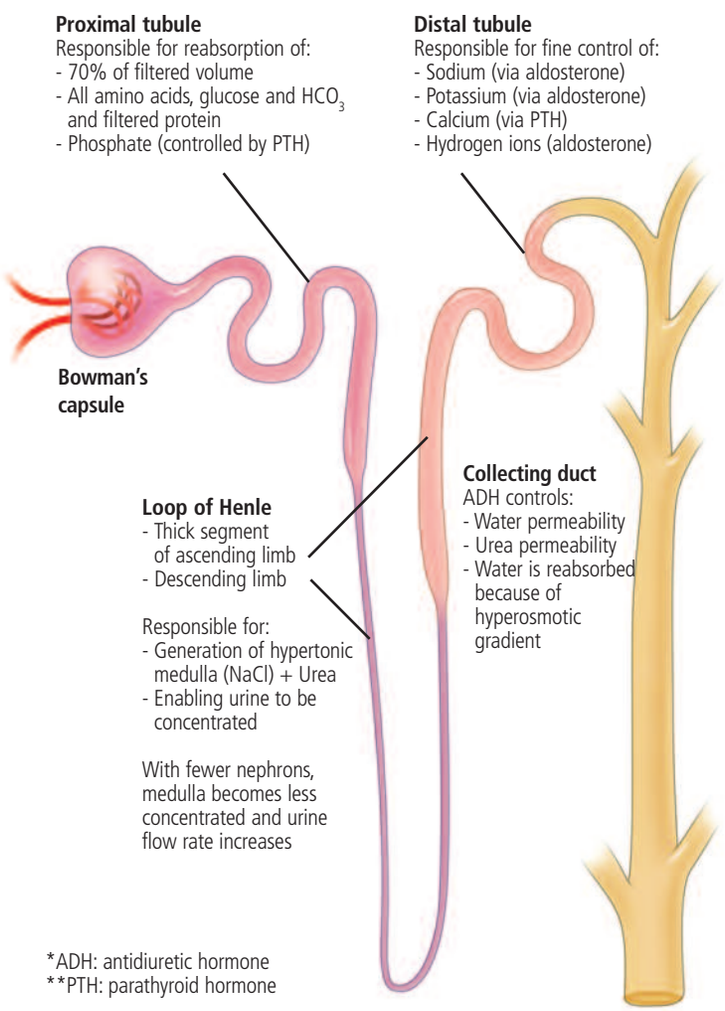
When CKD has been identified in an individual patient the diagnostic and therapeutic goals are:

1. identify factors that are affecting the quality of life of the cat
2. select treatments (pharmacologic or dietary) that should improve the quality of life of the cat
3. identify factors that increase the risk of progressive renal injury in the individual cat
4. select treatments (pharmacologic and/or dietary) that may reduce the risk of progressive renal injury
5. monitor the response to these treatments and ensure that each treatment is tailored to the individual cat

It is helpful to categorize an individual cat as to the stage of its kidney disease since this will inform the clinician as to the most appropriate treatments and the most likely complications that arise associated with the CKD syndrome.
The aims of this chapter are to:

1. Outline the physiological roles of the kidney that are key to understanding what homeostatic mechanisms fail in CKD
2. Define a staging process for feline CKD
3. Define the management of CKD, making reference to the goals outlined above and to identify the stage at which specific problems will need to be addressed.

FIGURE 1 - A SCHEMATIC DIAGRAM OF THE NEPHRON



Each nephron consists of a glomerulus (the filter), a proximal tubule, loop of Henle, distal and cortical collecting tubule and a collecting duct.

1 - Kidney physiology

The nephron **(Figure 1)** is the functional unit of the kidney. Each feline kidney has around 200,000 nephrons. The kidney has the following major roles:

- excretion of water soluble waste products in urine
- homeostasis of the volume and composition of body fluids
- endocrine functions (production of erythropoietin, angiotensin II and calcitriol)

The kidney functions by non-specifically filtering the blood such that the water components of plasma appear in the filtrate at the same concentration they are found in plasma. Proteins are excluded from the filtrate progressively as their molecular weight (MW) get higher such that very little protein of MW above 70,000 gets across the normal filter. Approximately 20% of the renal plasma flowing through the kidney appears within the glomerular filtrate. The proximal convoluted tubule then functions to return about 65 to 70% of the filtered load to the blood stream. It ensures that substances the body requires (such as glucose and amino acids) are readily returned whereas water soluble waste products, which are of no use to the body, stay in the filtrate and are excreted in the urine.

The rate of excretion of many water soluble waste products from the body is dependent on the glomerular filtration rate (e.g. creatinine - a waste product of muscle metabolism). Some relatively low molecular weight substances are also actively transported from the plasma into the tubular fluid. Specific transporters are able to secrete organic acids or bases from the peritubular capillaries into the proximal convoluted tubular fluid. There are many examples of these transporters. One of the best known is able to secrete penicillins into the tubular fluid where, due to its high hydrophilicity this drug will stay in the filtrate as water is reabsorbed. Hence the urinary concentration of penicillin G following administration of standard doses rates to a cat can exceed the plasma concentration by more than 300 fold.

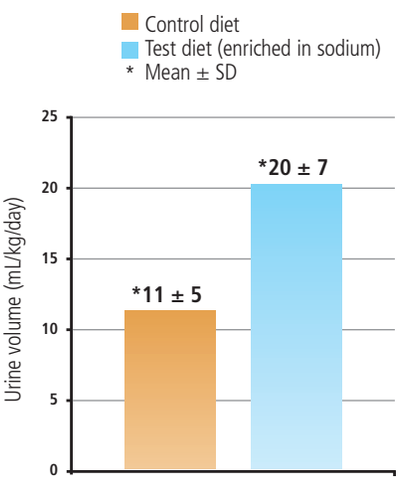
Whilst this early part of the nephron (proximal convoluted tubule) is responsible for the bulk return of filtered fluid and electrolytes to the plasma, the later parts are responsible for the fine control of urine composition. The loop of Henle is involved in generating a concentration gradient by trapping sodium chloride and urea in the interstitial area of the kidney. The so called "counter-current multiplier system" is responsible for this function. The descending limb of the loop of Henle is impermeable to sodium chloride but permeable to water whereas the ascending limb is impermeable to water and, the thick ascending limb actively transport sodium chloride into the medullary interstitium.

The cat is supremely adapted to produce concentrated urine having a relatively high proportion of nephrons with long loops of Henle. Cats can produce urine with a specific gravity of in excess of 1.080 and the maximal concentrating capacity of the cat kidney has not been assessed. This means that cats are able to exist with very small amounts of water to drink and, if fed a moist diet, often take in enough water with their food and so do not need to drink very much. The ability to produce concentrated urine and therefore conserve water is highly dependent on the number of functioning nephrons available to generate the gradient of sodium chloride in the medullary interstitium. Dietary sodium (or sodium chloride) and dietary moisture are highly effective in stimulating water consumption and diuresis in cats *(Burger et al, 1980)*. Increased diuresis promotes urine dilution **(Figure 2)**.

The later parts of the nephron are responsible for the fine control of the urine composition. Primitive urine passing from the loop of Henle to the cortical collecting tubule should be hypotonic (relative to plasma) when entering the cortical collecting tubule. This is because sodium chloride has been removed from the filtrate in excess of water. The early part of the distal tubule continues this process where sodium reabsorption occurs without water (diluting segment). In the later parts of the distal tubule, sodium reabsorption occurs under the regulation of the sodium conserving hormone, aldosterone. Calcium, hydrogen and potassium ion composition of the tubular fluid are all regulated by the action of hormones (parathyroid hormone and aldosterone) in the distal tubule and cortical collecting tubule (also known as the late distal tubule). The later parts of the cortical collecting tubule and the collecting ducts respond to antidiuretic hormone (ADH) which regulates water and urea permeability. ADH secretion from the neurohypophysis is regulated by the osmolality of plasma and water conservation is ensured by the kidney minimizing water losses with the production of maximally concentrated urine when necessary.

FIGURE 2 – INFLUENCE OF DIETARY SODIUM ON URINE VOLUME IN CATS

Biourge et al, 2001



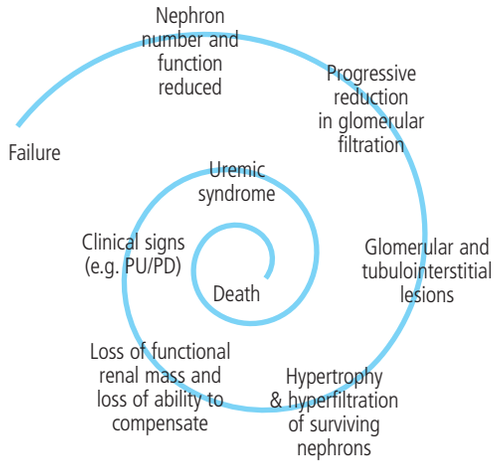
The control diet contains 1.1 g sodium/1000 kcal; the test diet contains 2.5 g sodium/1000 kcal. This study shows that a higher sodium intake significantly ($p < 0.05$) increases diuresis: urinary volume is almost doubled with a 1% sodium dry diet (4000 kcal/kg) compared with a 0.4% sodium diet.

An important concept to grasp when interpreting clinical laboratory data from cats is that urine composition is highly variable. Physiologically, the kidney is able to vary the composition of urine to ensure that homeostasis is achieved and the following equation balances:
Intake of substance = Non-renal losses + Renal losses

In CKD, as kidney function deteriorates (fewer functioning nephrons present), the homeostatic mechanisms struggle to regulate fluid, electrolyte and mineral balances since either:
- renal losses are limited by the reduced renal mass (limited excretion)
- tubular flow rates increase in the remaining functioning nephrons so fine control of the composition of urine becomes more difficult as the later parts of the nephron are presented with fluid flowing too quickly (hyperfiltration)
- compensatory mechanisms become counter-productive leading to a worsening of the electrolyte or mineral imbalance **(Figure 3)**

Careful regulation of the composition of the diet can help cats with CKD maintain homeostasis, leading to improvements in their quality of life. Possibly, in some cases, it can slow down the progression of CKD to the stage where renal replacement therapy is necessary. The next section of this chapter deals with the staging of CKD and puts forward intrinsic and extrinsic factors that may influence progression of CKD. In subsequent sections manipulation of the different components of the diet for feline CKD patients will be discussed and the rationale for these dietary changes at each stage of CKD explained.

FIGURE 3 - RELATIONSHIP BETWEEN RENAL INJURY, LOSS OF NEPHRONS, RENAL COMPENSATORY ADAPTATIONS, AND PROGRESSION OF RENAL FAILURE



The compensatory changes maintain clinically stable disease until structural and functional damage exceeds a threshold beyond which progression of renal function and clinical signs of uremia occur. Chronic renal disease typically progresses to end-stage renal disease after a critical number of nephrons have been damaged.

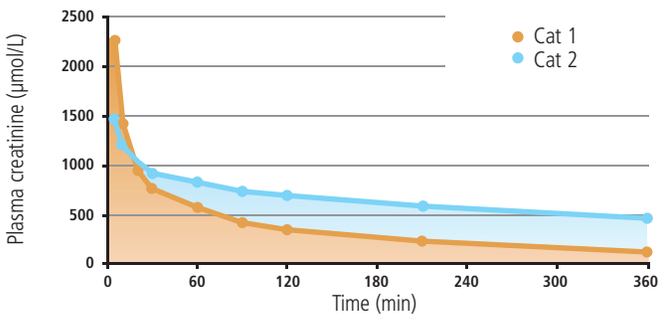
2 - Staging of kidney disease

A comprehensive scheme for staging CKD in cats (and dogs) has been proposed by the International Renal Interest Society (IRIS) and endorsed by the American and European Societies for Veterinary Nephrology and Urology (ASVNU and ESVNU). The staging system should be applied after a diagnosis of CKD. It has been made on the basis of clinical and laboratory tests and only once a clinical case has been shown to be in a stable state rather than acutely deteriorating and requiring supportive therapy to avert a uremic crisis.

The basis for the staging system is the plasma creatinine concentration. The IRIS group is well aware of the limitations of this approach as plasma creatinine concentration is influenced by:
- muscle mass
- hydration status
- diet composition

Plasma creatinine concentration is exponentially and inversely correlated to the gold standard measure of renal function and renal mass, namely the glomerular filtration rate (GFR). At the present time, practical methods that have been validated for use in the cat under primary care practice conditions for the measurement of GFR in the cat are not available. In the fullness of time, these methods will become available and then GFR will replace plasma creatinine concentration as the physiological measurement upon which staging of CKD will be based *(Le Garreres et al, 2007)* **(Figure 4)**.

FIGURE 4 - PLASMA CREATININE VS TIME CURVES IN 2 CATS AFTER INTRAVENOUS ADMINISTRATION OF EXOGENOUS CREATININE *(dose: 40 mg/kg BW)*
From B. Reynolds, National Veterinary School of Toulouse



The plasma creatinine clearances (i.e. a GFR estimate) for cat 1 and 2 were 2.6 and 1.3 mL/min/kg, respectively.
***Cat 1** was a 5 year old DSH cat (6.1 kg) with polycystic kidney disease incidentally identified when abdominal ultrasonography was performed for unrelated problems. Plasma creatinine concentration at that time was 158 µmol/L (1.79 mg/dL). Renal function was considered normal after GFR estimation.*
***Cat 2** was a 9 month old DSH cat (2.6 kg) screened for severe polyuria and polydipsia. Both kidneys were abnormal at ultrasonographic examination. Concurrent plasma creatinine concentration was 152 µmol/L (1.72 mg/dL). Renal function was considered impaired after GFR estimation and an appropriate diet prescribed.*
These two cases illustrate the importance of muscle mass influencing the rate of production of creatinine when interpreting plasma creatinine concentration as an indicator of renal function.

Table 1 - The *International Renal Interest Society* (IRIS) Staging System based on plasma creatinine

Stage	Creatinine *	Comments
I	< 140 µmol/L (< 1.6 mg/dL)	Non-azotemic Some other renal abnormality present e.g. inadequate concentrating ability without identifiable non-renal cause; abnormal renal palpation and/or abnormal renal imaging findings; proteinuria of renal origin; abnormal renal biopsy results; increasing plasma creatinine concentrations noted on serial samples
II	140-249 µmol/L (1.6-2.8 mg/dL)	Mild renal azotemia (lower end of the range lies within the reference range for many laboratories but the insensitivity of creatinine as a screening test means that animals with creatinine values close to the upper reference limit often have excretory failure) Clinical signs usually mild or absent
III	250-439 µmol/L (2.8-5.0 mg/dL)	Moderate renal azotemia Many extra-renal clinical signs may be present
IV	> 440 µmol/L (> 5.0 mg/dL)	Severe renal azotemia Many extra-renal clinical signs are usually present

*To convert µmol/L to mg/dL divide by 88.4

Table 1 defines the staging system based on plasma creatinine concentration. The main challenge to the veterinary profession is to identify kidney disease when it is in the non-azotemic stage (stage I and early stage II). The veterinary profession has traditionally identified CKD by the finding of chronically elevated plasma creatinine concentration in conjunction with relatively dilute urine (often inappropriately so for the hydration status of the animal). At this stage (late stage II to IV) the primary cause of the kidney disease is often not evident, even on renal biopsy, and so the opportunity to treat the underlying cause of the kidney disease has been lost. Routine screening of older cats (from 8 years on) for evidence of kidney dysfunction examining serial plasma creatinine concentrations on an annual basis (and eventually measuring GFR) will increase our ability to detect CKD at an earlier stage and perhaps address the primary disease process at a stage where we can treat the primary disease.

Progression is thought to occur through three basic mechanisms:

1. repeated episodes of the primary disease process leading to further damage and loss of functioning nephrons;
2. mal-adaptive mechanisms, intrinsic to the kidney leading to glomerular capillary hypertension, hyperfiltration and hypertrophy. This is thought to occur through local activation of the renin-angiotensin system. The appearance of increasing amounts of protein in the urine may indicate that this process is occurring and there is some evidence that excess filtered protein may damage the tubules and contribute to progressive renal injury;
3. mal-adaptive responses occurring extrinsic to the kidney resulting from reduced renal function which may have detrimental effects on the remaining functioning nephrons:
   - hyperphosphatemia, hyperparathyroidism and nephrocalcinosis
   - systemic arterial hypertension due to an inability to regulate extracellular fluid volume. The diseased kidney's ability to autoregulate and protect itself from systemic arterial hypertension is reduced and this can lead to hypertensive kidney damage.

Progression of CKD in cats, as alluded to above, occurs at different rates such that some cases remain stable in stage II/III CKD and later die of some other problem whereas others progress to stage IV and suffer a renal death. The pattern of progression seems to take at least two forms, namely:

- stepwise progression with a sudden decrement of kidney function leading to a uremic crisis
- gradual linear progression with increases in plasma creatinine occurring steadily over time

Stepwise decrement in kidney function is the more common pattern of progression seen in cats with naturally occurring CKD *(Elliott et al, 2003b; Ross et al, 2006)*.

It is clear from evidence in other species that risk factors for rapid progression of chronic kidney disease include proteinuria and systemic arterial hypertension. Thus, the IRIS staging system requires that CKD is sub-staged based on the urine protein to creatinine (UPC) ratio and on the

systemic arterial blood pressure. Recent evidence suggests that UPC is an independent risk factor for all cause mortality of cats with CKD *(Syme et al, 2006)* and in cats with systemic hypertension *(Jepson et al, 2007b)*. **Table 2** sets out the IRIS sub-staging system based on UPC.
The substaging of cases based on UPC refers only to renal proteinuria. Pre-renal and post-renal causes should be ruled out if the substaging system recommended below is to be utilized *(Lees et al, 2005)*. Thus, it is imperative to undertake a complete urinalysis and assess the microscopic sediment of a urine sample to ensure evidence of inflammation in the lower tract is absent before assessing the urine protein to creatinine ratio.

Table 3 presents the IRIS sub-staging system based on systemic arterial blood pressure.

The IRIS group recognizes that there is no agreed standard for measuring feline blood pressure. The method used in our practice is the Doppler method which gives readings of systolic pressure only. Cases should not be classified based on measurements taken at a single clinic visit. At least two or more visits should be used to establish their blood pressure status unless significant signs of target organ damage are evident (see above) whereupon specific antihypertensive therapy may be indicated.

TABLE 2 - SUBSTAGING ON URINE PROTEIN TO CREATININE RATIO (UPC)

UPC* value	Interpretation
< 0.2	Non-proteinuric (NP)
0.2 to 0.4	Borderline proteinuric (BP)
> 0.4	Proteinuric (P)

* Calculated using mass units

TABLE 3 - SUBSTAGING ON BLOOD PRESSURE

Risk	Systolic (mm Hg)	Diastolic (mm Hg)	Classification according to evidence of extra-renal complications*
Minimal [N]	< 150	< 95	- Minimal or no risk of end organ damage [N] - Highly unlikely to see evidence of extra-renal damage at this level
Low [L]	150-159	95-99	- Low risk of end organ damage - If no extra-renal complication seen [Lnc] - If evidence of extra-renal complications seen [Lc]
Moderate [M]	160-179	100-119	- Moderate risk of end organ damage - If no extra-renal complications seen [Mnc] - If evidence of extra-renal complications seen [Mc]
High [H]	≥180	≥120	- High risk of end organ damage - If no extra-renal complications seen [Hnc] - If evidence of extra-renal complications seen [Hc]

nc – no extra-renal complications present; c – extra-renal complications detected.
*Extra-renal complications might include:
- left ventricular concentric hypertrophy in the absence of structural/valvular heart problems identified
- ocular abnormalities compatible with damage by high blood pressure such as hyphema or hypertensive retinopathy
- neurological signs - dullness and lethargy, seizures

3 - Dietary therapy in detail

There are many diets available to assist in the management of CKD. These specifically formulated diets are different in several respects from standard diets formulated for feeding adult cats.

- **When dietary changes are introduced in Stages II and III of CKD**, the aim is mainly to address those factors which are likely to contribute to progressive renal injury and further loss of functioning nephrons. In this section the rationale will be reviewed for the manipulation of each element of the diet and published evidence for the efficacy of this treatment in slowing progression, presented.

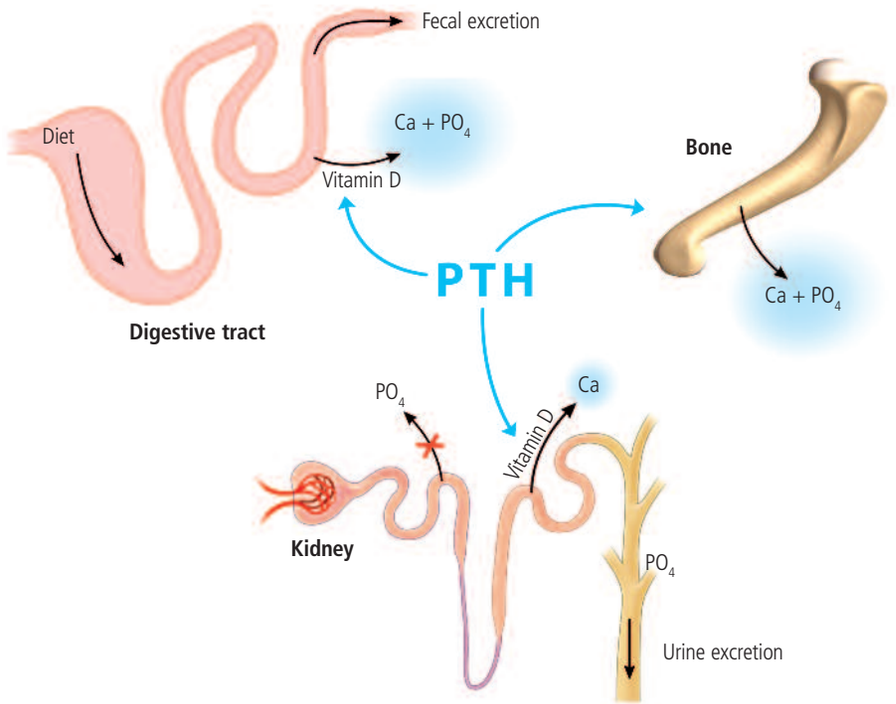
- **Once late stage III/IV has been reached**, clinical signs of the uremic syndrome are evident and dietary treatment is designed more to improve the quality of life of the patient than to slow disease progression. Section 5 will deal with the approach and the use of renal care diets and supplements to address the problems of the uremic syndrome.

► Phosphate restriction and management of secondary renal hyperparathyroidism

Phosphate is freely filtered by the normal kidney but not actively secreted by the tubule. Thus, the amount of phosphate excreted from the body each day is highly dependent on the GFR. Re-absorption of phosphate occurs in the proximal convoluted tubule through a carrier-mediated process (co-transported with sodium ions). The maximum capacity of this system to re-absorb phosphate is influenced by parathyroid hormone (PTH) which reduces phosphate re-absorption and so increases the amount of phosphate excreted in the urine at a given plasma phosphate concentration and a given GFR.

As GFR falls, if dietary phosphate intake remains the same, the daily amount of phosphate excreted in the urine will not match with the daily phosphate intake. Thus, phosphate will start to accumulate in the body. Both intracellular stores and extracellular fluid concentration of phosphate increase. As the plasma phosphate concentration increases, so its rate of excretion will increase until a new steady state is reached at a higher plasma phosphate concentration and higher level of intracellular stores of phosphate. PTH plays a role in this process since increased PTH synthesis and secretion is triggered by a rise in both intracellular stores of phosphate and plasma phosphate concentration. Initially, this adaptive response is helpful as it enhances urinary excretion of phosphate compensating for the effect of the fall in GFR (**Figure 5**).

FIGURE 5 - EFFECTS OF PARATHYROID HORMONE ON CALCIUM HOMEOSTASIS AND THE INVOLVEMENT OF ITS THREE TARGET ORGANS: BONE, KIDNEY AND THE GASTROINTESTINAL TRACT



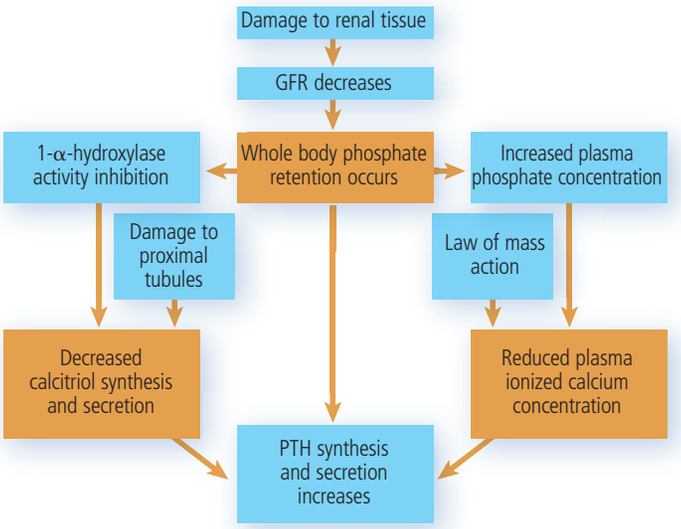
- *Parathyroid hormone (PTH) stimulates calcium and phosphate release from bone into the extracellular fluid (blue in the illustration).*
- *PTH stimulates the kidney to make active vitamin D (1,25 D_3); it inhibits phosphate absorption from the proximal tubule so more phosphate appears in the urine and it increases calcium uptake from the distal tubule, thus conserving calcium.*
- *1,25 D_3 stimulates calcium and phosphate uptake from the small intestine, increasing the proportion of dietary calcium and phosphate that are absorbed.*

Through the action of these hormones, calcium and phosphate homeostasis are achieved by balancing calcium and phosphate intake with urinary excretion of these minerals.

Unfortunately, the adaptive response of increasing PTH secretion to counterbalance the tendency for phosphate retention with loss of functioning nephrons and concomitant fall in GFR is limited by two factors:

1. at least 30% of the filtered load of phosphate has to be re-absorbed in the proximal tubule as part of the reabsorptive process for sodium and hence water
2. as increasing plasma concentrations of PTH are required, the actions of this hormone on bone bring more phosphate from bone stores into the extracellular fluid compartment adding to the problem of hyperphosphatemia.

FIGURE 6 - PATHOPHYSIOLOGY OF SECONDARY RENAL HYPERPARATHYROIDISM



As the CKD progresses and fewer functioning nephrons remain, secretion of PTH, driven by phosphate retention, becomes counter-productive and so mal-adaptive. Phosphate release from bone adds to the problem by inhibiting renal production of calcitriol and stimulating PTH synthesis and secretion and parathyroid gland growth. In the later stages of CKD (IRIS late stage III and stage IV), calcitriol deficiency (as a result of reduced kidney mass and the inhibitory effects of hyperphosphatemia on calcitriol synthesis) contributes to the problem of hyperparathyroidism in two ways:

- calcitriol inhibits PTH synthesis and secretion by a direct action on the parathyroid gland. This hormone also prevents parathyroid gland hypertrophy
- with a lack of calcitriol, absorption of calcium from the intestine is reduced and hypocalcemia can occur (particularly low ionized calcium) in the more severe stages of CKD. With very high plasma phosphate concentrations, ionized calcium will also decrease due to complexing of calcium with phosphate and other small anions.

The above outline of the pathophysiology of secondary renal hyperparathyroidism is shown schematically in **Figure 6**. Scientific understanding of this process has changed the emphasis from the view that ionized calcium concentration decreases, which were once thought to drive PTH secretion, to recognize that phosphate retention is now central to this process.

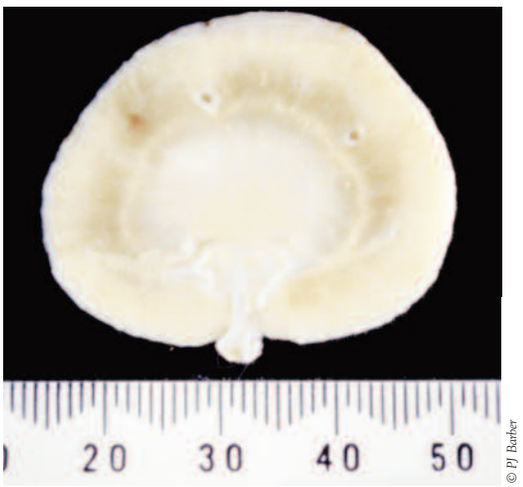


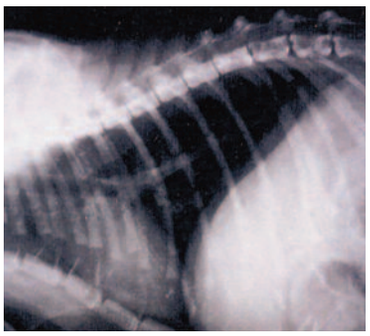
Figure 7 - Renal calcification due to renal hyperparathyroidism in a cat.
A band of calcification can be seen in the inner medulla which was confirmed on histological examinations (scale in mm).

That hyperphosphatemia and hyperparathyroidism are important in naturally occurring CKD is clearly evident from published studies *(Barber & Elliott, 1998)*. Whether phosphate retention and/or increased parathyroid hormone synthesis and secretion are detrimental to the health and well being of the cat with CKD has been a topic of debate. Evidence from laboratory animal models and from human medicine suggests hyperphosphatemia and hyperparathyroidism are detrimental to the quality of life of the patient and may contribute to progressive renal injury. Direct evidence supporting these conclusions apply to cats is relatively sparse although some data from both an experimental model in the cat *(Ross et al, 1982)* and naturally occurring feline CKD support the conclusions that reduction of phosphate intake to control parathyroid hormone secretion results in:

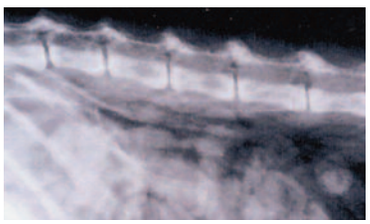
- reduced mineralization **(Figure 7)** and fibrosis in the remaining functioning kidney tissue (experimental model studies; *Ross et al, 1982*)
- a reduction in all cause mortality in cats with naturally occurring CKD *(Elliott et al, 2000)*.

The prospective diet study conducted by *Elliott et al*, (2000) was open label involving cats at stage II and III CKD where the aim was to use phosphate restriction by feeding a renal care diet to con-

Figure 8 - Radiographic evidence of soft tissue calcification of the vasculature due to hyperparathyroidism in cats with chronic renal failure.



A: Soft tissue calcification of the thoracic aorta in a 20 year old cat with chronic kidney disease (classified as uremic).



B: Soft tissue calcification of the abdominal aorta and some abdominal vasculature in a 19 year old cat with end stage chronic kidney disease.

trol plasma PTH and to study the effect this had on survival. The control group were permitted to continue eating their standard maintenance diet after their owners had rejected treatment with the renal care diet. Thus, scientifically the design of this study was not optimal since it was not masked and the control group were self-selecting.

A second study of a renal care diet has been published more recently where the design was a randomized controlled masked clinical trial *(Ross et al, 2006)* and the aim was to determine the benefit of the renal care diet on the time to uremic crises or renal death when fed to cats at stage II and III CKD. The renal care diet tested was compared to a standard maintenance diet that differed in protein, sodium, phosphate and lipid content. The renal care diet contained 0.5% phosphate on an as fed basis (1.2 g/1000 kcal for the dry renal diet, 1.0 g/1000 kcal for the wet renal diet) whereas the maintenance diet contained 0.9 or 1% phosphate on an as fed basis (1.8 g/1000 kcal for the dry maintenance diet, 2.3 g/1000 kcal for the wet maintenance diet). Feeding the renal care diet resulted in a lower plasma phosphate concentration at 12 and 24 months after introduction of the diets although plasma PTH concentrations did not differ significantly. The cats eating the renal care diet suffered significantly fewer uremic crises and there were significantly fewer renal deaths. In both of the above studies, because the renal care diets differed in a number of respects from standard maintenance diets, it is not possible to conclude whether phosphate restriction was responsible for the effect seen but it seems likely to have contributed.

Accumulation of phosphate and calcium in renal tissues will lead to nephrocalcinosis and may contribute to progressive renal injury and these processes are probably ongoing in IRIS stages II and III of CKD. Clearly, in the later stages of CKD (stage IV), extrarenal effects of hyperphosphatemia and hyperparathyroidism are evident with radiographic evidence of renal osteodystrophy and mineralization of soft tissues **(Figure 8)** accompanied by marked parathyroid gland hypertrophy. In human medicine, poor control of phosphate balance in the renal patient on dialysis leads to increased cardiovascular risk as calcium and phosphate accumulate in the vasculature *(KDOQI, 2003)*.

FIGURE 9A - EFFECT OF FEEDING A RENAL CARE DIET TO CATS WITH CKD (STAGES II AND III) ON PLASMA PHOSPHATE CONCENTRATION

Barber et al, 1999; From J Small Anim Pract *(1999)*
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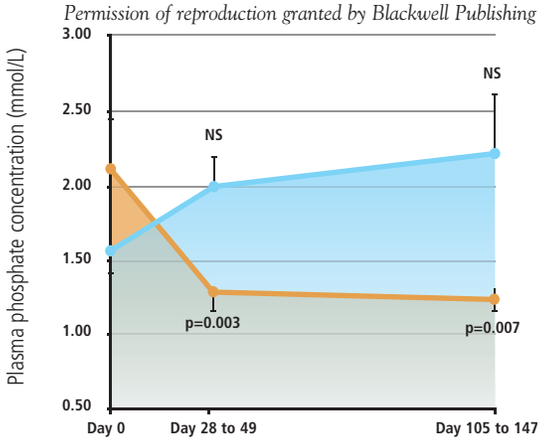

Data are mean values from 14 cats (orange) that were fed the renal care diet and 8 cats (blue) maintained on their maintenance diets. Error bars represent 1 SD of the mean. Significant differences compared to day 0 value by a paired t-test are illustrated (NS not significant).

FIGURE 9B - EFFECT OF FEEDING A RENAL CARE DIET TO CATS WITH CKD (STAGES II AND III) ON PLASMA PTH CONCENTRATION

Barber et al, 1999; From J Small Anim Pract *(1999)*
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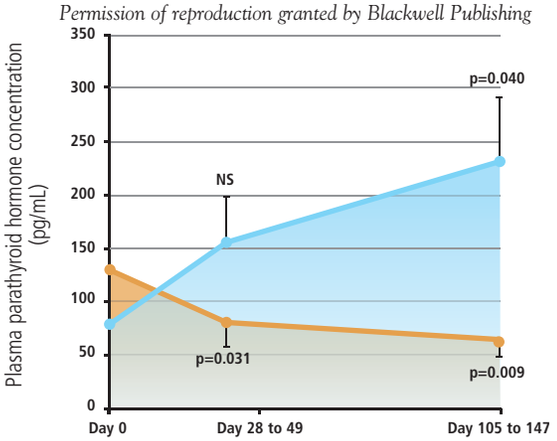


Data are mean values from 14 cats (orange) that were fed the renal care diet and 8 cats (blue) maintained on their maintenance diets. Error bars represent 1 SD of the mean. Significant differences compared to day 0 value by a paired t-test are illustrated (NS not significant).

> Management of secondary renal hyperparathyroidism

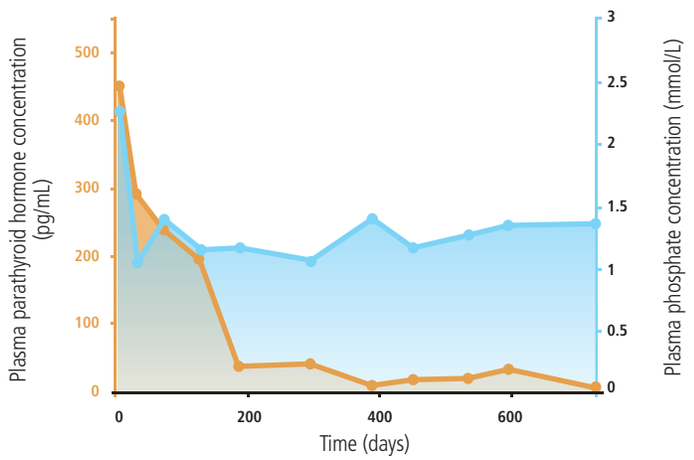
From the above discussion of the pathophysiology of hyperphosphatemia and hyperparathyroidism secondary to CKD, the logical way to address these problems is to restrict dietary phosphate intake in the first instance. This can be done by restricting the amount of phosphate in the ration fed and/or adding phosphate binders to reduce phosphate bioavailability in the food that is fed.

Evidence that feeding a commercially formulated renal clinical diet reduces both plasma phosphate concentration and PTH concentrations when fed to cats with naturally occurring CKD has been published (*Barber et al, 1999*; **Figure 9**). The effect on plasma PTH concentration tends to be prolonged with plasma PTH concentrations falling with continued dietary phosphate restriction after the plasma phosphate concentration has stabilized **(Figure 10)**. This probably results from depletion of intracellular stores of phosphate which influence PTH synthesis and secretion. In human medicine, the recommendations regarding control of plasma phosphate concentration have been published based on expert opinion and available clinical research evidence *(KDOQI, 2003)*. These guidelines have been adapted by a group of veterinary nephrologists to apply to the cat and have been adopted by the IRIS group as recommendations according to the stage of CKD that is being treated.

- **For stage II CKD**, the post-treatment plasma phosphate concentration should be below 1.45 mmol/L (4.5 mg/dL), but not <0.8 mmol/L (2.5 mg/dL). In our experience, cats where plasma phosphate can be maintained below 1.2 mmol/L (3.72 mg/dL) tend to remain very stable in stage II CKD for prolonged periods of time.
- **For stage III CKD**, the realistic post-treatment target is <1.61 mmol/L (5.0 mg/dL). Intestinal phosphate binders in addition to feeding a diet restricted in phosphate may be necessary to achieve this target in later stage III cases.
- **For stage IV CKD**, the realistic post-treatment plasma phosphate concentration target is 1.93 mmol/L (6.0 mg/dL) and this is unlikely to be achieved with dietary phosphate restriction alone.

FIGURE 10 - EFFECT OF FEEDING A RENAL CARE DIET ON PLASMA PHOSPHATE (BLUE) AND PTH (ORANGE) CONCENTRATIONS IN A CAT WITH CKD

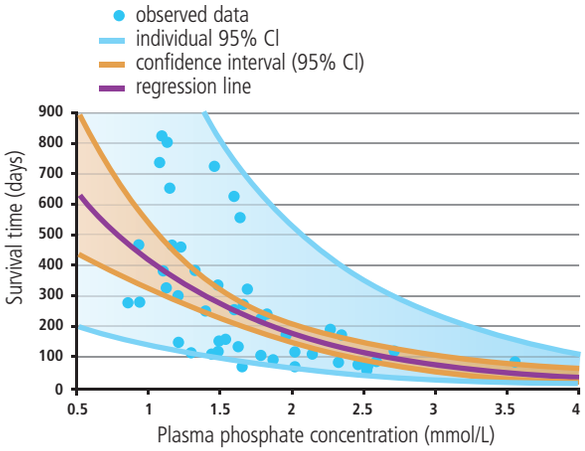
Barber, 1999



Note that whilst plasma phosphate concentration stabilized very quickly, plasma PTH continued to decrease and finally reached the reference range (2.5 to 20 pg/mL) after almost 400 days of diet therapy.

FIGURE 11 - RELATIONSHIP BETWEEN SURVIVAL TIME AND THE MEAN PLASMA PHOSPHATE CONCENTRATION ACHIEVED IN THE FIRST HALF OF THE SURVIVAL PERIOD

Data re-analyzed from Elliott et al (2000)



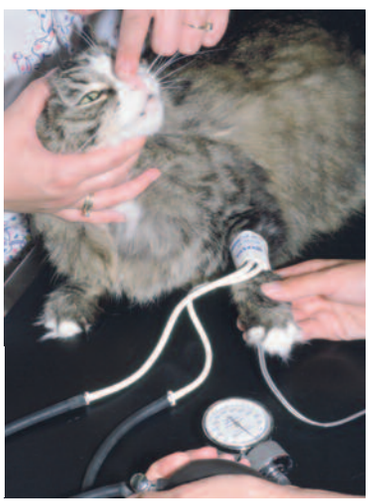
Fifty cats were entered into a prospective survival study (Elliott et al, 2000). *Blood samples were collected at 2 to 3 month intervals throughout the study. The average plasma phosphate concentration has been calculated for each cat during the first half of their survival period and plotted against their survival time. Linear regression analysis reveals an exponential relationship (R^2 value 0.45).*

Unpublished data from our research clinic shows that 55, 90 and 100% of cats presenting in stage II, III and IV CKD respectively have plasma phosphate concentrations above 1.45 mmol/L (4.5 mg/dL) at diagnosis. Re-analysis of the data from the prospective study of the effect of controlling plasma phosphate and PTH on survival of cats with stage II and III CKD *(Elliott et al, 2000)* demonstrated that:

- if the average plasma phosphate concentration was maintained at below 1.45 mmol/L (4.5 mg/dL) for the first half of their survival time (this was achieved in 18 of the 50 cats) their median survival time was 799 (interquartile range 569-1383) days
- for cats where the average plasma phosphate concentration exceeded 1.45 mmol/L (4.5 mg/dL) the median survival time was 283 (interquartile range 193 to 503) days **(Figure 11)**.

These data are supportive of the extrapolation of the *KDOQI* (2003) recommendations on the control of plasma phosphate from human to feline medicine. Further prospective studies are necessary which are specifically designed to address the benefit of maintaining plasma phosphate concentrations below 1.45 mmol/L (4.5 mg/dL) in cats with CKD are still required, however, to verify this recommendation.

Adverse effects of restricting phosphate intake are rare. It is recommended that plasma phosphate and calcium (preferably ionized calcium) are measured routinely every 2 to 3 months in cats that have been stabilized on restricted phosphate diets and that hypophosphatemia (plasma phosphate concentration <0.8 mmol/L [2.5 mg/dL]) is avoided. Occasionally, hypercalcemia has been reported *(Barber et al, 1998)*. This is a true hypercalcemia since ionized calcium as well as total calcium is outside of the reference range and plasma PTH is below the limit of detection. The underlying cause of the hypercalcemia in these cases is not understood but it appears to result from phosphate restriction since feeding more phosphate in the diet leads to the plasma calcium ion concentration returning to the reference range and the plasma PTH concentration increasing into the measurable range at the same time. Since PTH is important for normal bone turnover it does not seem appropriate to completely suppress PTH secretion in these cases, hence we would recommend feeding more phosphate to these cats. This small proportion of cases clearly do not need the degree of phosphate restriction provided by the commercial diets in order to control PTH and phosphate illustrating the point that any treatment should be tailored to the individual needs of the patient.



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Doppler blood pressure measuring device.

► Dietary sodium and kidney disease

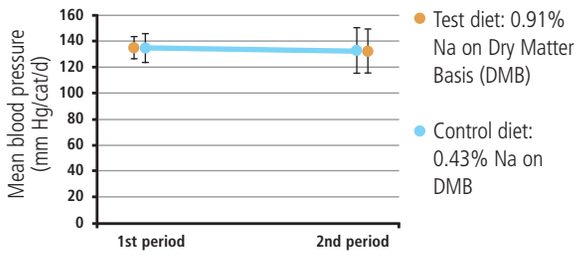
Sodium is the major determinant of extracellular fluid (ECF) volume and blood pressure being the main ECF cation. Sodium ions are maintained at a stable concentration in ECF and plasma through the osmoreceptor and thirst mechanisms that regulate water balance. Plasma osmolality is maintained at a stable 280 to 290 mOsm/L.

In the normal kidney usually more than 99% of the filtered load of sodium is reabsorbed and returned to the blood stream. The fraction excreted can be reduced considerably under the influence of aldosterone, the salt conserving hormone which acts on the late distal tubule (cortical connecting tubule) to increase sodium reabsorption from this part of the kidney. There is a steep relationship between urinary sodium excretion and systemic arterial blood pressure. Small increases in arterial blood pressure cause a marked increase in sodium excretion in the urine formed by a normal kidney. This occurs through inhibition of aldosterone secretion (reduced activity of the renin-angiotensin system) and through the action of natriuretic factors on the kidney to functionally antagonize aldosterone (e.g. atrial natriuretic peptides, endogenous digitalic like factors).

Thus, in cats with normal kidney function, a wide range of sodium intakes can be tolerated without detrimental effects on arterial blood pressure. Indeed, one strategy adopted to reduce the tendency for the formation of uroliths in feline urine is to increase dietary sodium intake. This results in a larger volume of urine being produced and the cats will drink more water to compensate. Hence the urinary calcium and magnesium concentrations are reduced and the tendency for urolith formation also is decreased. Normal cats fed such diets show no tendency for their blood pressures to increase *(Buranakarl et al, 2004; Luckschander et al, 2004)* **(Figure 12)**.

FIGURE 12 - INFLUENCE OF DIETARY SODIUM ON BLOOD PRESSURE IN HEALTHY CATS

(Luckschander et al, 2004)



Ten healthy cats were randomly divided into 2 groups. The 1st group was fed the control diet and the 2nd group was fed a diet with a moderately increased sodium content. After a 1-week wash-out period, each group was switched to the opposite diet for 2 weeks. Follow-up on moderately increased dietary salt intakes failed to show any impact on blood pressure in healthy cats.

Formulated clinical renal diets tend to have a lower sodium content per calorie than foods designed for healthy cats. The content of the renal diets still provides more than 2 to 4 times the National Research Council (NRC) recommended daily intake of sodium (0.4 to 0.9 mmol/kg/day or 9.2-20.7 mg/kg/day) *(Yu and Morris, 1999)* at around 2 mmol/kg/day (46 mg/kg/day). Standard grocery diets provide between 4 to 6 mmol/kg/day (92-138 mg/kg/day) **(Table 4)**. The rationale for this is that with loss of the number of functioning nephrons, ability to excrete sodium from the body is reduced. If dietary sodium intake remained the same then these cats would be at increased risk of developing hypertension associated with their CKD. There are no controlled studies in the published veterinary literature to demonstrate the benefit of reducing dietary sodium intake on blood pressure in cats with naturally occurring CKD.

In a cross-sectional study of cats presenting at different stages of CKD, we demonstrated that the fractional excretion of sodium increased with decreasing renal function (**Figure 12**; unpublished data taken from cats studied in *Elliott et al, 2003a*). The interpretation of urinary fractional excretion data from an individual case based on a spot urine sample should be made with caution since there appears to be significant intra-animal variability with time *(Adams et al, 1991; Finco et al, 1997)*. A 24 hour urine collection would yield more reliable results but is impractical in feline clinical research. In addition, the pattern observed in the data presented in **Figure 13** May well be blurred by the fact these cats were being fed heterogeneous diets. Nevertheless, despite these shortcomings there does appear to be a higher fractional excretion of sodium at the more severe stages of CKD, suggesting an adaptive change of the remaining functioning tubules ensuring more of the filtered load of sodium is excreted from the body. There was no difference in plasma sodium concentrations between the cats at the different stages of CKD in this cross-sectional study although the

TABLE 4 - SODIUM REQUIREMENT OF ADULT CATS FOR MAINTENANCE

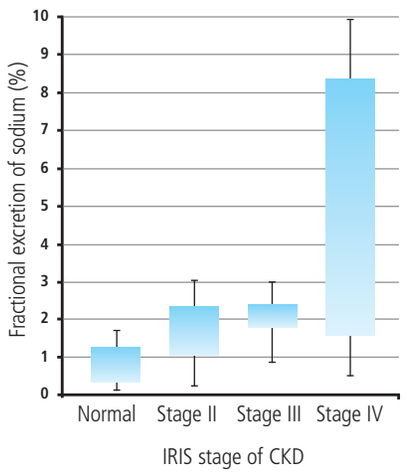
(National Research Council, 2006)

Minimal requirement (mg)			Recommended allowance (mg)			Safe upper limit (g/kg DM)
mg/kg DM	mg/1,000 kcal ME	mg/kg BW $^{0.67}$	mg/kg DM	mg/1,000 kcal ME	mg/kg BW $^{0.67}$	
650	160	16	680	170	16.7	> 15 g

mg/kg DM: amount per kg dry matter, assuming a dietary energy density of 4,000 kcal ME/kg
BW: body weight; the values in mg/BW $^{0.67}$ have been calculated for a lean cat with an energy intake of 100 kcal x BW $^{0.67}$
DM: dry matter
ME: metabolizable energy

FIGURE 13 - BOX AND WHISKER PLOTS SHOWING FRACTIONAL EXCRETION OF SODIUM IN NORMAL CATS AND CATS WITH CKD AT DIAGNOSIS

Data taken from cases included in Elliott et al, 2003a



plasma chloride ion concentrations were lower in the severe stage (equivalent to IRIS stage IV; *Elliott et al, 2003a*), possibly associated with the development of metabolic acidosis **(see section below)**.

Some cats with naturally occurring CKD do present with severe hypertension. **Figure 14** shows the distribution of blood pressure at initial diagnosis. These data are from 103 consecutive cases of naturally occurring CKD (*Syme et al, 2002a)*. Categorization of these cats according to the IRIS staging system gives the following:

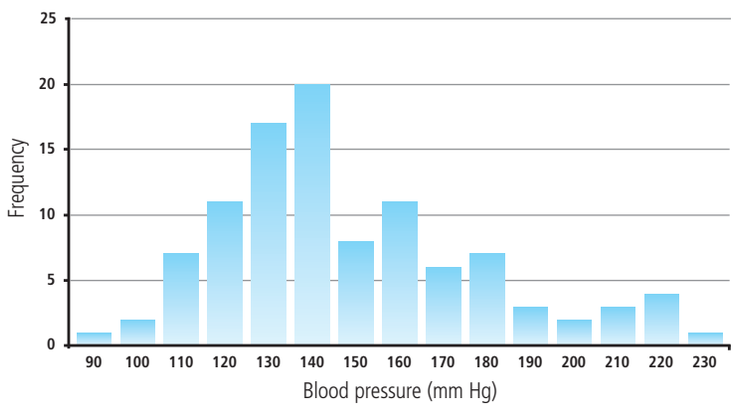
- minimal risk (<150 mmHg) – 62/103 or 60%
- mild risk (150-159 mmHg) – 10/103 or 10%
- moderate risk (160-179 mmHg) – 15/103 or 14.5%
- severe risk (>180 mmHg) – 16/103 or 15.5%

This study was a cross-sectional one and did not address the question as to whether blood pressure rises with time in the feline patient with CKD. If sodium retention occurs over time in the CKD patient due to an inability to excrete the daily quantity of sodium taken in the diet, one might expect blood pressure to increase over time. However, *Syme et al* (2002a) found the plasma creatinine was not a risk factor for high blood pressure – in other words blood pressure did not appear to be higher in cats with more severe CKD. Indeed, the majority of the cats found in the high-risk blood pressure group were in stage II or early stage III CKD according to the IRIS classification system. However, these data are difficult to interpret since cases presenting in stage IV CKD may well have lower blood pressure due to dehydration.

Syme (2003) analyzed data from a population of cats with CKD followed longitudinally to determine whether blood pressure increased from diagnosis of CKD. The inclusion criteria of this retrospective study were carefully defined to avoid extraneous factors that might influence blood pressure other than chronicity of CKD. The study included 55 cats each followed for more than 3 months. Seven of the 55 cats showed an increase in blood pressure to a point where medical treatment was deemed necessary (systolic blood pressure persistently >175 mmHg). Of the 55 cats, 17 showed progression of their CKD (as evidenced by >20% increase in plasma creatinine concentration) over the period of follow-up and 38 cats were classified as non-progressive. The cumulative hazard rate for an increase in blood pressure to a level where treatment was necessary was not significantly different between the progressive and non-progressive groups. Taking the group as a whole, blood pressure increased significantly over time (0.38 [0.2 to 0.56] mmHg/month; P<0.001 by repeated measures linear mixed model approach). These data suggest that blood pressure increases gradually over time in cats with naturally occurring CKD. This phenomenon does not appear to be associated with a decline in kidney function as assessed by repeated measures of plasma creatinine concentrations, although more sensitive measures of kidney function over time (e.g. repeated assessment of glomerular filtration rate) would be necessary to be confident renal function has not changed over time in the non-progressive cases.

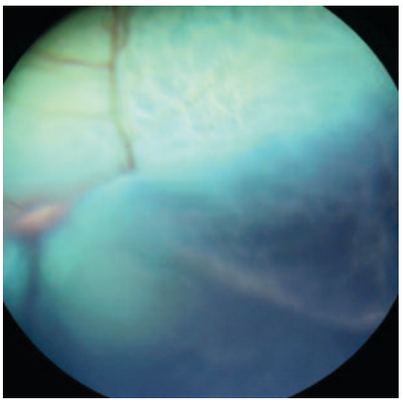
FIGURE 14 - DISTRIBUTION OF SYSTOLIC BLOOD PRESSURE MEASUREMENTS IN 103 CATS WITH CKD

From Syme et al (2002a)



Similar findings were reported by *Ross et al* (2006) in their prospective study of the influence of diet on spontaneous CKD. Seven of the 45 cats entered into this study developed hypertension (systolic blood pressure >175 mmHg) and required medical treatment over the 2 year follow-up period despite having normal blood pressure at entry to the study. The overall effect of the renal care diet on the blood pressure of the cats involved in this study was not reported. Nevertheless, the renal care diet did not appear to limit the development of hypertension in this study since 5 of the 7 cats developing hypertension did so despite being fed the renal care diet. The numbers of cats developing hypertension in both these longitudinal studies are too small to conclude anything definitively.

FIGURE 15 - SECONDARY CONSEQUENCES OF SEVERE HYPERTENSION IN CATS WITH NATURALLY OCCURING CHRONIC KIDNEY DISEASE



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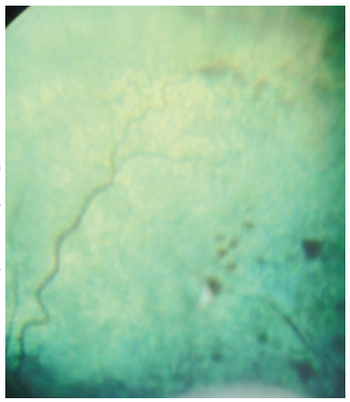
Infundibular retinal detachement and retinal bleeding secondary to systemic arterial hypertension in a cat.



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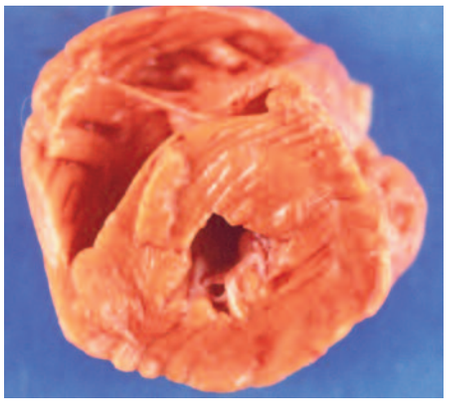
Hypertensive retinopathy in a 15 year old domestic shorthair cat.



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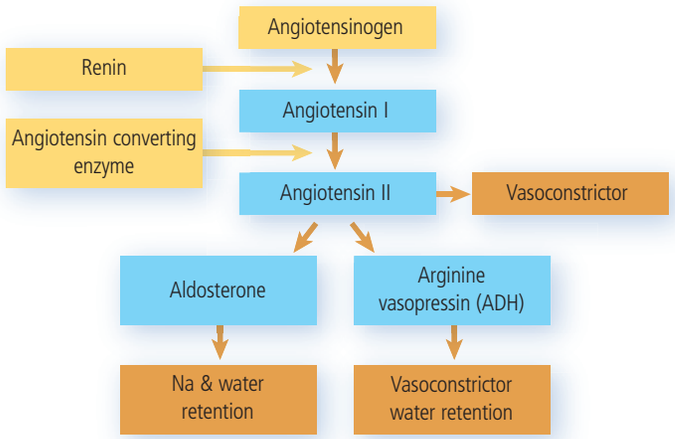
Post-mortem specimen taken from a cat with chronic kidney disease and hypertension demonstrating left ventricular concentric hypertrophy.

From the above theoretical considerations it appears to be logical to restrict sodium intake in cats with naturally occurring CKD. Nevertheless, controlled studies are lacking to determine the benefit of such an intervention on blood pressure control or progressive deterioration in kidney function. *Syme* (2003) reported data on the effect of introduction of a renal care diet on blood pressure in cats with naturally occurring CKD. This was an uncontrolled study as all animals included were fed a standard renal care diet. In addition, this study did not involve cats deemed to be at high risk of end organ damage **(Figure 15)** resulting from high blood pressure as these cases were treated with drugs to control their blood pressure. Systolic blood pressure was measured twice before introduction of the diet and at two time points after the intervention (a minimum of 4 weeks and a maximum of 12 weeks post introduction of the diet) and blood pressure measurements were averaged at the two pre-treatment and two post-treatment time points. Compliance was demonstrated by a significant decline in plasma phosphate concentration (1.55 ± 0.53 mmol/L vs. 1.31 ± 0.32 mmol/L; 4.8 ± 1.64 mg/dl vs. 4.04 ± 0.99 mg/dL; n=28). No changes in plasma sodium or potassium ion concentrations were detected as a result of feeding the renal care diet. Systolic blood pressure did not change in response to introduction of the diet (139 ± 24 mmHg vs. 141 ± 32 mmHg; n=28). The power of the study to detect a 10 mmHg change in systolic blood pressure was calculated to be 90%. A sub-group of cats enrolled in this study had plasma aldosterone and plasma renin activity (PRA) measured before the introduction of the diet and whilst consuming the renal care diet. Plasma aldosterone concentration was higher when the cats were consuming the renal care diet (73 [43, 105] pg/mL vs. 123 [65, 191] pg/mL; pre-diet vs. whilst consuming diet respectively; n=22). Similar changes in PRA were detected following the introduction of the renal care diet (0.53 [0.17, 1.11] vs. 0.75 [0.21, 1.38] ng/mL/h). Both plasma aldosterone concentration and PRA remained in the reference range (derived from aged normal cats fed heterogeneous grocery diets formulated for adult cats) both before and during the renal care diet feeding period.

Results from a study involving the remnant kidney model in cats *(Buranakarl et al, 2004)* suggest that reduction of sodium intake may cause activation of the renin-angiotensin-aldosterone system (RAAS) resulting acutely in a fall in plasma potassium ion concentration and was without beneficial effect on arterial blood pressure. Three diets (with a respective sodium content of: 0.34%, 0.65% and 1.27%) were fed for 7 days sequentially to three groups of cats. The different sodium chloride intake were 50, 100 and 200 mg per kg of body weight (i.e: 0.5 g, 1.4 g and 2.8 g sodium for 1000 kcal), the lowest intake being equivalent to many renal care diets. The three groups of cats involved in this study were:
- control cats with normal kidney function (young adults)

Figure 16 - Activation of the Renin Angiotensin Aldosterone System (RAAS)



- remnant kidney cats (11/12 nephrectomy model)
- cats which had had a bilateral partial nephrectomy with one kidney wrapped in silk and cellophane (renal wrap model causing severe hypertension) (see *Mathur et al, 2004*). During the feeding trial, these cats received amlodipine besylate treatment to control their blood pressure and prevent development of hypertensive encephalopathy.

Both these models led to renal insufficiency accompanied by elevated arterial blood pressure of the similar order of magnitude as seen in naturally occurring CKD. However, activation of the RAAS **(Figure 16)** with elevated PRA (2 to 6 fold) compared to the control group and markedly elevated aldosterone (4 to 25 fold higher than control cats) was associated with both models (particularly marked in the renal wrap model). Cats with naturally occurring CKD and blood pressures placing them at minimal to moderate risk of end organ damage (up to 175 mmHg) tend to have either normal or suppressed PRAs compared to age-matched control cats fed similar diets. Furthermore, plasma aldosterone concentrations also remain within the reference range and do not differ significantly from age-matched control cats *(Syme et al, 2002b)*. Marked activation of the RAAS does occur in unstable naturally occurring CKD patients in stage IV *(Syme, 2003)*. Thus, the remnant kidney and renal wrap models of hypertension appear to give rise to significant activation of the RAAS, a finding which is not relevant to naturally occurring CKD at stages II or III with no or only mild to moderate elevations in blood pressure. The relevance of these models to naturally occurring CKD in cats appears to be questionable.

Cats with naturally occurring CKD with marked elevations in arterial blood pressure (systolic pressure >180 mmHg; high risk of target organ damage) tend to have normal or suppressed PRA associated with normal or marginally elevated plasma aldosterone concentrations *(Jensen et al, 1997; Syme et al, 2002b)*. These cats also tend to have lower plasma potassium ion concentrations at diagnosis and are relatively resistant to the antihypertensive effects of standard doses of angiotensin converting enzyme inhibitors *(Littman, 1994)*, both findings suggesting that hypertension in these cases is possibly the result of increased secretion and/or activity of aldosterone but not through activation of the RAAS. It is clear that restriction of sodium chloride intake in these severely hypertensive cats is not sufficient alone to manage their hypertension and pharmacological interventions are required to control blood pressure. Whether dietary sodium restriction helps to achieve control of blood pressure with drugs in these patients has not been studied in feline clinical patients. A clearer understanding of why some cats with naturally occurring CKD develop severe hypertension associated with a high risk of end organ damage remains to be established. Once the reason for this is understood, the role of sodium restriction in managing these patients may become clearer.

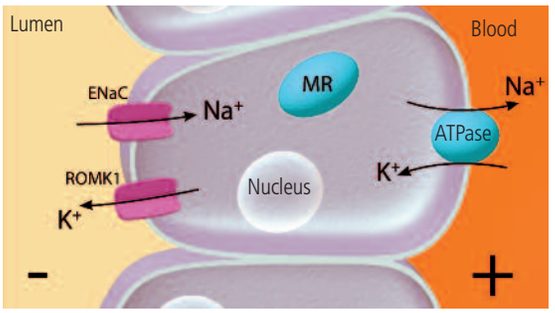
In summary, most renal care diets formulated for cats have reduced sodium content compared to standard adult maintenance foods. The logic behind this is that with reduced functional renal mass, maintenance of sodium homeostasis will prove more difficult to achieve and sodium retention could result in increased blood pressure. Hypertension could reduce the quality of life of cats with CKD and lead to further damage to the remaining functioning nephrons and so progressive renal injury. About 20% of cats with naturally occurring CKD do have arterial blood pressures at diagnosis which place them at severe risk of target organ damage (including renal damage) secondary to hypertension. Blood pressure does tend to increase gradually over time in the remaining 80% of cats with CKD where their blood pressure at initial diagnosis does not place them at high risk of target organ damage. However, certain observations have cast doubt on the routine restriction of dietary sodium in cats with naturally occurring CKD **(Table 5)**.

Table 5 - Observations that have cast doubt on the routine restriction of dietary sodium in cats with naturally occurring CKD

- Chronic feeding of excess dietary sodium does not lead to hypertension in cats with normal kidney function
- Reduction of sodium intake in experimental models of hypertension (where the RAAS is activated) leads to increased urinary losses of potassium ions and mild hypokalemia with further activation of the RAAS
- The same experimental models of CKD and hypertension tolerate an increase in dietary sodium chloride intake to 200 mg/kg of body weight for 7 days (1.27% sodium diet providing 2.8 g sodium for 1000 kcal) without an increase in blood pressure, a dietary manipulation which inhibited secretion of renin and aldosterone
- Pathological activation of the RAAS can lead to deleterious effects on renal function and exacerbate renal fibrosis in some models of feline kidney disease *(Mathur et al, 2004)* and in other species.

Despite these observations, renal care diets, which restrict sodium intake, continue to be routinely used in cats with naturally occurring CKD. Their clinical use does not appear to be associated with worsening of hypokalemia *(Elliott et al, 2000; Ross et al, 2006)* or proteinuria (unpublished data), despite an increase in plasma aldosterone concentration within the physiological range *(Syme, 2003)*. Whether reducing sodium intake is beneficial in limiting the chronic small increase in blood pressure detected over time in cats with naturally occurring CKD remains to be determined by future longitudinal studies, as does their potential benefit in managing severe hypertension in the cat in combination with antihypertensive drug therapy.

FIGURE 17 - CORTICAL COLLECTING TUBULE CELL



This diagram shows the potassium (ROMK1) and sodium (ENaC) channels on the apical or luminal surface, the mineralocorticoid receptor in the cell cytoplasm (MR) and the Na/K ATPase pump on the basolateral (blood) membrane. This epithelium is negatively charged on the luminal surface.

► Potassium and kidney disease

The cat is somewhat unique in that there appears to be an association between CKD and hypokalemia. Loss of functioning nephrons puts the dog or human patient at increased risk of hyperkalemia. In cats, adaptive changes in the remaining functioning nephrons appear, in some 20 to 30% of cases of CKD, to over compensate and excess loss of potassium in the urine leads to hypokalemia *(DiBartola et al, 1987; Elliott & Barber, 1998)* unless they move into an oliguric stage as part of a uremic crisis. In the face of CKD, hypokalemia also appears to be associated with an increased risk of systemic hypertension *(Syme et al, 2002a)*, possibly also due to the way the kidney responds to loss of functioning nephrons.

TABLE 6 – FACTORS INFLUENCING THE FRACTIONAL EXCRETION OF POTASSIUM

- Dietary potassium intake
- Plasma potassium ion concentration (high plasma potassium ion concentration stimulates aldosterone secretion from the adrenal gland)
- Plasma aldosterone concentration
- Number of remaining functioning nephrons and the tubular flow rate
- Acid-base status of the animal (acidosis tends to increase urinary potassium loss)

Potassium is the major intracellular cation and circulates in plasma at a concentration of around 4 mmol/L. This means measurement of plasma potassium concentration is an indirect assessment of whole body potassium status, particularly as potassium can change its distribution between the cells and ECF, for example in response to acid-base disturbances. Plasma potassium is freely filtered and most of the filtered load is returned to the plasma in the proximal convoluted tubule and the loop of Henle. The cortical connecting tubule is the site of potassium secretion into the tubular fluid **(Figure 17)**. Fractional excretion of potassium will vary depending on various factors **(Table 6)**.

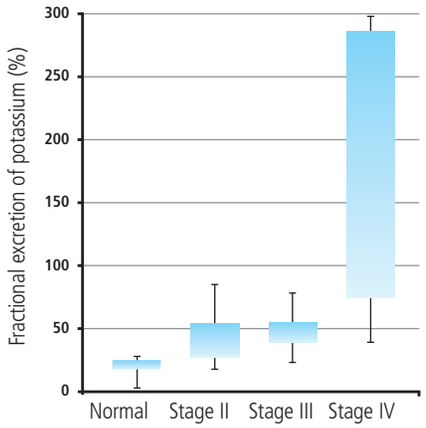
Aldosterone acts on the cortical collecting tubule to increase potassium ion loss in the urine by increasing the number of potassium channels in the apical plasma membrane of the tubular cells through which potassium ions can diffuse. In effect, these potassium ions exchange for sodium ions diffusing from the tubular fluid into the tubular cell through epithelial sodium channels whose synthesis is also under the control of aldosterone. Intracellular potassium is maintained at a high concentration and intracellular sodium is maintained at a low concentration by the action of aldosterone causing the synthesis of basolateral membrane sodium potassium ATPase (pumps) **(Figure 17)**.

Dow and Fettman (1992) hypothesized that potassium depletion may lead to a self-perpetuating cycle of renal damage and further potassium loss. This hypothesis is based on:

- The clinical observation of a strong statistical association between CKD and the occurrence of hypokalemia *(Dow et al, 1989)*.
- Naturally occurring CKD was observed in association with feeding an acidifying diet that was marginally replete in potassium – renal function appeared to improve when the diet was changed and the hypokalemia was corrected *(Dow et al, 1987)*.
- The experimental observation that feeding a diet that was deficient in potassium and supplemented with phosphoric acid (acidifying diet) led to severe hypokalemia and metabolic acidosis accompanied by a decline in glomerular filtration rate *(Dow et al, 1990)*.

FIGURE 18 - BOX AND WHISKER PLOTS SHOWING FRACTIONAL EXCRETION OF POTASSIUM IN NORMAL CATS AND CATS WITH CKD AT DIAGNOSIS

Data taken from cases included in Elliott et al, 2003a



Support for this hypothesis was provided by demonstration that feeding a similarly formulated diet (marginally replete in potassium but high in protein and acidifying) led to the development of hypokalemia, clinical and laboratory evidence of renal dysfunction and renal lesions in cats over a two-year study period *(DiBartola et al, 1993)*. However, despite a number of small well-controlled and detailed studies, the causal relationship between whole body potassium deficit and progressive renal injury remains to be proven. Whilst it appears possible to induce renal injury by prolonged feeding of acidifying diets marginally replete in potassium, in general it seems most likely that hypokalemia associated with renal disease is mild and occurs as a result, rather than being a major cause of progressive renal disease.

Urinary excretion of potassium (calculated as fractional excretion) increases with increasing severity of renal dysfunction **(Figure 18)**. In some cases, the fractional excretion of potassium can exceed 100%, indicating the capacity of the cortical connecting tubule to up-regulate potassium secretion in adaptation to nephron loss. Hypokalemia is found at all azotemic stages of CKD in our clinical patients with:
- 30% (6 of 20) in stage IV
- 25% (5/20) in stage III
- and 14.3% (3/21) in stage II *(Elliott et al, 2003a)*.

As stated previously, basing the assessment of whole body potassium status solely on plasma potassium concentration may under-estimate the prevalence *(Theisen et al, 1997)*. The higher prevalence at the later stages of CKD is likely to be associated with metabolic acidosis which is more likely to occur at this stage of CKD. In our clinical case-load, the diets consumed by the cats presenting with hypokalemia tend to be standard adult maintenance formulations which are in no way limited in the amount of potassium they supply. Furthermore, hypokalemia in these cases is relatively mild (plasma potassium concentrations usually between 3.0 and 3.4 mmol/L; reference range 3.5 to 5.5 mmol/L) and is not generally associated with overt clinical signs (e.g. severe muscle weakness). Clinical improvements are seen in response to potassium supplementation in these cases, including increased appetite and improved level of activity. However, changes in renal function (as assessed by serial measurements of plasma creatinine concentration) are not seen in response to potassium supplementation alone.

In human medicine, observational studies have shown an inverse relationship between dietary potassium intake and blood pressure in some *(Reed et al, 1985)* but not all studies *(Walsh et al, 2002)*. Randomized controlled clinical trials have shown that potassium supplementation reduces both diastolic and systolic blood pressure in human patients *(Whelton et al, 1997)*. The observation that low plasma potassium concentration increased the risk of hypertension in cats with CKD led us to conduct a randomized controlled clinical trial to determine the effect of potassium supplementation on blood pressure in cats with naturally occurring CKD *(Elliott & Syme, 2003)*. The trial was also designed to determine the benefits on general well-being (as assessed by body weight) and renal function (as assessed by serial plasma creatinine concentration). The supplement used was potassium gluconate at a dose of 2 mEq per cat twice daily as this formulation anecdotally is one of the best tolerated by cats. We chose to evaluate this supplement against corn starch rather than another salt of gluconate. Gluconate is a bicarbonate precursor and might assist in replenishing intracellular stores of potassium by addressing a sub-clinical metabolic acidosis exacerbating potassium loss from the body.

The trial was a prospective, randomized placebo controlled cross-over study with each phase lasting three months. Cases were selected that were in stages II or III CKD that had been on a stable diet for three months prior to enrolment. Cats treated for hypertension were excluded from the study, as were cats with plasma potassium concentrations <3.0 mmol/L. A total of

17 cats were evaluated in this protocol. The plasma potassium concentration (4.35 [4.21, 4.66] vs. 4.16 [3.92, 4.38] mmol/L) and the urine pH (6.08 [5.66, 6.51] vs. 5.63 [5.42, 5.96]) were significantly higher when the cats were taking the potassium supplement indicating at least partial compliance of the cases entered into the study. No beneficial effect of this level of potassium gluconate supplementation was detected on blood pressure or kidney function (as assessed by serial plasma creatinine concentrations and urine protein to creatinine ratio). This study was assessed on the basis of intention to treat. The major reason for owners withdrawing their cats from the study was that their cat would not eat the supplement (potassium gluconate or placebo).

In summary:

- cats with CKD adapt to nephron loss by up-regulating potassium ion excretion. In some cases this can lead to excess urinary potassium loss and hypokalemia
- hypokalemia occurs in about 20% of CKD cases and is found at all stages of this syndrome and clinical benefits are seen from correction of this electrolyte abnormality, particularly when the plasma potassium concentration is less than 3.0 mmol/L
- severe hypokalemia can occur with feeding of acidifying diets which are marginally potassium replete and the feeding of these diets has been associated with the development of renal lesions – this appears to be a relatively uncommon cause of renal damage in cats in the UK
- supplementation of dietary potassium by the addition of potassium gluconate (4 mEq/cat/day) for three months to cats with plasma potassium concentrations of >3.0 mmol/L did not result in any measurable clinical benefit on blood pressure or renal function in cats with naturally occurring stage II and stage III CKD
- ensuring cats with CKD are fed rations which provide potassium in excess of requirements and which are not acidifying should avoid problems of hypokalemic nephropathy in cats. Routine additional supplementation with potassium (over that which is provided in renal care diets) does not appear to be necessary for the majority of cases.

► Dietary management of proteinuria

The intact nephron hypothesis proposed by Hostetter et al, (1981) has shaped research into progression of CKD in the last 20 to 30 years. This hypothesis was based on observations involving experimental rats using surgical reduction of renal mass to mimic the loss of functioning nephrons that occurs in clinical kidney diseases. The observations that with surgical renal mass reduction results in the following adaptations in the remaining functioning nephrons form the basis of the intact nephron hypothesis.

These adaptations to loss of functioning nephrons appear to compensate for the reduction in the number of filtrating nephrons **(Figure 3)**. Ultimately, these adaptations are thought of as being mal-adaptive since glomerular hypertension and proteinuria have been shown to lead to glomerulosclerosis and demise of the remaining functioning nephrons, particularly in rat nephrectomy models, where progression is rapid and closely related to the degree of proteinuria.

Similar experimental models can be established using cats. Adaptive changes in feline nephrons following renal mass reduction include glomerular capillary hypertension, associated hyperfiltration and mild proteinuria *(Brown and Brown, 1995)*. Functional progression of this feline model to severe end-stage kidney failure is much slower than the rat model and so interventions to slow that progression are more difficult to assess. Proteinuria has been used in the rat model as the hallmark of progressive renal injury, either as a marker of glomerular and/or tubular health or as a mediator of tubular damage.

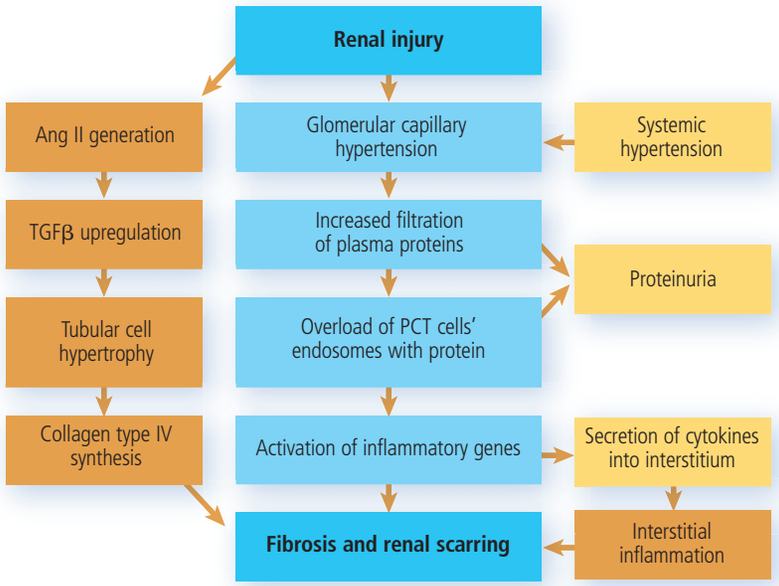
Hyperfiltration and glomerular capillary hypertension appears to be driven, at least in part, in the surgical reduction models by local activation of the RAAS. In the face of afferent arteriolar vasodilation, this system leads to constriction of the efferent arteriole, glomerular capillary hypertension and exacerbates transglomerular passage of plasma proteins, the most abundant of which is albumin.

INTACT NEPHRON HYPOTHESIS

1. Hypertrophy – the remaining nephrons increase in size
2. Glomerular capillary hypertension – these nephrons function at a higher glomerular capillary pressure, increasing one of the forces for filtration
3. Hyperfiltration – as a result of the increased glomerular capillary pressure the filtration rate per individual nephron increases, partially compensating for the loss of the functional renal mass
4. Increased amounts of protein entering the glomerular filtrate and being excreted in the urine (proteinuria)
5. Increased protein entering the filtrate is indicative of glomerular hypertension but also overloads the tubular resorptive processes for protein. This stimulates tubular cells to secrete inflammatory and profibrotic mediators into the interstitial compartment, possibly stimulating interstitial fibrosis and inflammation and contributing to progressive renal damage.

Figure 19 – Pathogenesis of interstitial fibrosis

From Remuzzi and Bertani (1998)



Schematic diagram illustrating how interstitial fibrosis may be triggered by overload of the endosomes of proximal convoluted tubular cells with protein leads to a change in phenotype of these cells stimulating them to secrete cytokines (e.g. MCP-1, RANTES and ET-1) into the interstitial compartment.

Leakage of protein into the glomerular filtrate has been implicated in causing renal pathology. Proteins that transfer across the glomerulus are normally taken back up by the proximal tubule through a process called pinocytosis, whereby the protein molecule is engulfed into a pinocytotic vesicle which buds off from the plasma membrane. This vesicle then fuses with a lysosome inside the cell, containing enzymes which break down the protein to its constituent amino acids which are returned to the plasma. Increasing the traffic through this uptake pathway seem to cause the proximal tubular cell to become overwhelmed with proteins taken up from the filtrate. This stimulates the cell to secrete a number of inflammatory cytokines from its basolateral surface, including endothelin-1, monocyte chemotractant protein-1 (MCP-1) and RANTES, leading to interstitial inflammation and fibrosis as a response to the proteinuria *(Remuzzi & Bertani 1998)* **(Figure 19)**.

Canine and human CKDs tend to be more proteinuric than feline CKDs. For example, in one pathological study, more than 50% of the dogs appear to have primary glomerular pathology *(MacDougall et al, 1986)*. In cats, the pattern of pathology is predominantly interstitial inflammation and fibrosis with glomerulosclerosis occurring as a consequence of the CKD rather than as a primary disease process *(Lucke, 1968)*. Loss of protein in the urine giving rise to urine protein to creatinine ratios greater than 2, usually indicative of primary glomerular pathology, is an uncommon finding in cats with CKD *(Lees et al, 2005)*. Nevertheless, studies have underlined the importance of mild renal proteinuria in cats with CKD as a predictor of all cause mortality *(King et al, 2006; Syme et al, 2006)* and uremic crisis *(Kuwahara et al, 2006)*.

Data from one of these studies *(Syme et al, 2006)* are presented in **Figure 20**. This study involved longitudinal follow-up of 94 cats from initial diagnosis of chronic kidney disease together with 28 aged-matched normal healthy cats and 14 aged cats with hypertension (systolic blood pressure >175 mmHg) but plasma creatinine concentrations within the laboratory reference range. The healthy aged normal cats used in this study defined a reference range for urine protein to creatinine ratio, the upper limit of which was 0.4. Multivariate regression analysis was used to identify risk factors at entry to the study that were associated with proteinuria. The variables identified were plasma creatinine concentration (the higher the creatinine the more likely the cats were to be proteinuric) and blood pressure. Survival analysis was undertaken using Cox's regression analysis. Age, plasma creatinine and proteinuria (assessed by urine protein to creatinine ratio) were significant and independent risk factors associated with reduced survival time. No attempt was made in this study to determine cause of death as this is often difficult to define in aged cats with multiple problems.

The results of this study had been presented in abstract form prior to the full publication and were used to inform the American College of Veterinary Internal Medicine (ACVIM) Consensus Statement on proteinuria *(Lees et al, 2005)*.

It is clear in cats with CKD as the number of functioning nephrons decreases (and plasma creatinine concentration increases) so the proteinuria worsens. This phenomenon has been confir-

med by longitudinal studies of progressive CKD in feline patients *(Hardman et al, 2004)*. The increase in UPC with progressive kidney disease probably underestimates the significance of the hyperfiltration that is occurring as progression occurs. This is because as the number of functioning nephrons decreases, so the surface area over which protein can be lost also decreases, tending to offset the amount of protein lost. The ACVIM Consensus statement on proteinuria recommends treatment for renal proteinuria should commence for azotemic cats when UPC exceeds 0.4. It should be accompanied by intensive investigation of factors that might cause or exacerbate proteinuria and extensive monitoring of the proteinuria to determine whether the prescribed treatments are effective.

> Anti-proteinuric therapy

As proteinuria seems to be a significant risk factor for reduced survival in cats with CKD it seems logical that treatments that reduce proteinuria should be prescribed when persistent proteinuria is identified in association with CKD. Specific treatment should be recommended when UPCs >0.4 are documented in an azotemic cat on 2 or more occasions in the absence of evidence of inflammation on urine sediment examination. The anti-proteinuric treatment for which there is greatest evidence of efficacy is ACE inhibitor therapy. Benazepril is authorized for use in the cat in Europe and has been shown to reduce glomerular capillary pressure in a renal reduction model in the cat *(Brown et al, 2001)* and to lower UPC in naturally occurring CKD in a randomized controlled masked clinical trial *(King et al, 2006)*.

Dietary interventions designed to reduce proteinuria include:

- feeding a reduced quantity of high quality protein
- supplementing n-3 polyunsaturated fatty acids to produce a diet enriched in this component relative to n-6 polyunsaturated fatty acids

IRIS STAGING SYSTEM ON PROTEINURIA FOR CATS

- UPCs <0.2 are considered normal,
- between 0.2 and 0.4 are considered borderline proteinuric
- >0.4 are considered to be proteinuric

> Restriction of protein intake

Each time a meal of protein is consumed, renal hemodynamics are altered and glomerular filtration rate increases to an extent which depends on the quantity and nature of the protein fed. Restricting protein intake should limit these feeding related hyperfiltration responses. Much controversy surrounds the efficacy of reducing dietary protein intake as a means of managing proteinuria in both dogs and cats. In experimental models in rats, this approach proved highly successful in limiting proteinuria and slowing the rate of decline of renal function and progression of renal lesions in the renal mass reduction model *(Brenner et al, 1982)* and so was recommended for use in other species. Similar studies were conducted in cats, initially with results suggestive of a beneficial effect of protein restriction on glomerular lesion development in the remnant kidneys *(Adams et al, 1993; 1994)* although the cats fed a reduced amount of protein (2.7 g/kg/day) in these studies also consumed fewer calories (56 calories/kg/day) than the comparator group fed a higher quantity of protein (75 calories/kg/day and 6.8 g protein/kg/day). Furthermore, cats in the low protein group had evidence of protein malnutrition with reduced serum albumin concentration by the end of the study. In a subsequent study addressing the same question, the effect of calorie intake was distinguished from the effect of limiting protein intake and a markedly different pattern of renal lesions resulted with no evidence of a beneficial effect of restricting protein intake *(Finco et al, 1998)*.

FIGURE 20 - SURVIVAL CURVES DEMONSTRATING THE EFFECT OF URINE PROTEIN TO CREATININE RATIO AND ALL CAUSE MORTALITY IN CATS WITH CKD

Reproduced with permission from Syme et al, (2006); From J Vet Intern Med 2006
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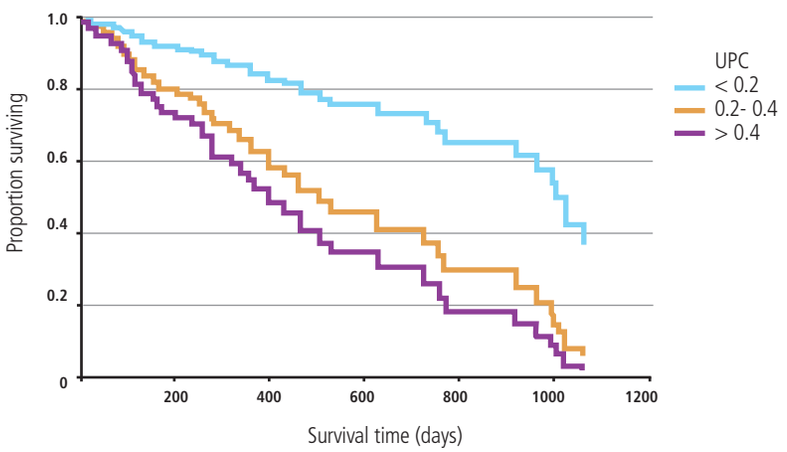

The data have been categorized according the the IRIS classification of non-proteinuric (<0.2); borderline proteinuric (0.2 – 0.4) and proteinuric (>0.4).

One problem with the model used in these two studies is that functional progression (progressive decline in GFR) is not evident over the 12 month post-surgery follow-up period, regardless of the diet that was fed. In the study reported by *Finco et al* (1998), surgical renal reduction caused cats to develop borderline proteinuria (UPC 0.24 to 0.27) whereas pre-surgery they were non-proteinuric (UPC 0.06 to 0.08). No significant difference in UPC was noted between any of the 4 groups of cats used in this study, thus diet had no effect on UPC. Renal histology of the remnant kidneys did, however, reveal a beneficial effect of reducing calorie (but not protein) intake on the severity of renal interstitial (but not glomerular) lesions. Cats in the low calorie intake groups consumed 55 and 58 calories/kg/day and those in the high calorie intake groups consumed 73 and 71 calories/kg/day. Protein consumption was 5.2 and 5.3 g/kg/day in the low protein diet groups and 9 g/kg/day in the high protein diet groups.

The differences between the results of these two studies are striking and are extensively discussed by *Finco et al* (1998), including:
- the source of protein (predominantly animal protein in the *Adams et al*, (1994) study whereas vegetable proteins made a major contribution to the diets fed in the *Finco et al* (1998) study)
- dietary potassium which was lower in the *Adams et al* (1994) study (with cats developing hypokalemia when consuming the high protein diet)
- and dietary lipids which provided a higher proportion of the calories in the *Adams et al* (1994) study.

It is difficult to extrapolate from these two studies recommendations that can be confidently applied to stage II and III cats in terms of diets which will limit proteinuria and therefore possibly slow progressive renal injury by the mechanisms referred to above. Avoidance of diets which deliver a high quantity of animal protein would seem logical. Most renal diets formulated to limit phosphate intake will avoid excessive animal protein in their formulation. Restricting protein intake per se at these stages of kidney failure in the absence of other dietary modifications commonly encountered in renal care diets have not been investigated in the cat. By extrapolation from other species, the cases that are most likely to benefit from the potential renal hemodynamic modifying effects of dietary protein reduction are those with relatively marked proteinuria (UPCs >1.0).

The cats that are most likely to benefit from the potential renal hemodynamic modifying effects of dietary protein reduction are those in stage II and II CKD with relatively marked proteinuria (UPCs >1.0).

> Supplementation of n-3 polyunsaturated fatty acids

Dietary lipids impact a variety of important parameters, including plasma cholesterol concentration and cell membrane structure. In people, hypercholesterolemia and hypertriglyceridemia are important risk factors for cardiovascular and renal disease. This does not appear to be the case in cats, at least partially because they possess only small amounts of low density lipoprotein (LDL) particles, which have been implicated, in their oxidized form, in human cardiovascular and renal disease progression.

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However, there is potential in dogs, and possibly cats, for alterations in cell membrane structure through dietary lipid manipulations, specifically by altering the type of polyunsaturated fatty acid (PUFA) present in the diet. The manipulation that has been most well studied in dogs is alteration of the dietary ratio of n-6 PUFA (plant oils) to n-3 PUFA (fish oils). The n-6 and n-3 PUFA are incorporated into cell membrane phospholipids to serve as precursors for eicosanoids of importance in the renal vasculature, such as prostaglandin E_2 and thromboxane A_2. Altering the dietary n-6/n-3 ratio was hypothesized to be a nutritional method for altering renal hemodynamics in an effort to provide renoprotection, limiting the maladaptive hyperfiltration discussed above.

Support for this hypothesis has been provided by studies in dogs using surgical renal reduction as a model of CKD. Feeding a diet markedly enriched in long chain n3-PUFAs lowered glomerular capillary pressure, reduced proteinuria and slowed progres-

sive decline in GFR seen in this model *(Brown et al, 1998)*. By contrast, feeding a diet markedly enriched in n6-PUFAs raised glomerular capillary pressure, increased proteinuria and caused an accelerated rate of decline in GFR in the same renal reduction model *(Brown et al, 2000)*. These studies used extreme levels of PUFA supplementation but provide the proof of concept for the application of dietary manipulations adopted by some renal care diets where dietary lipids have been manipulated to provide a favorable n6:n3 PUFA ratio, generally achieved by the addition of fish oils. No such data are available in cats, which have somewhat unique PUFA metabolism. Providing long chain n-3 PUFA (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) is probably even more important in cats than in dogs because the delta 6 desaturase is deficient in feline species. Renal care diets have been produced for cats where dietary lipids have been similarly manipulated.

One such diet has been used in a randomized controlled masked clinical trial in cats with naturally occurring CKD and was shown to be superior to a standardized maintenance diet when fed to cats in stage II and stage III CKD in preventing uremic crises and renal related deaths over a 2 year study *(Ross et al, 2006)*. This positive beneficial effect was not associated with a detectable reduction in UPC in the group receiving the renal care diet. As discussed above, the renal care diet used in this study was also restricted in protein, phosphate and sodium as well as having a different lipid profile when compared to the standard maintenance diet against which it was compared. Further studies are necessary to determine whether n-3 PUFA supplementation to cats is effective in the management of proteinuria in cats and to determine what effect their use has on progression of CKD in the cat.

► Other dietary manipulations designed to slow progressive renal injury

The dietary manipulations discussed above are the main approaches used in the formulation of renal care diets for CKD in cats. There are, however, a number of newer approaches for which a rationale could be put forward based on extrapolation from data derived in other species. Much interest has centered on the phenomenon of endothelial cell dysfunction and the role this plays in progression of CKD in human patients. Endothelial cells line the entire cardiovascular system and they produce a plethora of mediators which in a healthy situation:

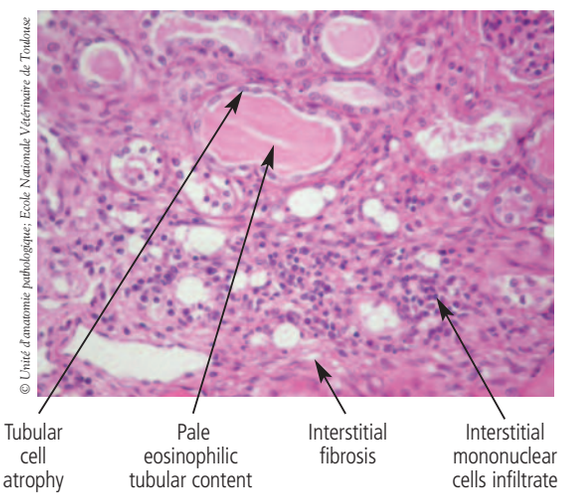
- maintain a thromboresistant surface
- produce tonic vasodilation of underlying smooth muscle cells to counter-balance vasoconstrictor mediators produced locally or present in the circulation
- resist leucocyte adhesion and migration in the absence of major inflammatory stimuli
- inhibit inappropriate smooth muscle and fibroblast proliferation

In some disease states, endothelial cell dysfunction is thought to contribute to the chronic and progressive nature of the disease **(Figure 21)**. Examples include congestive heart failure, hypertension, cardiovascular complications that accompany diabetes mellitus and kidney diseases. In human patients and in some experimental models of CKD there is strong evidence to support the role of endothelial cell dysfunction in systemic hypertension, glomerular pathology, progressive proteinuria and tubular interstitial inflammation and fibrosis. In human patients, CKD is a major risk factor for cardiovascular disease and cardiovascular complications are a common cause of mortality.

Endothelial cell dysfunction in renal disease may result from:

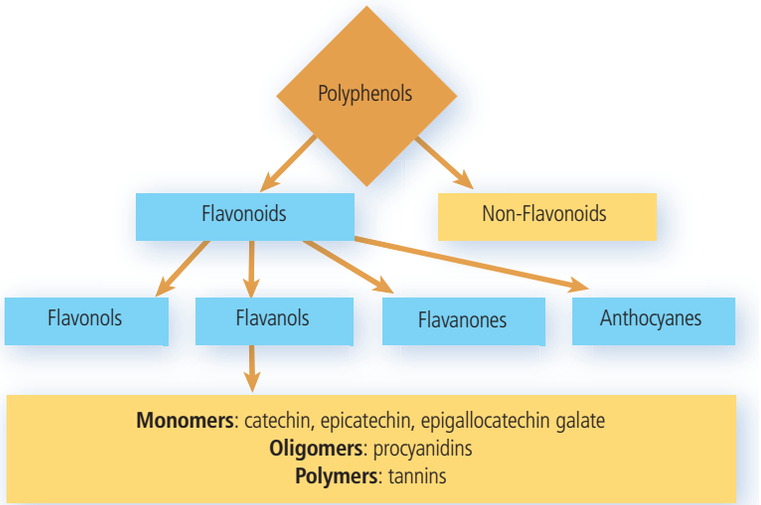
- dyslipoproteinemia associated with disturbances in cholesterol metabolism

FIGURE 21 - TYPICAL MICROSCOPIC FEATURES OF FELINE CHRONIC TUBULOINTERSTITIAL NEPHRITIS



Typical microscopic features of feline chronic tubulointerstitial nephritis are: interstitial mononuclear cells infiltrates, interstitial fibrosis and tubular cell atrophy. Pale eosinophilic tubular content is consistent with concomitant glomerular damage and associated leakage of proteins.

FIGURE 22 - ORIGIN OF FLAVANOLS



The principal sources of flavanols are cocoa, grapes and especially green tea, where 40 to 50% of flavanols are present as epigallocatechin gallate, which is one of the most active flavanols.

- accumulation of inhibitors of endothelial nitric oxide synthase (principally asymmetric dimethylarginine [ADMA]) as a result of reduced renal excretion of ADMA and reduced catabolism by dimethylarginine dimethylamino-hydrolase as a result of oxidative stress *(Baylis, 2006)*
- reduced renal synthesis of L-arginine, the amino acid substrate required for the synthesis of nitric oxide by the endothelium
- increased oxidative stress which accompanies CKD and results in:
  - reduced bioavailability of nitric oxide released from the endothelium
  - stimulation of production of profibrotic, promitotic and vasoconstrictor mediators by the endothelium (e.g. endothelin-1, thromboxane A_2 and hydrogen peroxide)

Although there is little published work relating to the relevance of these factors in progressive CKD in cats, some data have been published in abstract form supporting the problems of oxidative stress in naturally occurring feline CKD *(Braun, 2000; personal communication)* and the accumulation of ADMA in stages II, III and IV of CKD *(Jepson et al, 2008)*, where the plasma concentration of ADMA correlated closely to the plasma creatinine concentration.

There are a number of dietary therapeutic approaches to correcting endothelial cell dysfunction associated with CKD. None of these approaches have been studied in the cat and their application to cats with CKD remains speculative at present. Possible approaches include:

- supplementation of dietary L-arginine to boost the nitric oxide (NO) system, overcome inhibition induced by ADMA
- dietary supplementation with flavanols **(Figure 22)** which have been shown to boost endothelial production of nitric oxide and improve endothelial cell health generally. By trapping free radicals, flavanols have a protective function in areas of necrosis that occur in the glomeruli following alternating ischemia-reperfusion arising from circulatory disorders that occur in CKD. The anti-hypertensive action of flavanols is due to several combined effects:
  - relaxation of smooth muscle fibers *(Duarte et al, 1993; Huang et al, 1998)*. This property is beneficial in augmenting the filtration rate in surviving nephrons when functional renal tissue has decreased
  - stimulation of endogenous production of NO from arginine *(Chevaux et al, 1999; Duarte et al, 2002)*. Nitric oxide is responsible for local vasodilation
  - inhibition of angiotensin converting enzyme (ACE), which has an important role in vasoconstriction *(Hara et al, 1987; Cho et al, 1993)*
- use of diets enriched in antioxidants (e.g. vitamin E, vitamin C, taurine, lutein, lycopene, beta-carotene etc.), adressing the balance between pro- and antioxidants and correcting the problem of oxidative stress in CKD.

Effective measures that address the problems of endothelial cell dysfunction are being actively sought for human medicine and some of the approaches listed above have shown promise. Endothelial cell dysfunction clearly complicates both the early stages of CKD as well as the end stage when renal replacement therapy is necessary and cardiovascular complications are a major cause of morbidity and mortality. Whether these measures will prove of benefit in cats with CKD and at what stage of the syndrome they are best applied remains to be determined.

► Role of fiber

Fermentable fiber is a recent addition to the nutritional management of CKD. It is hypothesized that the fermentable fiber provides a source of carbohydrate for gastrointestinal bacteria which consequently utilize blood urea as a source of nitrogen for growth. The increase in bacterial cell mass increases fecal nitrogen excretion and has been suggested to decrease the blood urea nitrogen concentration. However, unlike BUN, the classical uremic toxins (middle-molecules) are too large in molecular size to readily cross membrane barriers. As a consequence, it is highly unlikely that these toxins are reduced by bacterial utilization of ammonia. Fermentable fibers do have beneficial effects for modulating gastrointestinal health in patients with chronic kidney disease.

► Summary

Section 3 of this chapter has dealt with the dietary manipulations commonly used in the production of a renal care diet and discussed them in relation to their application to stage II and early stage III CKD patients. The use of dietary therapy before obvious clinical signs of the uremic syndrome are evident has been somewhat controversial. The main treatment goal in this group of clinical patients is to slow the progression of CKD to stage IV and beyond. The rational basis for dietary modification by:

- limiting phosphate intake
- limiting sodium intake
- supplementing potassium intake
- limiting protein intake and modifying the lipid composition of the diet

has been presented with the evidence for the efficacy of each of these dietary strategies in slowing progressive renal injury reviewed.

Evidence was presented from two prospective trials using renal care diets that clearly indicate that these diets can be beneficial in Stage II and Stage III CKD patients when assessed against the outcome of all cause mortality *(Elliott et al, 2000)* and time to uremic crisis or renal death *(Ross et al, 2006)*. Although these two studies used diets which adopt a combination of the above dietary modifications and it is not possible to conclude precisely which provided the observed benefits, they do provide strong evidence for dietary intervention at stage II and III CKD in the cat.

4 - Treating the uremic patient [Late stage III/stage IV CKD]

In this section use of renal care diets and dietary supplements or additives to treat the uremic syndrome (encountered in late stage III and stage IV CKD) is discussed. The average life expectancy of uremic cats is around 8 months **(Figure 23)**, although cats presenting for the first time suffering from CKD and a uremic crisis often have a much shorter survival time in our experience. In this group of patients the dietary therapeutic goal is to improve the quality of life of the patient rather than trying to address factors which influence progression of CKD.

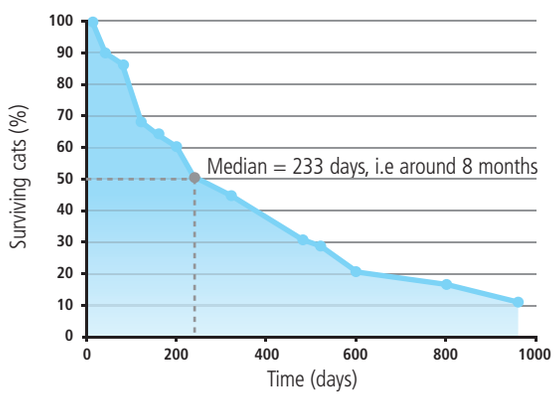
This group of patients are particularly likely to be unstable and so close attention should be paid to:

1. fluid balance – ensuring these patients receive the right quantity and quality of fluids to ensure they regain an adequate hydration status, particularly if their kidney function has suddenly deteriorated and they face a uremic crisis
2. making any changes to their dietary management slowly and gradually with regular monitoring to ensure they are responding in an appropriate manner.

FIGURE 23 - AVERAGE LIFE EXPECTANCY OF UREMIC CATS

(N = 28 uremic cats)

From Elliott and Barber, 1998



► Management of uremia

Once the nitrogenous waste products reach high levels they start to influence appetite and cause nausea and vomiting due to their irritant effects on mucous membranes. Once plasma urea concentrations exceed 30 mmol/L (84 mg/dL), dietary protein restriction is recommended to limit uremia and counteract these effects on the quality of life of the cat. It is important to ensure adequate calorie intake is maintained in these patients and close monitoring of body weight and body condition score is recommended. The urea to creatinine ratio can be used to factor out the effect of renal dysfunction on plasma urea and to determine the effect of response to dietary protein restriction on nitrogenous waste product formation. Reference ranges have been suggested according to the level of protein intake in dogs but have not been published for cats.

Very high ratios suggest owner noncompliance, dehydration, gastrointestinal bleeding or a hypermetabolic state (e.g. sepsis). Very low values indicate inadequate intake of diet and protein calorie malnutrition, such that body proteins are being used as a source of energy. If this state persists for any length of time, the animal will lose significant amounts of body mass and will exhibit signs of muscle wastage. Such a state can occur if the animal does not find the clinical diet palatable and so consumes inadequate quantities. In these cases, continuing to offer such a diet will be counter-productive and an alternative should be sought. Offering a variety of diets to find the individual animal's preference may well be necessary.

The uremic syndrome is very often accompanied by oral, gastric and intestinal lesions leading to vomiting, diarrhea and anorexia. Incorporation of sodium silico-aluminate into the diet can be very useful to protect the digestive mucosa *(Droy et al, 1985)*.

In the later stages of renal failure (late stage IV) **(Figure 24)**, the animal's voluntary appetite may be inadequate and protein-calorie malnutrition may be unavoidable unless the animal is fed via an enteral feeding device (see chapter 14 about Critical Care). Some owners may find this mode of treatment unacceptable and opt for euthanasia at this point.

In addition to reducing dietary protein to limit the formation of nitrogenous waste products, inclusion of dietary fiber/indigestible polymers that can bind nitrogenous waste and draw these substances into the gastro-intestinal tract is a complementary approach adopted by some renal care diets. Objective data demonstrating the efficacy of such products in lowering plasma urea concentrations and the clinical benefits which ensue following the introduction of such diets to stage IV CKD feline patients have not been published in the peer reviewed literature.

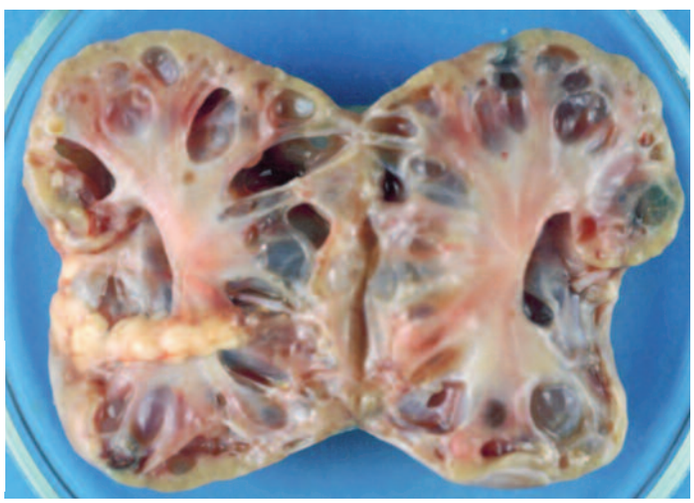


Figure 24 - Post-mortem specimen of a kidney taken from a six year old Persian cat euthanazed with end stage kidney disease. *The kidney shows the gross appearance of polycystic kidney disease.*

One practical problem encountered in the later stages of CKD in older cats is constipation. This probably results from a combination of factors:

- dehydration leading to hard dry stools of low volume being formed
- muscle weakness and reduced gastrointestinal motility, exacerbated by hypokalemia
- unwillingness to defecate due to chronic pain on adopting the position to defecate (chronic arthritis; bone pain from renal osteodystrophy)
- use of high doses of intestinal phosphate binders which can cause constipation as an adverse effect
- use of calcium channel blockers as anti-hypertensive agents which may reduce intrinsic gastrointestinal motility.

Constipation can create a vicious cycle of reduced appetite and food intake leading to reduced stimulation of gastrointestinal motility and further problems with potassium balance. Dietary strategies which increase fecal bulk and ensure the production of soft but formed feces and maintain gastrointestinal motility will also be of benefit to the stage IV CKD patient.

► Management of metabolic acidosis and hypokalemia

The stage of CKD at which problems of metabolic acidosis become evident on laboratory testing tends to be late stage III and stage IV. The prevalence of metabolic acidosis was 15% at stage III (3/20) and 52.6% at stage IV (10/19) *(Elliott et al, 2003a)*. This suggests that in the earlier stages of CKD, animals are able to excrete the acid ingested in the diet or that small imbalances between intake and excretion are being buffered in the body such that significant changes in plasma bicarbonate concentration are not detectable. The most likely place acid buffering would occur in these animals is in bone, resulting in the leeching of calcium from bone, thus contributing to renal osteodystrophy and increasing the risk of soft tissue mineralization *(Leemann et al, 2003)*.

The contribution of metabolic acidosis to bone disease associated with CKD is well recognized in human medicine but has not been studied in cats. Indeed, in a longitudinal study of cats with CKD, the occurrence of metabolic acidosis was not detected on laboratory tests until cases had progressed from stage II to stage III/IV *(Elliott et al, 2003b)*. Whether providing alkali supplementation prior to the detection of metabolic acidosis would be beneficial remains to be determined although no effect of three months of potassium gluconate supplementation on bone turnover (assessed by measurement biochemical markers of bone synthesis and degradation) was detectable *(unpublished data)*. Clearly, at the later stages of CKD, metabolic acidosis contributes to the uremic syndrome and measures should be taken to treat this problem.

Treatment of metabolic acidosis involves alkali supplementation **(Table 7)**. Response to treatment can be monitored by repeated measurements of plasma bicarbonate concentration with the aim to bring this back to the middle of the reference range if possible.

The choice of agent will be dictated by other factors, including palatability when added to the diet, presence of hypertension (when supplementation of sodium should be avoided), presence of hypokalemia (where potassium salts will be chosen) and the presence of hyperphosphatemia, where calcium salts may be considered because of their phosphate binding capabilities (provided hypercalcemia does not become a problem).

Metabolic acidosis tends to exacerbate the likelihood of hypokalemia occurring. Potassium tends to move out of the cells in response to metabolic acidosis and is lost in urine. In addition, reduced food intake and vomiting may accompany metabolic acidosis, both exacerbating loss of potassium ions. As described above, treatment with potassium gluconate or potassium citrate would be appropriate in such circumstances. The use of H_2 blockers, such as famotidine (2.5 mg/cat once daily) can also improve the appetite in these cats by reducing gastric acidity. Hyperacidity occurs in CKD due to hypergastrinemia *(Goldstein et al, 1998)* secondary to reduced renal clearance of gastrin.

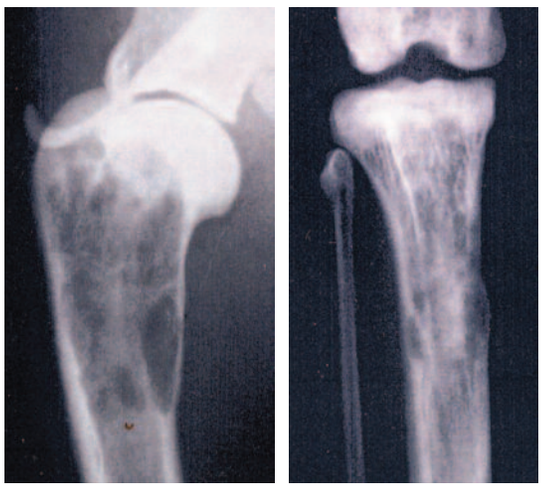
► Management of hyperphosphatemia

The degree of dietary phosphate restriction required to attain the post-treatment targets of plasma phosphate concentration will increase with the severity of kidney disease. At late stage III/IV it is unlikely this will be possible by feeding a renal care diet alone and intestinal phosphate binders may be needed to lower the plasma phosphate concentration below the target of 1.9 mmol/L (5.88 mg/dL) **(Table 8)**. It is important to recognize that phosphate binders interact with the food and so should be mixed into the food to ensure maximal efficacy. This can create problems in that their addition to the food can reduce the palatability of the diet.

The following are generic recommendations for dosing phosphate binders:
- starting dose 30 to 60 mg/kg should be used
- powered and granular preparations are recommended in preference to liquids and gels which might affect palatability of the diet

FIGURE 25 - RADIOGRAPH OF A CAT WITH SEVERE CKD AND MARKED SECONDARY RENAL HYPERPARATHYROIDISM

Reproduced from Barber (1999)



Lateral radiograph of the proximal humerus.

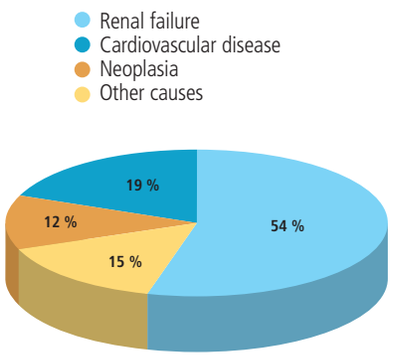
Antero-proximal view of the tibia.

Note the cystic lesions in both long bones leading to thinning of the cortices. This is the same cat shown in Figure 8.

- the binder must be mixed with the diet
- plasma phosphate concentration should be reassessed every 4 weeks
- increase the dose to effect (doubling increments to a maximum tolerable dose), reassess.
- for aluminum containing binders, drug-induced microcytosis, muscular weakness, and encephalopathy are possible
- higher doses of binder will be required if consuming low amounts of clinical renal diets (or a diet which is relatively higher in phosphate) and as the stage of CKD increases
- constipation is a potential complication of higher doses of any of the available intestinal phosphate binding agents
- plasma calcium concentration should be monitored, particularly if using calcium containing phosphate binders to avoid problems of hypercalcemia.

As CKD progresses, achieving control of plasma phosphate concentration and maintaining voluntary consumption of adequate calories per day becomes increasingly difficult. If a gastrostomy tube is placed and food mixed with phosphate binders is administered via this route, control of plasma phosphate is more likely to be achieved. Quality of life is affected by marked hyperphosphatemia as metabolic bone disease becomes more pronounced and radiographically evident **(Figure 25)**. Deposition of calcium and phosphate in the vasculature increases the risk of cardiovascular complications of CKD in human patients. Interestingly, the cause of death in cats was attributed to cardiovascular problems in about 20% of cases (**Figure 26**; data from cases presented in *Elliott et al, 2000*).

FIGURE 26 - CAUSES OF DEATH IN 50 CATS STUDIED FROM DIAGNOSIS OF STAGE II AND III CKD



► Prevention of anorexia and loss of body mass

Sufficient energy needs to be provided to prevent endogenous protein catabolism which will result in malnutrition and exacerbation of azotemia. Cats require 50-60 kcal/kg/day. Energy intake should be individualized to the patient needs based on serial determinations of body weight and body condition score.

Carbohydrate and fat proved the non-protein sources of energy in the diet. Fat provides approximately twice the energy per gram than carbohydrate. Therefore fat increases the energy density of the diet, which allows the patient to obtain its nutritional requirements from a smaller volume of food. A smaller volume of food minimizes gastric distention, which reduces the likelihood of nausea and vomiting.

The efficiency of a renal diet depends upon it being fed exclusively and on a continuing basis. Thus, the diet must be palatable enough to avoid any risk of refusal. Correct energy content and high digestibility of the diet are important to maintain sufficient nutritional intake **(Figure 27)**.

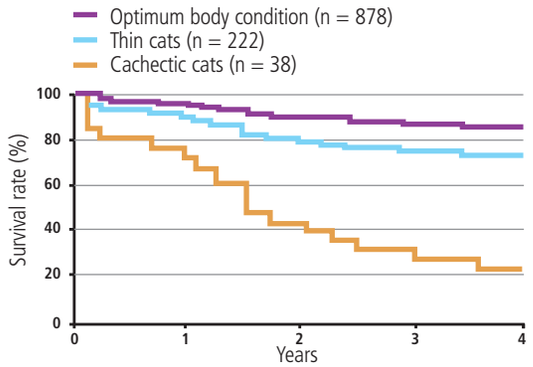
At the later stages of CKD, appetite becomes a problem and consumption of sufficient calories to maintain body weight and condition is an issue. Adding flavorings (there are some commercially available products) to the formulated renal care diets can help improve the amount of food consumed. Sometimes warming the food and offering frequent small servings can assist in maintaining daily intake of calories. At the later stages of CKD when voluntary food intake is reduced, it may be necessary to provide additional vitamin supplements, particularly the water soluble vitamins (B and C) may be required since urinary losses of these nutrients may exceed intake. Evidence of vitamin deficiencies associated with CKD have not been documented although many renal care diets are formulated to provide increased amounts of water soluble vitamins when compared to standard maintenance diets.

Conclusion

Diet plays an important role in the management of the feline patient with CKD. It is important to tailor the diet to the needs of the individual patient and to understand the goals in the use of renal care diets at different stages of CKD. These are summarized below.

FIGURE 27 - BODY SCORE AND LIFE EXPECTANCY IN CATS

From Doria-Rose & Scarlett, 2000



- **At stages II and III** formulated renal care diets have been shown to be of benefit improving survival and limiting uremic crises. The principles of therapy include:
  - limiting phosphate intake prevents whole body phosphate overload and progressive renal injury induced by nephrocalcinosis
  - reducing protein intake may have some utility to limit hyperfiltration and proteinuria in markedly proteinuric cases (UPC>1.0)
  - the beneficial effects of supplementing n-3 PUFAs remain to be studied in the cat
  - supplementation of potassium is necessary in cats that are hypokalemic but appears to have no detectable benefit in normokalemic cats
  - the benefit of reducing dietary sodium intake on control of blood pressure remains to be determined.

- **At late stage III and stage IV** diet can be used to improve the quality of life of cats entering the uremic phase of CKD. The important principles of therapy at this stage include:
  - limiting protein intake to reduce the build up of nitrogenous waste products, particularly when plasma urea concentration exceeds 30 mmol/L (84 mg/dL). The origin of the protein has to be taken into consideration: very highly digestible protein limits the protein by-products release in the blood
  - the use of dietary components that remain in the gastrointestinal tract and trap urea and other nitrogenous waste products
  - supplementing alkali in the diet to treat metabolic acidosis which contributes to metabolic bone disease, inappetance and malaise
  - supplementing potassium as required to treat hypokalemia which contributes to inappetance, muscle weakness and general malaise
  - further reducing phosphate bioavailability in the diet by the use of intestinal phosphate binding agents to limit the extra-renal effects of hyperphosphatemia and hyperparathyroidism including metabolic bone disease and vascular calcification which affect quality of life.

TABLE 7 - DIFFERENT FORMS OF ALKALI SUPPLEMENTATION

• Sodium bicarbonate • Potassium citrate • Calcium carbonate
Dose rates of 1 to 3 mEq of base per kg per day are usually effective. Animals with a renal tubular acidification defect may require substantially higher dose rates (3 to 9 mEq/kg/day).

TABLE 8 - CURRENTLY AVAILABLE PHOSPHATE BINDING AGENTS

• Aluminium carbonate • Aluminium hydroxide • Aluminium oxide • Calcium carbonate (+/- Chitosan) • Calcium acetate • Lanthanum carbonate • Selevamer hydrochloride
A lanthanum based intestinal phosphate binder has recently been tested for its palatability when mixed with standard maintenance diets of cats *(Schmidt et al, 2006)* and dogs *(Spiecker-Hauser et Schmidt, 2006)*. This product appeared to be acceptable at an inclusion rate of 3g/kg of feed (wet weight) and, in normal cats increased the fecal content of phosphate from 30.7 ± 10.4 mg/day to 66.7 ± 21.0 mg/day. The efficacy and tolerability of this product in cats with advanced CKD remains to be determined.

Frequently asked questions about dietary therapy for feline chronic kidney disease

Q	A
Is chronic kidney disease a single disease entity?	No. Chronic kidney disease is a syndrome resulting from the loss of functioning kidney tissue. It is a heterogeneous syndrome. Many disease processes can result in loss of functioning nephrons (infectious, immune-mediated, degenerative, neoplastic, toxicologic, congenital, metabolic, inherited). The response to loss of functioning kidney tissue (whatever the cause) leads to a number of adaptive responses of the remaining function nephrons (intrinsic mechanisms) and of other body systems (extrinsic mechanisms) which can lead to further nephron damage and so are termed mal-adaptive and are common therapeutic targets regardless of the initial underlying cause of the chronic kidney disease.
Why is chronic kidney disease so common in elderly cats?	This is a question, the answer to which is not well understood. The kidney of the cat is adapted to produce a highly concentrated urine enabling this animal to live in climates where water is in short supply. It is possible that the process of generating such a concentrated urine means that nephrons in the cat kidney (of which there are 200,000 per kidney to begin with) 'wear out' over the life-span of the cat. This coupled with other extrinsic insults to the cat's kidneys mean that towards the end of its natural life, less than 25% of its functioning nephrons survive. Hence cats start to show clinical signs of chronic kidney disease as they age. This is certainly not the complete story and is purely a hypothesis since the definitive reason for the high prevalence of chronic kidney disease in the cat is not known.
Why is the composition of urine so variable?	The physiological role of the kidney is to balance dietary intake of substances (water, electrolytes and minerals) with non-renal losses and requirements for growth, lactation and other activities such that homeostasis is achieved. Since dietary and water intake vary from one day to the next, urine composition is highly variable so that body fluid composition remains stable and homeostasis can be achieved.
How do we identify IRIS stage I chronic kidney disease patients if they are not azotemic?	It is important to remember that the IRIS staging system is to be applied only to animals in which a diagnosis of chronic kidney disease has been made. In stage I, kidney disease is not diagnosed based on elevated plasma creatinine so some other clinical/laboratory finding indicates the presence of chronic kidney disease. This may be anatomical abnormality of the kidneys identified on physical examination or imaging confirmed by renal biopsy; a persistent inability to concentrate urine effectively with no evidence of an extra-renal problem as a cause of this renal dysfunction; persistent proteinuria with no evidence of extra-renal disease causing this finding or serial increases in plasma creatinine concentration measured sequentially over time (although these are still within stage I range).
In IRIS stage II chronic kidney disease, there are often no outward clinical signs of chronic kidney disease. Is it necessary to alter the diet at this stage?	The goals in managing the chronic kidney disease patient, if the primary underlying cause of the disease damaging the kidney can not be identified, are to improve the quality of life of the patient and to slow intrinsic progression of the disease towards end stage. There is good evidence from naturally occurring feline chronic kidney disease patients that feeding a specifically formulated renal diet increases long term survival and reduces the occurrence of uremic crises. The patients in these controlled prospective clinical trials were in stage II and early stage III chronic kidney disease according to the IRIS classification where the major benefit of feeding formulated diets is in slowing progressive renal injury.

Q	A
Why are clinical diets beneficial to feline patients in stage II chronic kidney disease?	As the clinical trials that have been conducted have involved diets that differ in a number of respects to standard maintenance diets it is not possible to say for certain which dietary manipulation benefits the clinical patient most at which stage of their kidney disease. It is likely that some of the benefit observed is derived from restricting dietary phosphate intake and limiting whole body phosphate overload.
If cats will not eat specifically formulated clinical diets is there anything that can be done?	Restricting phosphate intake is an important part of managing the cat with CKD. It may be possible to achieve appropriate phosphate restriction for the stage of CKD by adding a phosphate binder to a standard maintenance cat food. This is not as desirable as feeding a specially formulated clinical renal diet. The effect of phosphate binding agents can be monitored by measuring plasma phosphate concentration. The dose of phosphate binder to be mixed with the food will depend on the stage of CKD and the phosphate content of the food and should be titrated to effect (starting at 30 to 60 mg/kg) until plasma phosphate concentration is below the target level (i.e. 1.45 mmol/L, 4.5 mg/dL, for stage II).
Should all cats with chronic kidney disease receive an oral potassium supplementation?	No – this is not necessary provided the cat is being fed a non-acidifying diet with an appropriate level of potassium for an adult cat and has a plasma potassium concentration within the laboratory reference range. About 20% of cats with CKD are hypokalemic at diagnosis and require additional potassium by the oral route to correct this. These cats will have an improved appetite and level of activity. These cats can sometimes maintain plasma [K+] within the reference range when fed clinical renal diets, in which case oral supplementation may not need to be continued. Cats with CKD with normal plasma [K+] which are given oral potassium supplementation merely excrete more potassium in their urine to maintain homeostasis.
Why do clinical kidney diets have lower protein content than standard maintenance diets?	Protein restriction was originally thought to benefit the CKD patient by lowering glomerular capillary pressure and so reducing hyperfiltration associated with the intake of food, particularly consumption of a meal high in protein. Whilst this phenomenon clearly slows progressive renal injury in rats with experimental kidney disease, extrapolation to cats and dogs has not proved appropriate. Feeding a diet restricted in protein in stage II and early stage III is usually undertaken because lowering protein enables diets that are restricted in phosphate to be formulated. Clinical benefits of restricting protein are observed in late stage III and stage IV cases where levels of nitrogenous waste products accumulate and restricting protein intake reduces the formation of nitrogenous waste products, thus reducing clinical signs. Such a benefit is not usually evident until the plasma urea concentration approaches 30 mmol/L (87 mg/dL).
What is the most reliable prognostic indicator in a cat with CKD?	CKD in cats tends to progress at very variable rates such that within a given IRIS stage the survival time from diagnosis is highly variable. The most reliable predictor of rapidly progressive CKD is the severity of proteinuria at initial diagnosis. If the UPC is persistently >0.4 (note low level proteinuria is normal for cats with CKD) this is a poor prognostic indicator and survival time is highly likely to be much shorter than cats with UPCs <0.2. Cats with UPCs >0.4 are also likely to benefit most from anti-proteinuric therapies although this remains to be documented by a randomized controlled prospective clinical trial.

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Focus on:

Phosphorus

Etymologically speaking, the word phosphorus means 'light-bringing.' It was discovered in 1669 by a German alchemist, Hennig Brandt. By evaporating urine and calcifying the residue, he obtained phosphorus in gas form that shone in the dark.

In the form of phosphates, phosphorus enters into the composition of bone. Eighty-six percent of the phosphorus in the organism is stored in the structure of the skeleton.

Phosphorus is also incorporated into large molecules such as DNA, RNA and membrane phospholipids. In addition, it is an active constituent of the adenosine triphosphate molecule (ATP), which stores the energy living organisms need to function properly.

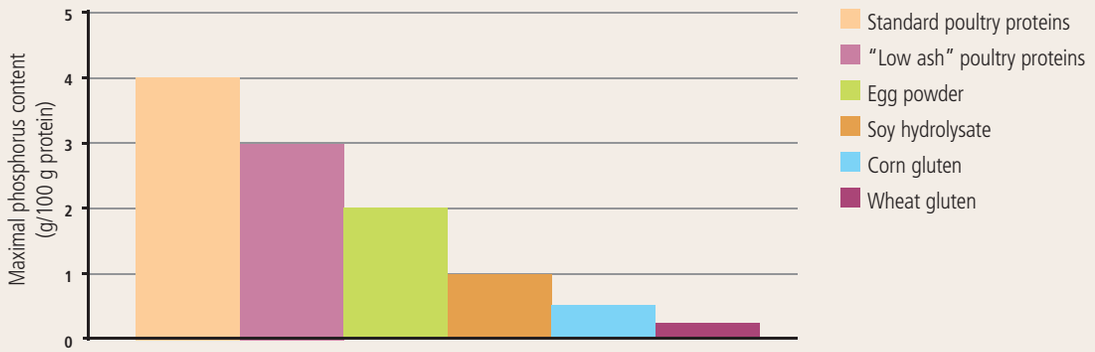
Following the reduction of the glomerular filtration rate (GFR), phosphorus accumulates in the organism that responds by increasing the secretion of parathyroid hormone (PTH). This response initially helps maintain the phosphorus within normal thresholds, but also leads to the release of phosphate and calcium from bone reserves.

In time, even this compensatory response is not enough to restore homeostasis. Phosphorus and calcium accumulate, leading to the mineralization of soft tissue (kidney, heart). In the kidney, this phenomenon accelerates the loss of functional nephrons.

While it is vital to limit the phosphorus content in the food, the difficulty lies in the necessity of finding raw ingredients that are low in phosphorus. Animal protein sources traditionally used in dog food are fairly high in phosphorus. For example, there is 1.6-2.5% phosphorus on a a dry matter basis in dehydrated poultry proteins. This level is dependent on the overall content of remaining mineral matter after sieving. Vegetable protein sources that are lower in phosphate concentration (wheat or corn gluten, soy protein isolate hydrolysate) are an interesting alternative

PHOSPHORUS CONTENT OF SEVERAL PROTEIN SOURCES USED IN DOG FOOD

(Royal Canin internal data)



Wheat or corn gluten helps supply high quality proteins while simultaneously reducing the ingestion of phosphorus.

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Key points

Treatment and prevention of chronic kidney disease in cats

Diet composition plays an important role in maintaining homeostasis in cats suffering from chronic kidney disease (CKD). The recommendations with respect to nutritional treatment must be tailored to the patient, based on the clinical and laboratory results. CKD is a progressive disease and so examinations must be conducted regularly if treatment is to be efficient.

The priority dietary modifications have the following objectives:

- combating against anorexia and maintaining sufficient energy consumption
- preventing secondary renal hyperparathyroidism by controlling hyperphosphatemia
- limiting azotemia and/or uremia
- preventing hypokalemia
- combating the risk of metabolic acidosis
- strengthening the antioxidant defenses

Combating anorexia and maintaining sufficient energy consumption

The palatability of the food is a key factor in stimulating food consumption in cats with CKD and promoting observance of the nutritional treatment.

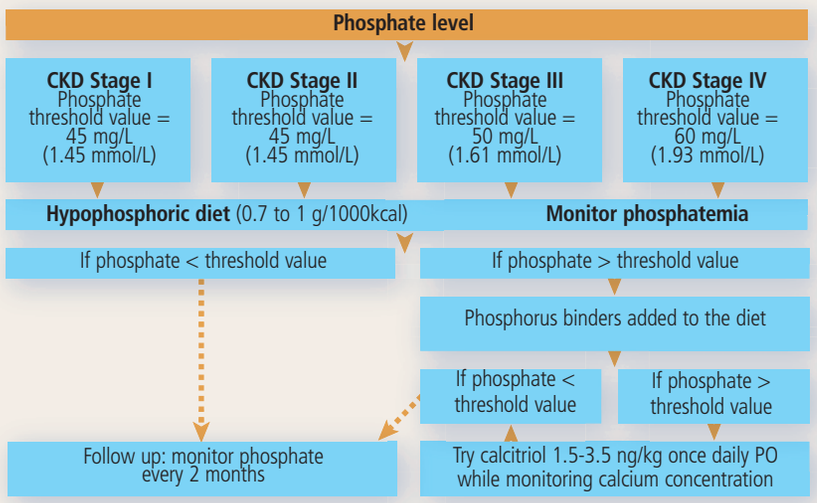
A high-energy food permits the volume of the meal to be reduced, which facilitates the feeding of animals whose appetites are affected by the disease.

Preventing secondary renal hyperparathyroidism by controlling hyperphosphatemia

The aim is to limit the phosphorus level of foods to 0.7-1.0 g/1000 kcal (around 0.3-0.4% of a dry food of 4000 kcal/kg). This restriction helps double the life expectancy of cats with renal insufficiency *(Ross et al., 2005)*. If such a low level does not stabilize the phosphatemia at the desired level **(Figure 1)**, the use of phosphorus binders must be considered.

FIGURE 1 - THERAPY BASED ON THE PLASMA PHOSPHATE CONCENTRATION MEASUREMENT

From F. Hebert, 2008



Limiting azotemia and/or uremia

When CKD leads to uremia, it is recommended to reduce the protein intake to prevent the uremia altering the cat's well being to too great a degree. Measurement of the protein/creatinine ratio in the urine is helpful to appreciate the response to protein restriction (reduced production of nitrogenous waste).

It is also important to provide the cat suffering from renal insufficiency with long-chain omega-3 polyunsaturated fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]). In dogs with CKD, the administration of a diet with a high-fish oil content slows down the deterioration of GFR *(Brown et al., 2000)*.

Preventing metabolic acidosis and hypokalemia

Metabolic acidosis requires oral alkaline treatment. Metabolic acidosis increases the risk of hypokalemia: potassium gluconate or potassium citrate treatment is therefore indicated.

Preventing metabolic acidosis and hypokalemia in cats with CKD entails avoiding acidifying foods and make sure the potassium intake exceeds the requirement. The systematic prescription of potassium supplements will generally be redundant if a food tailored to the needs of the kidneys is used.

Strengthening the antioxidant defenses

Enriching the levels of vitamin E, vitamin C, taurine, lutein, lycopene, beta-carotene, etc. in the food helps limit the oxidative stress that aggravates CKD lesions.

The nutritional diet is the cornerstone in the treatment of renal insufficiency. In cats, it has been proven to contribute to a significant increase in life expectancy by slowing down the progression of the kidney disease.

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Nutritional management of feline lower urinary tract disorders

ABBREVIATIONS USED IN THIS CHAPTER

DMB: dry matter basis
FIC: feline idiopathic (or interstitial) cystitis
FLUTD: feline lower urinary tract disease
GAG: glycosaminoglycan
GFR: glomerular filtration rate
IRIS: international renal interest society
PMR: proportional morbidity rate
RSS: relative supersaturation

Nutritional management of feline lower urinary tract disorders

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Dr. Houston graduated from the Ontario Veterinary College in 1980, spent 4 years in private practice in Thunder Bay, Ontario and then returned to the OVC for further education (Internship, Residency and DVSc in Internal Medicine). She became a Board Certified Diplomate of the American College of Veterinary Internal Medicine (ACVIM) in 1991. Doreen joined the Western College of Veterinary Medicine at the University of Saskatchewan in 1990 and climbed the ranks to Full Professor in 1995. During her tenure in academia, Doreen received numerous teaching awards. In July 1996, Doreen left academia to become part of the team at Veterinary Medi-Cal (Royal Canin) Diets in Guelph, Ontario. She is currently the Clinical Trial Research Director for Medi-Cal Royal Canin Veterinary Diets in Canada. Dr. Houston is the author of several published papers, book chapters and a textbook.

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Denise Elliott graduated from the University of Melbourne with a Bachelor in Veterinary Science with Honors in 1991. After completing an internship in Small Animal Internal Medicine and Surgery at the University of Pennsylvania, Denise moved to the University of California-Davis where she completed a residency in Small Animal Internal Medicine, a fellowship in Renal Medicine and Hemodialysis, and a residency in Small Animal Clinical Nutrition. Denise received board certification with the American College of Veterinary Internal Medicine in 1996 and with the American College of Veterinary Nutrition in 2001. The University of California-Davis awarded a PhD in Nutrition in 2001 for her work on Multifrequency Bioelectrical Impedance Analysis in Healthy Cats and Dogs. Denise is currently the Director of Scientific Affairs for Royal Canin USA.

Feline lower urinary tract disease (FLUTD) refers to a heterogeneous group of disorders all characterized by similar clinical signs including hematuria (macroscopic and microscopic), dysuria, stranguria, pollakiuria, inappropriate urination (periuria or signs of irritative voiding outside of the litter box), and partial or complete urethral obstruction *(Kruger et al, 1991; Osborne et al, 1996a).*

Figure 1 - Conditions responsible for the clinical signs of non-obstructive feline lower urinary tract disease in cats
(Adapted from Buffington et al, 1997)

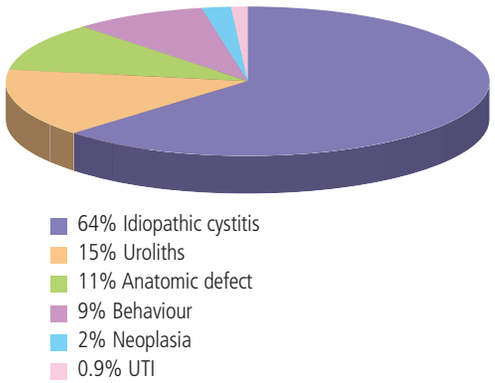
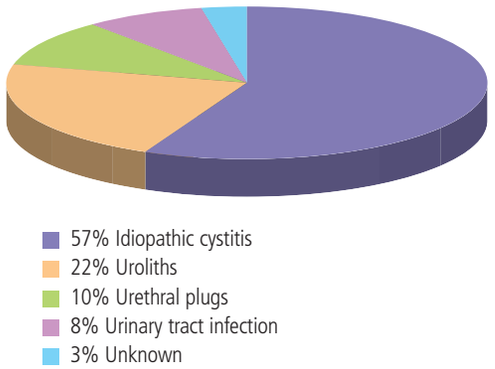


Figure 2 - Conditions responsible for the clinical signs of lower urinary tract disease in European cats
(Adapted from Gerber et al, 2005)

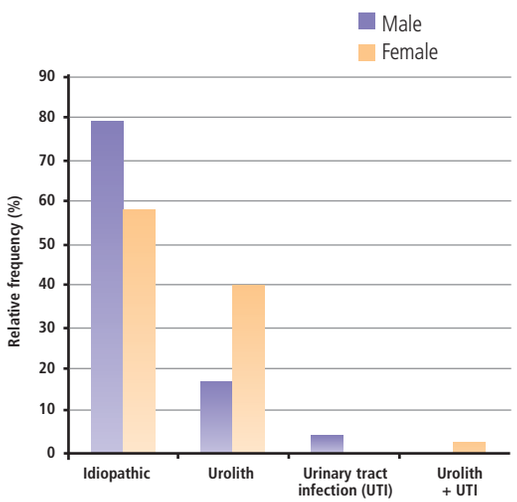


1 - Epidemiology

Incidence, prevalence and proportional morbidity rate are all terms used to describe the frequency of disease.

- **The incidence** rate of FLUTD is defined as the number of new cases of FLUTD occurring in the population during a defined time interval (often annual). The incidence of disease is useful to epidemiologists because it is used as a measure of the risk of disease. The incidence rate of FLUTD has been estimated at approximately 0.85% in the USA *(Lawler et al, 1985)*. In the United Kingdom, the incidence rate was estimated at 0.34 to 0.64% *(Fennell, 1975; Walker et al, 1977; Willeberg, 1984)*.
- **The prevalence** of FLUTD is defined as the total number of pets with FLUTD in the population at a specific time. Prevalence differs from incidence in that it does not convey information about risk.
- The ratio of FLUTD cases to all cases seen in a clinic or hospital in a given time period is the **proportional morbidity rate** (PMR). The PMR of FLUTD in North America has been estimated at 1.5-8% *(Bartges, 1997; Lund et al, 1999; Lekcharoensuk et al, 2001a)*.

Figure 3 - Frequency of disorders in male and female cats in the United States with signs of FLUTD
(Adapted from Osborne et al, 2000)



2 - Etiology

Worldwide, idiopathic cystitis is by far the most common cause of FLUTD reported in male and female cats *(Kruger et al, 1991; Buffington et al, 1997; Osborne et al, 2000; Lekcharoensuk et al; 2001a; Gerber et al, 2005)* **(Figures 1, 2, 3)**.

Urolithiasis is the second leading cause of FLUTD. Uroliths can form anywhere in the urinary tract but the vast majority in cats occur in the bladder *(Cannon et al, 2007)*. The majority of uroliths in the bladder are composed of magnesium ammonium phosphate (struvite) or calcium oxalate. Conversely, nephroliths are typically composed of calcium oxalate *(Lulich et al, 1994)*.

The prevalence of struvite and calcium oxalate uroliths in cats has changed over the last 20 years **(Table 1)**. Struvite uroliths analyzed at two laboratories in the USA performing quantitative analysis far outnumbered calcium oxalate uroliths before the late 1980s *(Cannon et al, 2007)*. Between 1984 and 1995, the proportion of calcium oxalate uroliths submitted to the University of Minnesota Urolith Center increased from 2% to 40% *(Osborne et al, 1996b)*. By the mid 1990's, struvite urolith submissions began to decline and calcium oxalate became the number one sub-

TABLE 1 - CHANGE IN STRUVITE AND CALCIUM OXALATE UROLITH SUBMISSIONS IN THE USA OVER THE LAST TWO DECADES

(Adapted from Osborne et al, 1986; 1992a; 1995a,b; 2000; Forrester, 2006; Cannon et al, 2007)

Year	1984	1986	1989	1990	1993	1995	1997-98	2001	2002	2003	2004	2005
Struvite (%)	88-90	85	70-80	65	54	50	42	34	40	42.5	44.9	48
Calcium oxalate (%)	2.4	3	10.6	19	27	37	46	55	50	47.4	44.3	41
Urate (%)	2		5.6+	6.3+		6.80+	5.60+					4.60+

Struvite predominated throughout the 1980's and early 1990's.
Calcium oxalate predominated through the latter part of the 1990's and early 2000's.
Struvite predominates again in 2005.
+includes data from 1984 and 1986

mission in North America and other parts of the world *(Lekcharoensuk et al, 2001a; Cannon et al, 2007; Forrester, 2006; Houston et al, 2003; 2006; Gerber et al, 2005)*. However, since 2002, struvite uroliths have been on the rise and have surpassed calcium oxalate as the number one urolith submission in the USA **(Figure 4)**. Based on 9221 feline uroliths analyzed at the Minnesota Urolith Center in 2005, the most common mineral types were struvite (48%), calcium oxalate (41%) and purine (4.6%) *(Forrester et al, 2006)*. In Canada, equal numbers of struvite and calcium oxalate uroliths were submitted in 2005 *(Houston et al, 2006)*. In Hong Kong, Italy and Great Britain, struvite uroliths were the most common submission in the time period studied (1998-2000) with calcium oxalate second *(Stevenson, 2001)*. In the Netherlands, calcium oxalate was the most common submission in the same time period with struvite uroliths second *(Stevenson, 2001)*. Less frequently reported uroliths include ammonium urate, cystine, silica, xanthine, calcium phosphate, pyrophosphate and dried solidified blood uroliths.

In male cats with obstructive FLUTD, urethral plugs are the number one cause followed by idiopathic cystitis **(Figure 5)** *(Kruger et al, 1991)*. Less common causes of FLUTD in both male and female cats are those caused by anatomical defects, neoplasia, urinary tract infections and neurological disorders *(Kruger et al, 1991)*. In cats older than 10 years, idiopathic cystitis is uncommon and urinary tract infection is the leading cause of FLUTD followed by urolithiasis **(Figure 6)** *(Bartges, 1997)*. Bacterial cystitis is typically identified in cats less than one year of age, in older cats, and in cats with compromised host factors (perineal urethrostomies, diabetes mellitus, chronic kidney disease etc).

FIGURE 4 - CHANGING PREVALENCE OF CALCIUM OXALATE AND STRUVITE UROLITHS FROM 2001 TO 2005

(Adapted from Forrester, 2006)

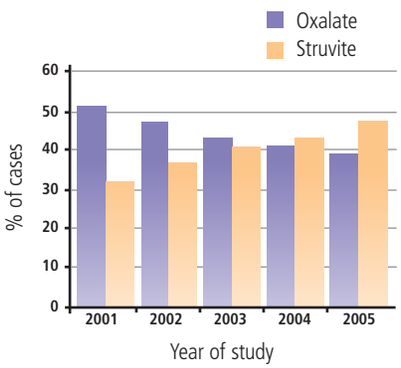


FIGURE 5 - PERCENTAGE OF OBSTRUCTIVE CAUSES OF FLUTD IN 51 MALE CATS IN THE UNITED STATES

(Adapted from Osborne et al, 2000)

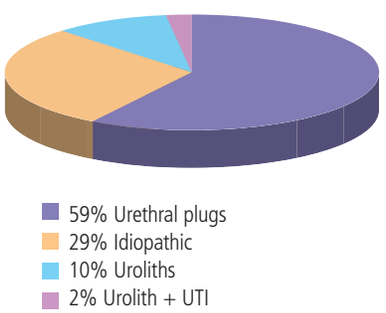
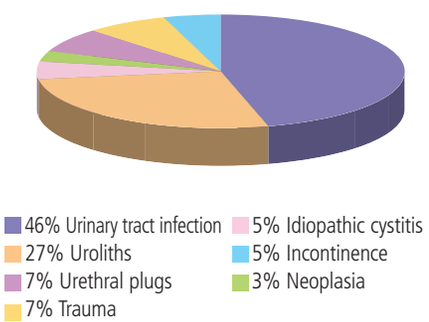


FIGURE 6 - CONDITIONS RESPONSIBLE FOR THE CLINICAL SIGNS OF FLUTD IN CATS OLDER THAN 10 YEARS OF AGE

(Adapted from Bartges 1997)



3 - Pathophysiology

► Feline idiopathic cystitis

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Significantly more owners of cats with FIC than owners of healthy cats or cats with other diseases perceived that their cats had fear, nervousness, and aggression supporting the theory that affected cats have an underlying stress disorder (Buffington et al, 2006a,b).

Feline idiopathic (or interstitial) cystitis (FIC) is thought to be a noninfectious, inflammatory, psychoneuroendocrine disorder with abnormalities in the bladder, central nervous system and hypothalamic-pituitary-adrenal response system **(Figure 7)**. It is hypothesized that decreased levels of glycosaminoglycans (GAG) reduce the protective effect of the uroepithelium permitting urine constituents such as calcium and potassium ions to penetrate the epithelium and cause inflammation *(Buffington et al, 1994; 1999a; Buffington & Pacak, 2001; 2002; 2004; Westropp et al, 2002; 2003; Pereira et al, 2004)*. In addition, the ions may stimulate the sensory neurons (C-fibers) in the submucosa, which, via the spinal cord and brain, are perceived as pain. Stressors in a sensitive cat's environment may precipitate clinical signs by activation of the efferent sympathetic nervous system, which stimulates the dorsal root ganglia. The dorsal root ganglia cause the peripheral release of neuropeptides and mediators responsible for inflammation and pain *(Buffington et al, 1994; 1999a; Buffington & Pacak, 2001; Westropp et al, 2002; 2003; Pereira, 2004)*.

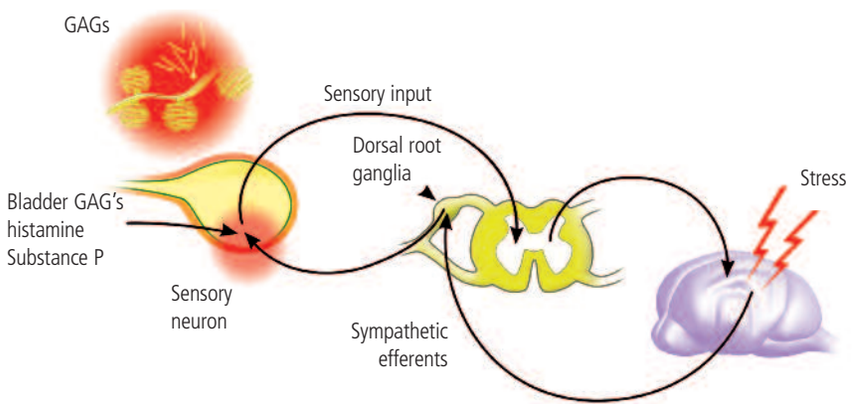
Cats may be born with a predisposition to FIC and clinical signs of FLUTD are manifested if such a cat is placed in a "provocative or stressful" environment. FIC is a chronic, waxing and waning disease characterized by periods of remission interspersed with relapse precipitated by stress. Some affected cats have been shown to have small adrenal glands *(Westropp et al, 2003)*.

► Urethral plugs

Urethral plugs are disorganized precipitates typically composed of sloughed tissues, blood or inflammatory cells, mixed with large quantities of matrix. Crystalline material may or may not be present. Struvite is the predominate mineral type in those urethral plugs that contain a mineral component. There are physical differences and probably etiological differences between uroliths and urethral plugs however, the actual cause of the matrix-crystalline plugs has not been clearly determined. It has been suggested, but not definitively established that Tamm-Horsfall mucoprotein is the predominant matrix compound which has been hypothesized to be a local host defense

FIGURE 7 - SCHEMATIC REPRESENTATION OF THE PROPOSED PATHOPHYSIOLOGICAL ALTERATIONS IN CATS WITH FELINE IDIOPATHIC/INTERSTITIAL CYSTITIS

(Adapted from Buffington et al, 1999a)



mechanism. *(Kruger et al, 1991; Osborne et al, 1992b; 1996c; 1996d; Houston et al, 2003; Forrester, 2006)*. Urethral plugs are much more common in male cats and cause partial or complete urinary tract obstruction. FIC may predispose some cats to forming urethral plugs.

► Uroliths

A urolith (commonly referred to as a stone) is defined as the formation of sediment, consisting of one or more poorly soluble crystalloids, in the urinary tract. Microscopic sediment is referred to as crystals, and macroscopic precipitates are called uroliths.

Urinary crystals form when the urine is supersaturated with respect to a specific mineral or mineral compound. Precipitation is a result of increasing supersaturation. The initial phase, or nucleation, of urolith formation involves the formation of a crystal nidus. This phase is dependent on supersaturation of urine with calculogenic crystalloids and is influenced by the extent of renal excretion of the crystalloid, the urine pH, urine temperature, the presence or absence of various inhibitory factors (e.g., citrate, pyrophosphate), and the presence of promoters of crystallization (e.g., dead cells, cellular debris, protein, bacteria or other crystals). Crystal growth depends on the ability of the nidus to remain within the urinary tract, the duration of supersaturation of the urine and the physical ultra structure of the crystal. The actual rate of growth of the urolith depends on numerous factors including mineral composition and risk factors such as infection *(Osborne et al, 1996a,b; 2000)*.

4 - Diagnosis

► History and clinical signs

Regardless of cause, cats with FLUTD present with hematuria (macroscopic and/or microscopic), dysuria, stranguria, pollakiuria, inappropriate urination (periuria or signs of irritative voiding outside of the litter box), or partial or complete urethral obstruction *(Kruger et al, 1991; Osborne et al, 1996a)*. Male cats may be observed to lick the tip of the penis. Cats are often observed to spend longer amounts of time than normal in the litter box attempting to urinate or are observed to pass small amounts of urine frequently. Restless behavior or excessive grooming of the caudal abdomen may indicate discomfort.

Urinary tract obstruction may occur suddenly or over a period of weeks. Complete obstruction is characterized by depression, anorexia, lethargy, dehydration, hypothermia, and vomiting. In severe cases the bladder may rupture providing a transient relief of signs followed rapidly by the development of peritonitis and death.

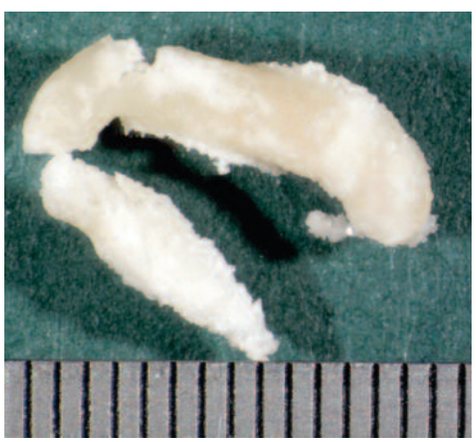


Figure 8 - Feline urethral plug.
A cream to straw-colored urethral plug may be visualized protruding from the urethra. Struvite crystals are the predominant crystals found.

► Physical examination

A complete physical examination should be performed in any cat presenting with FLUTD. Special attention should be paid to the hydration status, bladder, and external urethral orifice. The bladder should be palpated to evaluate its size (degree of distension), shape, contours, thickness of the bladder wall, intramural or intraluminal masses (tumors, uroliths, clots), or grating within the bladder lumen. Most uroliths cannot be detected by abdominal palpation *(Osborne et al, 2000)*. Palpation frequently elicits an expression of pain such as crying, resistance to further abdominal palpation, straining to urinate, or passage of a few drops of blood-tinged urine. The penis, prepuce, or vulvar area should be examined for urethral abnormalities and evidence of blood, mucus, or mineral crystals.

In cats with obstructive FLUTD, the bladder is distended, turgid, and painful. In obstructed cats, the tip of the penis may appear discolored because of inflammation and trauma from licking or because of the presence of a urethral plug **(Figure 8)**. Urethral obstruction is a medical emergency that requires immediate relief of the urethral obstruction. The patient's fluid, electrolyte (especially hyperkalemia), and acid-base status should be assessed and appropriate therapeutic maneuvers initiated **(see below in treatment section)**.

► Laboratory evaluation

In the non obstructed cat, the initial evaluation should include a urinalysis with sediment examination, urine culture, and abdominal imaging. A complete blood count can be conducted; however, it is nearly always normal. A comprehensive biochemical profile should be obtained from cats that are sick or have urethral obstruction. In cats with urate urolithiasis, serum urea nitrogen may be low in cases of portosystemic shunts or liver failure; some cats with calcium oxalate urolithiasis have hypercalcemia.

Urine for analysis may be collected by the owner using a special litter or in the clinic by obtaining a midstream sample during natural voiding, catheterization, or cystocentesis. Manual expression should be avoided as iatrogenic hemorrhage/trauma can be a significant consequence. In addition, in the rare occasion where infection is present, retrograde ascension from the bladder to the kidney and the development of pyelonephritis is possible.

The method of collection will influence the diagnostic results and their interpretation. Cystocentesis is preferred because it prevents contamination of the urine sample by the urethra or genital tract. It is minimally invasive, well tolerated, and safe so long as proper technique is used to prevent iatrogenic urinary tract trauma or infection. The main contraindications to cystocentesis are insufficient volume of urine in the urinary bladder, patient resistance to restraint and abdominal palpation, and coagulopathy or bleeding disorders. Cystocentesis should not be performed if the bladder cannot be palpated.

Urinary catheterization may be performed for:
- **diagnostic indications:** collection of urine for analysis, detection of urethral obstacles (e.g. uroliths, tumors), and instillation of contrast medium for radiographic studies
- **therapeutic indications:** relief of urethral obstruction and facilitation of surgery of the bladder, urethra, or surrounding structures.

The time of day at which the urine is collected should be recorded. In addition, the owner should be questioned on when the cat last ate and how stressed the cat was coming into the hospital. The urine pH is generally the most acidic first thing in the morning, prior to the animal eating. The pH may be higher if the urine is collected in the post prandial period (anywhere from 2-6 hours after a meal). Once the urine pH is above 6.5, struvite crystals can form. If the cat was stressed by transportation to the clinic, hyperventilation may have occurred and this too can raise the urine pH above 6.5 resulting in the appearance of struvite crystals *(Buffington & Chew, 1996a)*.

The urine sample should be collected into a sterile collection container. If culture is to be performed, a portion of the urine should be refrigerated immediately in an airtight sterile container. For sediment analysis, the urine should not be refrigerated but is kept at room temperature and covered to avoid light exposure. Analysis should be performed on fresh urine (within 15-60 minutes of collection); otherwise struvite and calcium oxalate crystals can form *(Albasan et al, 2003)*. Physical properties of the urine, chemical properties of the urine and examination of urinary sediment should all be determined. Abnormalities consistent with FLUTD that may be noted on urinalysis and sediment examination include hematuria, proteinuria, pyuria, and crystalluria (struvite, amorphous phosphates, urate, calcium oxalate, cystine and xanthine **(Figures 9-12)**.

The identification of crystals in the urine is dependent on the urine pH, temperature, and specific gravity. However, it is important to note that the presence of struvite or calcium oxalate crystals in the urine does not necessarily signify a problem. A few crystals in highly concentrated urine generally have less significance than a few crystals in dilute urine *(Laboto, 2001)*. Absolutely fresh urine must be examined as crystals may form in urine that is allowed to stand and cool prior to examination (in-vitro crystallization) **(Table 2)**. The presence of crystals observed in stored samples should be validated by reevaluation of fresh urine *(Albason et al, 2003)*.

Quantitative bacterial culture of the urine is indicated to conclusively diagnosis urinary tract infection. Urine should be obtained by cystocentesis to prevent iatrogenic bacterial contamination and submitted for culture within 30 minutes of collection. If this is not possible, urine should be refrig-

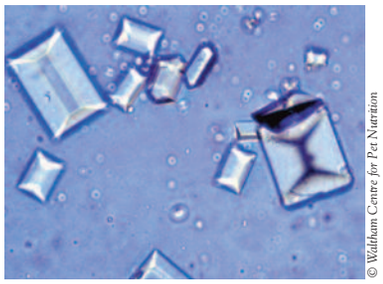


Figure 9 *- Struvite urinary crystals.*

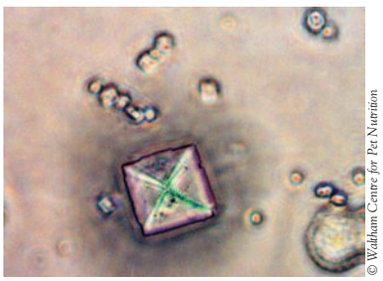


Figure 10 *- Calcium oxalate urinary crystals.*

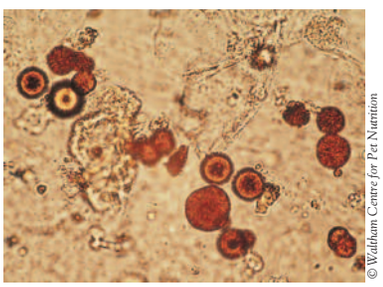


Figure 11 *- Ammonium urate urinary crystals.*

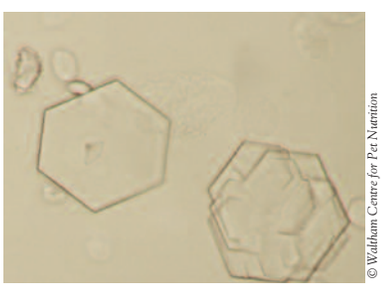


Figure 12 *- Cystine urinary crystals.*

TABLE 2 - TIPS TO HELP INTERPRET CRYSTALLURIA

- Crystals must be evaluated in absolutely fresh urine.
- Crystals observed in stored or refrigerated urine may be artifactual and urine should be restored to room temperature before examination.
- Struvite and/or calcium oxalate crystals may be a normal finding in some cat's urine, especially if the urine is highly concentrated; it is abnormal when they appear in large numbers or are clumped together.
- The presence of crystals in urine indicates that the urine is able to support crystal growth.
- The presence of crystals in urine does not necessarily indicate urolithiasis.
- Crystals may be absent in cats with urolithiasis.
- Cats may pass crystals that are different than the urolith they may have.
- Cats with cystine crystals have cystinuria and this predisposes them to cystine uroliths.

erated. Once positive identification of the organism is obtained, antimicrobial sensitivity should be performed to guide appropriate antimicrobial therapy.

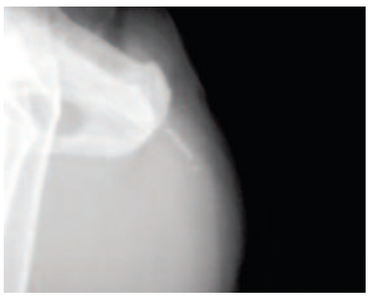


Figure 13 - Lateral radiograph of a male cat with urolithiasis. *The image indicates numerous small, radio-dense uroliths in the urethra of a male cat presenting with obstructive feline lower urinary tract disease.*

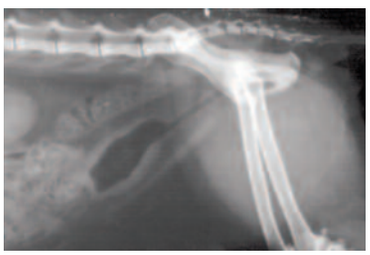


Figure 14 - Lateral radiograph of a two year old cat with feline idiopathic/interstitial cystitis. *Note the bladder wall appears thickened and non-distensible.*

► Diagnostic imaging

Diagnostic imaging techniques include survey radiographs, ultrasound, contrast radiography (excretory urography, cystography, urethrography), computed tomography, and magnetic resonance imaging *(Samii, 2003)*.

- **Survey radiographs** are used to screen for changes in the size, shape, position, or radiodensity of the urinary tract. It is important to radiograph the entire urinary system including the perineal urethra to ensure no abnormalities are overlooked **(Figure 13)**. In some cases, a cleansing enema may be needed to ensure adequate visualization of the urinary system. In cats with FIC, the bladder may appear thickened and non-distensible on radiographic examination **(Figure 14)**.
- **Ultrasound** allows assessment of intra-luminal abnormalities not seen on survey radiographs, determines what area is affected and to what extent, and provides information regarding tissue composition, i.e. solid versus cystic lesions.
- **Positive contrast cystography** is used to determine bladder location, rupture, diverticulae, and fistulas.
- **Double contrast cystography** is used to evaluate the mucosal surface of the bladder and luminal contents. A good quality double contrast study requires only a small volume (1-2 mL) of positive contrast medium. It is important to palpate the bladder as it is being filled with contrast in order to monitor the degree of distension and to avoid over inflation. The bladder should

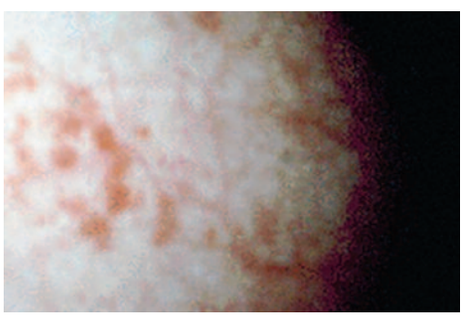


Figure 15 - Endoscopic appearance of the bladder mucosa in a cat with lower urinary tract disease. *The endoscopy demonstrates glomerulations consistent with feline idiopathic/interstitial cystitis.*

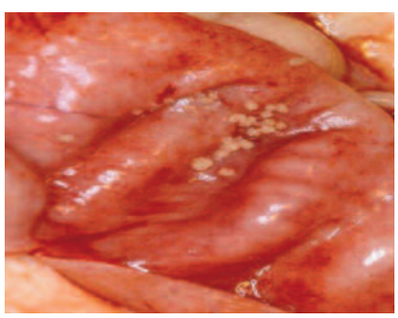


Figure 16A - Multiple calcium oxalate calculi in a cat bladder. *Note the bladder has been opened fully to allow for complete removal of all uroliths, a number of which are embedded in the bladder mucosa.*

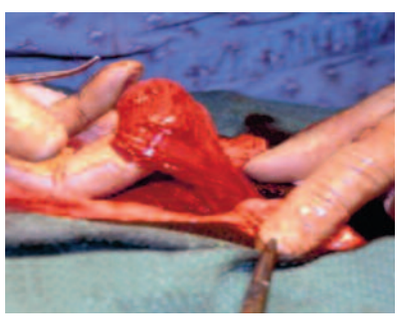


Figure 16B - Surgical removal of uroliths in the bladder. *The bladder of the cat has been entirely opened and the mucosal surface everted to ensure complete removal of uroliths. A post operative radiograph confirmed the complete removal of all of the uroliths.*

be well distended with the negative contrast medium and a small volume of positive contrast (the so called contrast puddle) should lie on the dependant surface of the bladder lumen. Radiolucent uroliths are identified as filling defects in the contrast puddle. Blood clots are identified as irregular filling defects either at the margin of the contrast puddle or adherent to the mucosal surface. Recognition of small alterations of the contour of the mucosal surface is an important clue in the diagnosis of both cystitis and tumor, but can be artifactual as a result of incomplete filling of the bladder. Urethrography is used to examine the urethra.

► Uroendoscopy

Endoscopy of the urethra and bladder is now possible using a flexible fiber optic scope in male cats and a rigid human pediatric cystoscope in female cats *(Chew et al, 1996; McCarthy 1996)*. The mucosal surface of the bladder of cats with FIC displays characteristic findings of submucosal petechial hemorrhages (glomerulations) during cystoscopy following bladder distension to 80 cm H_20 *(Chew et al, 1996; Buffington et al, 1999a)* **(Figure 15)**.

► Surgery

When surgery is performed for exploration, biopsy or urolith removal, the bladder should be fully opened **(Figure 16).** Because many feline uroliths are very small, complete surgical removal of all uroliths may be difficult and post surgical radiography should always be performed to ensure all uroliths have been removed *(Lulich et al, 1993a)*. Failure to remove all uroliths at the time of cystotomy is common and seems to be more likely with calcium oxalate uroliths. *Lulich et al* (1993a) reported that calcium oxalate uroliths were incompletely removed in 20% of cats.

► Histopathology

Biopsies of the bladder mucosa of cats with FIC may show relatively normal epithelium and muscularis with submucosal edema and vasodilation; infiltration of inflammatory cells is mild to moderate **(Figure 17)**. Some cats have increased numbers of mast cells; others have erosions, ulcerations or fibrosis of the bladder wall.

► Analysis of urolith composition

Uroliths may be collected by spontaneous voiding (use an aquarium fishnet to catch the urolith), voiding urohydropropulsion, aspiration into a urethral catheter, via cystoscopy, or surgical removal *(Lulich et al, 1992,1993b; Osborne et al, 2000)*. Uroliths need to be submitted in a clean dry container without preservatives or additional fluids. In many cases, uroliths cannot be identified simply by visual characteristics. All uroliths retrieved should be quantitatively analyzed by specialized laboratories to determine mineral composition of any/all of the 4 layers that may be present **(Figure 18)**. There are

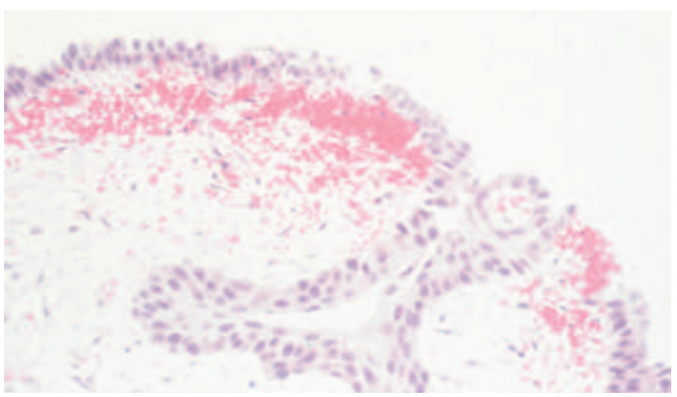


Figure 17 - Histological appearance of the bladder mucosa of a cat with lower urinary tract disease.
Submucosal edema and erosions consistent with feline idiopathic/interstitial cystitis.

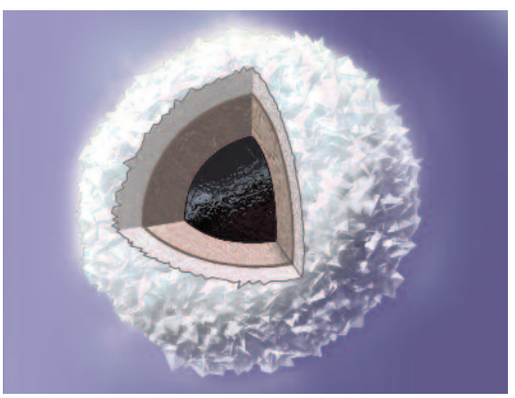


Figure 18 - Illustration of the layers of a urolith.
Quantitative analysis allows accurate determination of the mineral composition of any of the four layers that may be present: nidus, stone, shell and surface crystals.

Table 3 - Age, sex and breed predispositions and other potential risk factors for uroliths in cats

Urolith Type	Breed	Age	Sex	Other
Struvite	- **USA:** Foreign Shorthair, Ragdoll, Chartreux, Oriental Shorthair, DSH, Himalayan *(Lekcharoensuk et al, 2000; 2001a)*; Himalayan and Persian *(Cannon et al, 2007)*, DSH, DLH *(Ling et al, 1990)*; No breed predilection *(Osborne et al, 1995a; 1995b; 2000)* - **Canada:** DSH, DLH, DMH, Himalayan, Persian *(Houston et al, 2004; 2006)* - **Great Britain:** DSH, Persian *(Stevenson, 2001)*	- Sterile: 3 months-22 years; average 7.2 + 3.5 years *(Osborne et al, 2000)* - Infection induced-any age *(Osborne et al, 1995a)* - Average 5 years for females and <2 years for males *(Ling et al, 1990)* - 1-2 years *(Thumachai et al, 1996)* - 6.8 + 3.7 years *(Stevenson, 2001)*	- Female slightly > male *(Ling et al, 1990; Osborne et al, 2000; Houston et al, 2004; 2006)* - Male <2 more common than female <2 years *(Ling et al, 1990)* - Male slightly >female *(Lekcharoensuk et al, 2000)* - Male = female *(Stevenson, 2001)*	- Overweight/inactive - Low water intake *(Osborne et al, 1995)* - Alkaline urine *(Osborne et al, 1995)* - Indoor housing *(Kirk et al; 1995)*
Calcium oxalate	- **USA:** Himalayan, Persian *(Kirk et al, 1995; Cannon et al, 2007)*; Himalayan, Persian, Ragdoll, Shorthair, Foreign Shorthair, Havana brown, Scottish fold, Exotic shorthair *(Lekcharoensuk et al, 2000; 2001a)*; Burmese, Persian and Himalayan *(Thumachai et al, 1996; Osborne et al, 1995b; 1996b; Kirk et al, 1995)* - **Canada:** Himalayan, Persian *(Houston et al, 2004; 2006)* - **Great Britain:** DSH, Persian *(Stevenson, 2001)*	- 7 years; 3 months -22 years *(Osborne et al, 2000)* - Older cats and greatest risk at 10-15 years *(Thumachai et al, 1996)* - Bimodal peaks at 5 and 12 years *(Kirk et al, 1995)* - 7-10 years *(Lekcharoensuk et al, 2000)* - 6.8 + 3.5 years *(Stevenson, 2001)*	- Male > female *(Ling et al, 1990; Kirk et al; 1995, Thumachai et al, 1996; Lekcharoensuk et al; 2000; 2001a; Osborne et al, 2000; Houston et al, 2004; 2006; Cannon et al, 2007)* - Male = female *(Stevenson, 2001)*	- Overweight/inactive - Low water intake - Indoor housing *(Kirk et al, 1995)* - Serum hypercalcemia *(Osborne et al, 1996b; McClain et al, 1995; Savary et al, 2000; Midkiff et al, 2000)*
Urate	- **USA:** None *(Osborne et al, 2000; Ling & Sorenson, 1995)* - **Canada:** Siamese and Egyptian mau *(Houston, 2006)*	- 5.8 years (5 months-15 years) *(Osborne et al, 1996b)* - 4.4 + 2 years *(Stevenson, 2001)*	- Male = female *(Osborne et al, 2000; 1995b; Westropp et al, 2006)* - Male slightly > female *(Ling et al, 1990; Houston et al, 2004; 2006)*	- Low water intake - Portovascular shunts - Urinary tract infections *(Hostutler et al, 2005)*
Cystine	- **USA:** None *(Osborne et al, 1995)* SH, Siamese (Osborne et al, 2000) - **Canada:** None *(Houston et al, 2004; 2006)*	- > 3.6 years (4 months-12 years) *(Osborne et al, 2000)*	- Male = female *(Osborne et al, 2000)* - Male slightly > female *(Osborne et al, 2000)*	- Low water intake - Indoor housing - Inborn error of metabolism *(Dibartola et al, 1991; Osborne et al, 1992a)*
Xanthine	- **USA:** None *(Osborne et al, 2000)*	- 2.8 + 2.3 years (4 months to 10 years) *(Osborne et al, 1992a)*	- None *(Osborne et al, 1992a)*	- Inborn error of purine metabolism? *(Osborne et al, 1992; White et al, 1997)*
Silica	- **USA:** None *(Osborne et al, 2000)*	?	- None *(Osborne et al, 2000)* - Male? *(Houston, 2006)*	- Low water intake
Calcium phosphate (brushite)	- **USA:** None *(Osborne et al, 2000)* - **Canada:** None *(Houston et al, 2004; 2006)*	- 8 + 5 years (5 months-19 years) *(Osborne et al, 2000)* - 7.1 + 3.6 years *(Stevenson, 2001)*	- Female >male *(Osborne et al, 2000)* - Male > female *(Houston, 2006)*	- Low water intake - Primary hyperparathyroidism *(Osborne et al, 1995; 1996b)*
Pyro-phosphate	- **Canada:** None *(Houston, 2006)* - **Europe:** Persians? *(Frank et al, 2002)*		- None *(Houston, 2006)*	
Dried solidified blood calculi	- **USA:** None *(Westropp et al, 2006)*			

4 techniques available for quantitative analysis including polarizing light microscopy, x-ray diffraction, infrared spectroscopy, and scanning electron microscopy. Accurate identification of the type or types of minerals present in a urolith is paramount in order to apply the appropriate therapeutic and preventative regime.

► Predicting urolith type

Effective treatment and prevention of uroliths depends on knowledge of their mineral composition. Ideally, a urolith should be retrieved and quantitatively analyzed, however, there are a number of factors that can help in predicting urolith composition including signalment (age, sex, breed, **Table 3**), history of underlying disorders, radiodensity of the uroliths and urine parameters (pH, specific gravity, crystalluria, **Table 4**). It is important to remember that crystals may or may not be present in the urine sample and the urine sample may contain crystals that differ from the underlying urolith composition *(Buffington & Chew, 1999b)*.

5 - Specific diseases

► Feline idiopathic cystitis

The diagnosis of FIC requires documentation of signs of chronic irritative voiding (dysuria, hematuria, pollakiuria, inappropriate urination), sterile urine, negative imaging studies, and cystoscopic observation of submucosal petechial hemorrhages (glomerulations). In addition, there may be increased urinary bladder permeability, decreased urine concentrations of glycosaminoglycans, increased mucosal vascularity, erosions, ulcerations, edema, fibrosis, and neurogenic inflammation *(Buffington et al, 1994; 1996b; 1999a; Buffington & Chew 1999b; Buffington & Pacak, 2001; Buffington, 2002; 2004; Westropp et al, 2002; 2003; Pereira et al, 2004)*.

> Epidemiology

Cats with FIC tend to be young to mid-age (<10 years) and otherwise healthy. Male and females are affected and many of the predisposed cats eat dry food exclusively *(Buffington et al, 1997; Jones et al, 1997; Markwell et al, 1998; Buffington, 2002)*. A significant number have high urine specific gravities.

> Management

One of the cornerstones of therapy is to identify and relieve the stressors in the cat's environment. Potential sources of stress include environmental aspects such as other cats, changes in weather, lack of activity, litter box placement, litter type, diet, owner work schedule, and the addition or removal of people or animals. Stress can be managed by providing the cat with hiding places and equipment such as climbing posts and toys that can be chased and caught which allow the cat to express predatory behavior *(www.indoorcat.org/: The Indoor Cat Initiative 2006, Buffington et al, 1994; 1999b; 2006a,b; Buffington, 2002; Cameron et al, 2004)*.

Diet plays an important role in the pathophysiology and treatment of interstitial cystitis. An abrupt change or frequent changes in diet has been associated with the recurrence of clinical signs. Therefore, it is reasonable to limit the frequency of diet changes in sensitive cats *(Buffington et al, 1994; 1996b; 2006a,b; Jones et al, 1997)*.

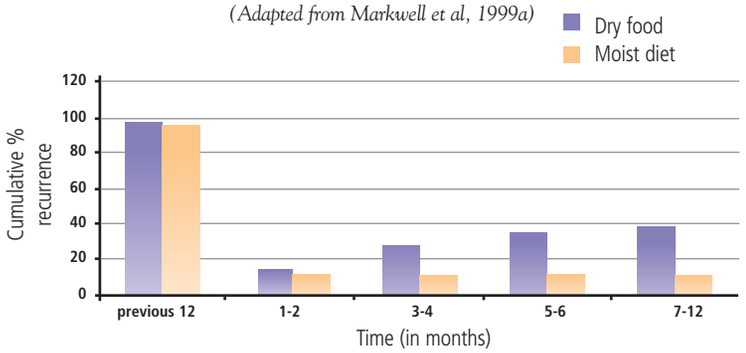
Urine dilution is thought to help cats with FIC because it decreases the concentration of substances in urine that may be irritating to the bladder mucosa. In one study, cats with FIC were significantly more likely to eat dry pet food exclusively (59%) compared with cats in the general population (19%) *(Buffington et al, 1997)*. In a one year, non-randomized

TABLE 4 - RADIODENSITY AND URINE PH OF FELINE UROLITHS
(Adapted from Osborne et al, 2000; Frank et al, 2002; Westropp et al, 2006).

	Radiodensity	Urine pH
Struvite	++ - ++++	> 6.5
Calcium oxalate	++++	Variable
Calcium phosphate	++++	Alkaline to neutral (apatite forms)
Ammonium urate	0 - ++	Acid to neutral
Cystine	+ à ++	Acid to neutral
Xanthine	0 - ++	Acid to neutral
Silica	++ - ++++	Acid to neutral
Pyrophosphates	++ - ++++	Unknown
Dried solidified blood clots	0 - ++	Unknown

FIGURE 19 - RECURRENCE RATES OF FELINE IDIOPATHIC CYSTITIS ON MOIST VERSUS DRY DIET

(Adapted from Markwell et al, 1999a)



prospective study of 46 cats with FIC, feeding a moist therapeutic food specifically designed to promote lower urinary tract health was associated with significant improvement compared with feeding a dry diet. At the end of the one year study, the recurrence of clinical signs in cats eating the moist food was significantly less (11% of 18 cats), compared with cats eating the dry food (39% of 28 cats) *(Markwell et al, 1999a)* **(Figure 19)**. Compared with the cats consuming the dry food, the urine specific gravity was significantly less in the cats eating the moist food. The mean urine specific gravity ranged from 1.032-1.041 in the cats eating the moist food compared to 1.051-1.052 in the cats eating the dry food.

Highly acidifying diets are not recommended as highly acid urine may increase sensory nerve fiber transmission in the bladder and increase pain perception *(Chew & Buffington, 2003)*.

In some cases, additional therapy may be indicated. Cats naturally release pheromones during facial rubbing when they feel content in their environment. A synthetic analogue of a naturally occurring feline facial pheromone may help decrease anxiety-related behaviors in some cats *(Chew et al, 1998; Mills & Mills, 2001; Gunn-Moore & Cameron, 2004)*. Although a number of additional treatments have been advocated over the years, none, except diet, have been clinically proven to make a significant difference. Additional therapeutic options will likely evolve to decrease central noradrenergic drive and normalize the responsiveness of the stress response system in these sensitive cats *(Buffington et al, 1999a; 2006a,b; Buffington, 2004)*. In the interim, a number of drugs have been suggested including amitriptyline and pentosan polysulfates (glycosaminoglycan or GAG replenishment agents) *(Chew et al, 1998; Buffington et al, 1999a; 2006a,b; Buffington & Chew, 1999b; Buffington, 2002; Kraiger et al, 2003; Kruger et al, 2003; Gunn-Moore & Shenoy, 2004; Mealey et al, 2004)*.

Clinical signs resolve spontaneously in as many as 85% of cats with FIC within 2-3 days, regardless of therapy. However, about 40-50% of these cats will relapse within 12 months, and some will have multiple recurrences *(Markwell et al, 1998; 1999a; Kruger, 2003)*.

► Urethral plugs

Relief of urinary tract obstruction and reestablishment of urine flow is mandatory in a cat with urethral obstruction. In addition, correction of fluid, electrolyte and acid-base imbalances associated with the obstruction and post-renal azotemia are needed. A number of excellent references are available on the emergency management of uretheral obstruction *(Osborne et al, 2000; Westropp et al, 2005)*.

► Uroliths

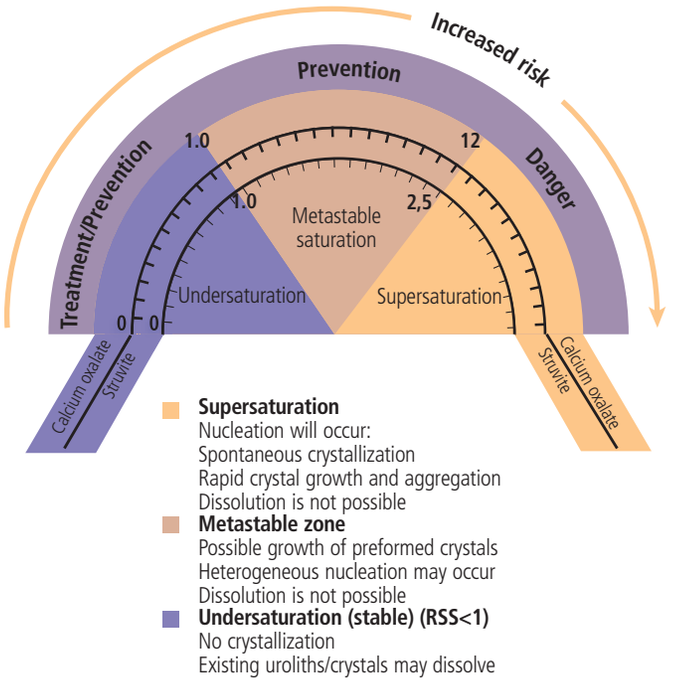
> Universal risk factors: relative supersaturation

Urine supersaturation is the driving force for the formation of crystals within the urinary tract. More than 40 years ago, human researchers began exploring ways of evaluating urine parameters and predicting urolithiasis risk. This led to a research methodology called Relative Supersaturation (RSS) ratio, a technique first introduced in human medicine in 1960's by Dr. W.G. Robertson *(Nordin & Robertson, 1966)*. The measurement of the RSS predicts the crystallization potential of that urine. This technique has become the gold standard for urine evaluation in human patients *(Pak et al, 1977)*.

The ability to predict the crystallization potential of urine is a useful tool for clinicians and researchers who wish to develop therapeutic interventions for patients with urolithiasis. In the late 1990's, Dr Robertson began collaborative work with scientists at the Waltham Centre for Pet Nutrition (WCPN) to validate the relative supersaturation ratio for use in dog and cat urine and a number of publications have now appeared in the veterinary literature on the technique and interpretation thereof *(Smith et al, 1998; Markwell et al, 1999b; Robertson et al, 2002)*.

In order to study urine parameters using RSS, it is necessary to obtain complete urine collections over a 2 to 5 day-period. The urine is analyzed for the concentration of 10 solutes (calcium, magnesium, sodium, potassium, ammonium, phosphate, citrate, sulfate, oxalate and uric acid) and the urine pH *(Robertson et al, 2002)*. The number of interactive complexes that could occur between these ions, together with activity coefficients of the salts is calculated and the activity product determined. The activity product is an indicator of the likelihood of a urolith forming. The activity product is divided by the thermodynamic solubility product of the crystal and the resultant RSS ratio is produced. (The thermodynamic solubility product is the activity product at which a urolith will remain static and not grow or dissolve.)

FIGURE 20 - URINE RELATIVE SUPERSATURATION



The RSS is unique for each crystal type. RSS can be used to define three different zones of urine saturation: undersaturated, metastable or oversaturated. Each of these zones has different implications for the risk of urolith formation **(Figure 20).** The higher the RSS, the greater the risk of crystal formation, and with low RSS values, the risk of crystal formation is much less likely *(Robertson et al, 2002)*.

A RSS less than one means that the urine is undersaturated and that crystals will not form. In a complex media such as urine, it is possible to have a RSS above one without spontaneous precipitation of crystals *(Markwell et al, 1999b)*. This is due to electrical fields (ionic strength) induced by the numerous ions in solution and the presence of inhibitors of crystallization. Both prevent the free fractions of minerals (e.g. calcium and oxalate) to interact to form crystals. This level of supersaturation is qualified as metastable supersaturation. At this level of saturation, calcium oxalate crystals will not spontaneously form, but might occur in the presence of a nucleus. In the zone of metastable supersaturation, crystals, and thus uroliths, will not dissolve.

At higher levels of minerals in the urine, crystals will form spontaneously within minutes to hours. This is the labile supersaturation zone. The limit between metastable and labile supersaturation is called the formation product. Kinetic precipitation studies in urine have shown that the RSS for the formation product for struvite is 2.5 and for calcium oxalate is 12 **(Tables 5 & 6)**.

TABLE 5 - USING RSS TO ASSESS THE RISK OF STRUVITE UROLITH FORMATION

If a diet has an RSS for struvite of:	The urine produced by cats fed that diet is	The risk for struvite formation is
Less than 1	Under-saturated	• New struvite uroliths will not form. • Existing struvite uroliths will dissolve.
Between 1 and 2.5	Metastable	• New struvite uroliths will not form. • Any existing struvite uroliths will not dissolve and may grow.
Over 2.5	Over-saturated	• New struvite uroliths may form. • Any existing struvite uroliths will grow.

TABLE 6 - USING RSS TO ASSESS THE RISK OF CALCIUM OXALATE UROLITH FORMATION

If a diet has an RSS for calcium oxalate of:	The urine produced by pets fed that diet is said to be	The risk for calcium oxalate formation is
Less than 1	Undersaturated	• New calcium oxalate uroliths will not form. • Existing calcium oxalate uroliths will not grow.
Between 1 and 12	Metastable	• New calcium oxalate uroliths will not form. • Any existing calcium oxalate uroliths may grow.
Over 12	Oversaturated	• New calcium oxalate uroliths may form. • Any existing calcium oxalate uroliths will grow.

Table 7 - Methods to encourage water intake

Increase water consumption by feeding increased amounts of canned food or feeding a dry diet formulated to stimulate diuresis. It has been shown that salt significantly increases water intake and urine production *(Hawthorne & Markwell, 2004)*. Salt has not been shown to contribute to hypertension or renal disease in healthy cats *(Devois et al, 2000a; Buranakarl et al, 2004; Luckschander et al, 2004; Cowgill et al, 2007)*.
Multiple small meals may help. It has been suggested that, for a given energy level, the water intake significantly increases by increasing meal frequency *(Kirschvink et al, 2005)*.
Provide easy access to fresh water at all times. Cats are nocturnal and may prefer to drink in the evening.
Provide a bowl with a wide surface area. Cats have very sensitive whiskers and many seem to prefer a large bowl in which the whiskers do not touch the sides of the bowl. The water bowl should be kept full at all times.
A variety of water types: (Brita, distilled, bottled, warm tap water, cold tap water) can be offered.
Do not sweeten the water as cats lack sweet taste receptors (defective Tas 1r2) *(Li et al, 2006)*
Flavoring the water or providing ice cubes flavored by tuna or clam juice may help encourage water consumption. Some companies provide different flavors to add to the drinking water to encourage water consumption.
Some cats prefer a source of running water (water fountains are available for cats).
It is important **to keep water bowl away from the litter box area**. The water bowl must be clean (cats have a very keen sense of smell and are easily turned off by odors on the edge of the bowl).
Some cats prefer a clear glass bowl; others stainless steel or ceramic.
Some cats prefer not to share their bowl (especially with dogs).

Table 8 - Water intake significantly increases when cats were fed three meals versus one meal per day.
(Adapted from Kirschvink et al, 2005).

	Daily energy intake (kcal/kg BW)	Na intake (mg/kg BW)	Water intake (mL/cat/day)
1 meal	71	103	72 ±10
2 meal	71	103	89 ± 4
3 meal	71	103	95 ± 6

BW: body weight
Na: sodium

Table 9 - Poorly digestible diets are associated with increased fecal water loss
(internal data from the Waltham Centre of Pet Nutrition)

	Diet A	Diet B
Digestibility	79.5%	50.6%
Fecal water loss (per 1000 kcal)	89 g	330 g

> Universal management

Stimulate diuresis

The easiest way of reducing supersaturation and indeed, one of the simplest and most effective treatments for all causes of FLUTD, is to increase urine volume and promote diuresis. There is a great deal of evidence in cats that low urine volume as well as urine concentration are risk factors for urolith formation. High urine volumes will actually reduce the risk of urolith formation by increasing the frequency of micturition, which helps remove any free crystals, proteinaceous material and debris from the urinary tract. In addition, urine dilution and increased urinary flow is known to help cats with urolithiasis and urethral plugs as it reduces the concentration of lithogenic substances and reduces the time available for urinary solutes to form crystals or stones.

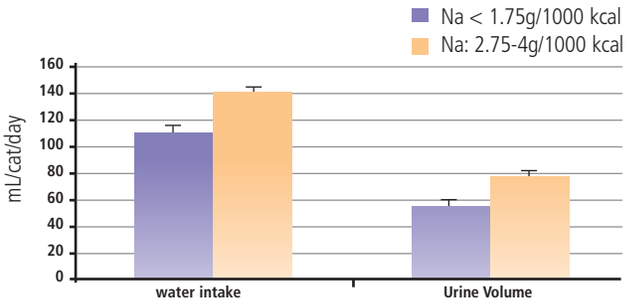
To stimulate diuresis, drinking must be encouraged **(Table 7)**. Cats when fed two identical diets except for their moisture content tend to consume less water, to urinate less frequently and to produce less, but more concentrated urine on the lower moisture diet *(Burger et al, 1980)*. An increase in water turnover can be achieved by feeding diets that contain 70-85% moisture (canned, pouch, tray), by increasing feeding frequency (increasing number of meals/day), by increasing the sodium chloride content of the diet, or by adding water to the diet *(Dumon et al, 1999)*.

The water intake of a cat is significantly influenced by the number of meals per day. *Kirschvink et al* (2005) reported that that water intake increased from 72 mL/cat/day to 95 mL/cat/day by feeding three meals rather than one meal per day **(Table 8)**.

The digestibility of the diet will influence the absolute amount of water available to dilute urine. Less digestible diets have been associated with increased fecal water loss **(Table 9).** The increased loss of water into the feces decreases the amount of water absorbed and subsequently excreted in the urine. The risk of urolithiasis increases the more concentrated the urine. Therefore, cats with

Figure 21 - Influence of the dietary sodium content on mean daily water intake and urine volume in cats

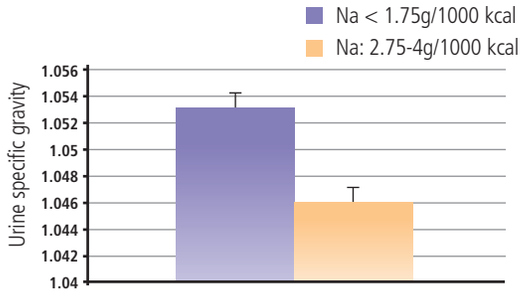
(Data adapted from Hawthorne & Markwell, 2004).



The sodium content is either < 1.75 g/1000 kcal or included in the 2.75-4.0 g/1000 kcal range. Increasing dietary sodium content resulted in a significant ($p < 0.001$) increase in water intake and urine volume.

Figure 22 - Influence of the dietary sodium content on mean daily urine specific gravity in cats

(Data adapted from Hawthorne & Markwell, 2004)



The sodium content is either < 1.75 g/1000 kcal or included in the 2.75-4.0 g/1000 kcal range. Increasing dietary sodium content resulted in a significant ($p = 0.003$) decrease in urine specific gravity.

lower urinary tract disease should be fed highly digestible diets to minimize fecal water loss.

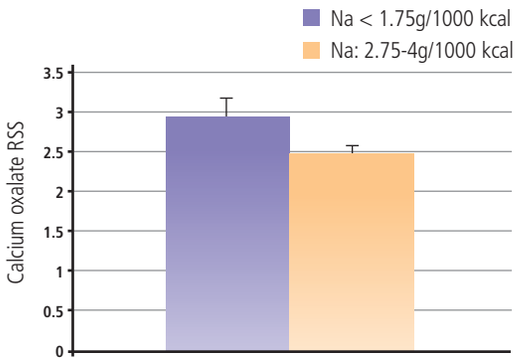
Increased dietary sodium content has been used to increase water intake and cause subsequent urine dilution in cats. The effectiveness of dietary sodium on increasing urine volume was clearly shown in a study by *Biourge et al* (2001). Healthy cats fed 1.1 g NaCl/1000 kcal had a mean urine volume of 11 ± 5 mL/kg/day. Urine volume increased significantly to 20 ± 7 mL/kg/day when the dietary sodium intake was increased to 2.5 g NaCl/1000 kcal.

Effect of dietary sodium on urinary calcium excretion

Historically, there has been controversy about the use of sodium chloride to stimulate thirst and diuresis, as it could also potentially affect urinary calcium excretion, blood pressure and renal disease *(Osborne et al, 2000)*. However, recent studies in cats have refuted this theory, and support the use of moderate increases in sodium to help maintain urinary tract health.

Figure 23 - Influence of the dietary sodium content on mean calcium oxalate RSS in cats

(Data adapted from Hawthorne & Markwell, 2004)



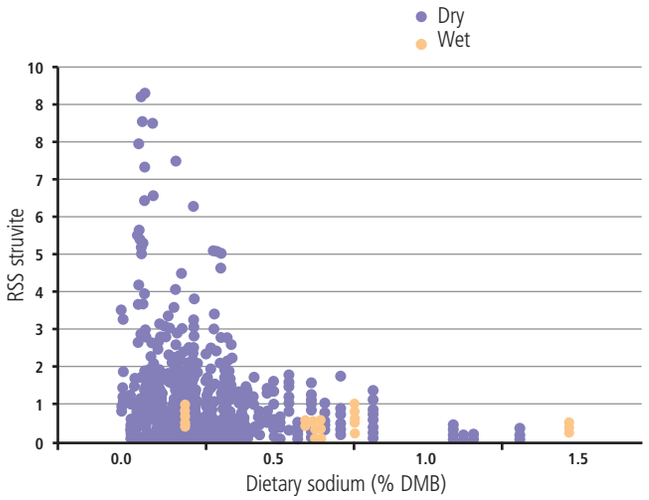
The sodium content is either < 1.75 g/1000 kcal or included in the 2.75-4.0 g/1000 kcal range. Increasing dietary sodium content resulted in a significant ($p = 0.04$) decrease in calcium oxalate RSS.

In studies by *Devois et al* (2000a, b), it was shown that a sodium intake of 1.04% DMB was associated with an increase in 24 hour calcium excretion and urine output. However, as urinary output increased by 100%, the sodium intake resulted in similar calcium and lower oxalate urinary concentrations compared with a sodium intake of 0.30-0.39% DMB. Due to the significant effect of sodium on urine volume, increasing dietary NaCl does not increase the urinary calcium oxalate RSS and therefore does not increase the risk for calcium oxalate urolith formation. The results of this study is supported by epidemiological studies that report that diets with a salt content of 1.43-3.70 g/1000 kcal have a decreased risk of calcium oxalate urolith formation compared with diets containing 0.48-0.77 g/1000 kcal *(Lekcharoensuk et al, 2001b)*.

Hawthorne & Markwell (2004) evaluated the effect of the dietary sodium content of 23 commercially available extruded diets on water intake and urine composition in 55 healthy adult cats. Cats fed diets containing higher levels of dietary sodium content had significantly higher water intake and urine volume **(Figure 21)**, and significantly lower urine specific gravity **(Figure 22)**, and calcium oxalate RSS values **(Figure 23)** compared to cats fed lower sodium diets. Urinary

Figure 24 - Dietary sodium content is very effective at reducing the RSS for struvite in healthy cats

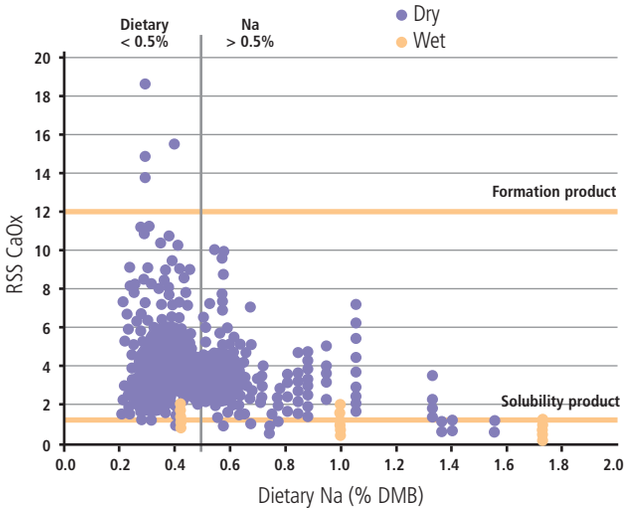
(Royal Canin Research Center 2005; internal data collected during a 2 year-period)



Individual data collected with 125 different diets fed to a group of 7 cats. Each point represents one cat fed one diet.

Figure 25 - Relationship between dietary sodium and calcium oxalate (CaOx) RSS in healthy cats

(Biourge, 2007)



Dietary sodium content is very effective at reducing the RSS for calcium oxalate in healthy cats.

calcium concentration did not differ significantly between cats fed the moderate and lower sodium diets. The results of this study indicate that dietary sodium concentrations up to 4 g/1000 kcal did not increase the urine calcium concentrations in cats, but did however, increase water turnover and urine volume compared to cat foods with sodium content less than 1.75 g/1000 kcal.

Zu et al (2006) evaluated the effect of dietary sodium content on water intake, urine volume, urine specific gravity, mineral excretion, relative supersaturation and activity product ratios of calcium oxalate and struvite in nine healthy cats. Increasing sodium content from 0.4 to 1.2% DMB was associated with a significant increase in urine volume. Increased dietary sodium did not increase calcium excretion in these healthy cats.

Effect of dietary sodium on urinary RSS values

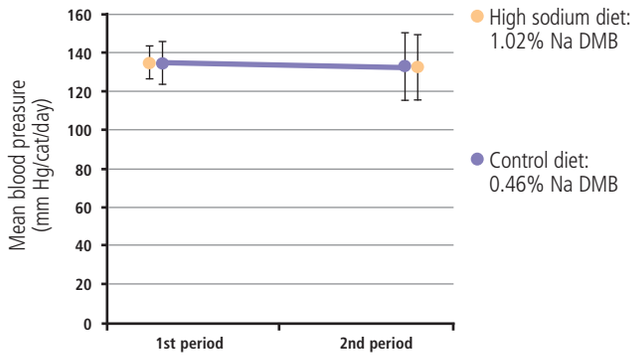
The calculation of RSS from the urine of cats fed a specific diet can be used to study the effect of that diet on the crystallization potential of urine *(Markwell et al, 1999b; Robertson, 2002)*. Studies have confirmed that increasing the dietary intake of sodium significantly reduces the RSS of struvite and calcium oxalate in healthy cats **(Figure 24-25)** *(Tournier et al, 2006a; Xu et al, 2006)*. *Tournier et al* (2006a) evaluated 11 extruded diets with a sodium content ranging from 0.44% to 1.56% DMB on urinary parameters in healthy cats. A significant linear correlation was found between dietary sodium and calcium oxalate RSS, demonstrating that increasing dietary sodium content significantly decreases calcium oxalate RSS in cats by increasing urine volume and thus urine dilution. Increased moisture intake has also been shown to reduce calcium oxalate RSS in urolith former cats *(Lulich et al, 2004)*.

Effect of dietary sodium on blood pressure and renal function

As in humans, the long term risks of increased (1.75 to 3.25 g/1000 kcal) dietary NaCl intake on the health of cats are controversial. The levels of dietary NaCl that will stimulate diuresis do not appear to affect blood pressure in healthy pets, in cats with early renal disease as well as in feline models of renal failure *(Buranakarl et al, 2004; Luckschander et al, 2004; Cowgill et al, 2007)*. More-

FIGURE 26 - THE EFFECT OF SODIUM CHLORIDE ON SYSTOLIC BLOOD PRESSURE IN HEALTHY ADULT CATS

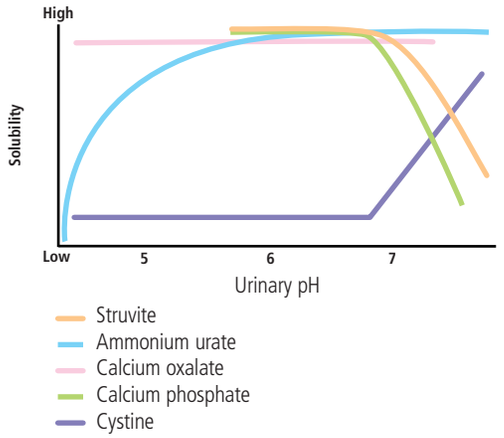
(Data adapted from Luckschander et al, 2004)



The study was a cross-over design. 10 European cats (4 males, 6 females, 2.6 +/- 0.5 years, 4.5 +/- 0.89 kg) received a control diet for 14 days. The diets contained respectively 0.46% sodium DMB (control diet) and 1.02% DMB sodium (study diet). The systolic blood pressure was not affected by altering the dietary sodium intake.

FIGURE 27 - SOLUBILITY AND PH

(personnal communication with Dr WG Robertson)



Urinary pH can have a marked influence on the solubility of certain crystals and calculi. Struvite crystals are sensitive to changes in urine pH. Acidification of urine increases the solubility of struvite crystals, reducing the risk of struvite urolithiasis. Calcium oxalate is less sensitive to urine pH.

over, an epidemiological study concluded that feeding cats' higher level of Na among other nutrients reduced the odds of suffering from chronic renal failure (*Hughes et al, 2002*).

Short-term feeding of high-sodium foods (1.02% Na versus 0.46% DMB) to young, healthy cats for 14 days was associated with a significantly increased water intake and decreased urine specific gravity without increasing systolic blood pressure **(Figure 26)**. Blood pressure measurements remained within the reference range throughout the study in all 10 cats (*Luckschander et al, 2004*). The results of this study suggests that feeding a diet with moderately increased salt content increases water intake and causes diuresis without increasing systolic blood pressure in healthy adult young cats.

Cowgill et al (2007) evaluated the effect of dietary sodium concentration on renal function in adult cats. There were no differences in plasma creatinine, BUN or glomerular filtration rate (GFR, assessed by 10-hour pharmacokinetic analysis of exogenous plasma creatinine clearance) when cats were fed 0.22% versus 1.3% sodium diets. These data suggest that extremes of dietary salt have no short-term effect on renal function in healthy cats.

Buranakarl et al (2004) evaluated the effect of salt intake on blood pressure in cats with induced azotemia similar in degree to IRIS Stages II and III in cats. Salt intake had no effect on blood pressure. Further, the lowest level of salt intake was associated with the lowest values for GFR, inappropriate hypokalemic kaliuresis and activation of the renin-angiotensin-aldosterone system. The results of this study suggest that, similar to healthy cats, cats with induced renal disease are not salt sensitive.

Adjusting urine pH

Adjusting urine pH via dietary manipulation or medical means can be very effective in the management of some but not all uroliths **(Figure 27)**. Urine acidification markedly increases struvite solubility and is essential in the medical dissolution of these uroliths (*Stevenson et al, 2000; Smith et al, 2001*). In contrast, urine alkalinization is important in increasing the solubility of metabol-

ic uroliths including some urate uroliths and cystine uroliths. Alkalinization above 7.5 is not recommended as this may contribute to calcium phosphate urolithiasis. Calcium oxalate uroliths appear at any urine pH and to date, medical dissolution is impossible.

The effect of urine pH on the risk of forming crystals, and as a method of treatment or prevention will be discussed further as it relates to individual uroliths.

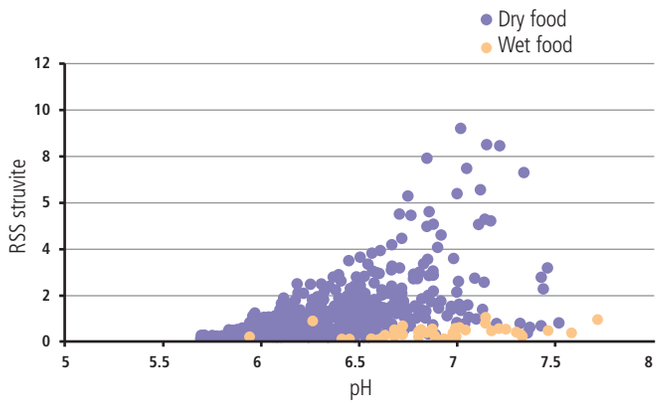
> Struvite

Risk factors

Unlike dogs, the majority of struvite (magnesium ammonium phosphate hexahydrate; Mg NH_4 $P0_4$ $6H_20$) uroliths in cats are sterile *(Buffington et al, 1997; Lekcharoensuk et al, 2000; 2001a; Cannon et al, 2007)*. Struvite uroliths form when the urine becomes supersaturated with magnesium, ammonium, and phosphorus and when the urine pH is greater than 6.5. Struvite crystals are more soluble when the urine pH is less than 6.5 and crystallization is unlikely to occur when the pH is less than 6.3. However, pH is less critical when food promotes diuresis and urine dilution as it is the case with wet food **(Figure 28)**.

FIGURE 28 - THE ASSOCIATION BETWEEN URINE PH AND RSS FOR STRUVITE IN FELINE URINE

(Royal Canin Research Center 2005; internal data collected during a 2 year-period)



Individual data collected with 125 different diets fed to a group of 7 cats. Each point represents one cat fed one diet. The more alkaline the urine, the higher the risk of struvite formation.

TABLE 10 - THE RISK OF FORMING STRUVITE DEPENDS ON THE URINE PH AND FORM OF MAGNESIUM

(Adapted from Buffington et al, 1990)

	Basal diet 0.05% Mg	$MgCl_2$ diet 0.5% Mg	MgO diet 0.5% Mg
pH	7.2 ± 0.3	5.8 ± 0.1	7.9 ± 0.3
Magnesium (mMol)	7.3 ± 2.8	53.1 ± 16.3	49.1 ± 14.4
Calcium (mMol)	4.7 ± 1.5	15.5 ± 8.2	8.1 ± 3.6
RSS struvite	24.7	0.7	87.1
RSS calcium oxalate	41.3	12.8	8.6

A case-control study reported that diets with the highest magnesium, phosphorus, calcium, chloride and fiber, moderate protein and low fat content were associated with an increased risk of struvite urolithiasis *(Lekcharoensuk et al, 2001b)*.

Magnesium

Diets containing 0.15 to 1.0% magnesium on a dry matter basis were associated with the formation of struvite uroliths *(Lekcharoensuk et al, 2001b)*. However, the magnesium effect depends on the form of magnesium and on the urine pH *(Tarttelin, 1987; Buffington et al, 1990; Reed et al, 2000a)*. *Buffington et al.* (1990) reported that cats fed 0.5% magnesium as $MgCl_2$ did not form struvite uroliths whereas cats that were fed 0.5% magnesium as MgO did form struvite uroliths **(Table 10)**. The difference in susceptibility to struvite formation was due to magnesium oxide promoting the formation of alkaline urine whereas magnesium chloride promoted the formation of a protective acidic urine.

Phosphorus

Cats fed diets high in phosphorus (3.17-4.70 g/1000 kcal) were almost four times as likely to develop struvite uroliths compared to cats fed diets with 0.85-1.76 g/1000 kcal phosphorus *(Lekcharoensuk et al, 2001b)*. High dietary intake of phosphorus enhances urinary phosphorus excretion and therefore, promotes superaturation of urine with magnesium, ammonium, and phosphate *(Finco et al, 1989)*.

Management

Elimination of the urinary tract infection

Although not common, infection-induced struvite uroliths require a combination of an appropriate antimicrobial and dissolution dietary therapy (see below).

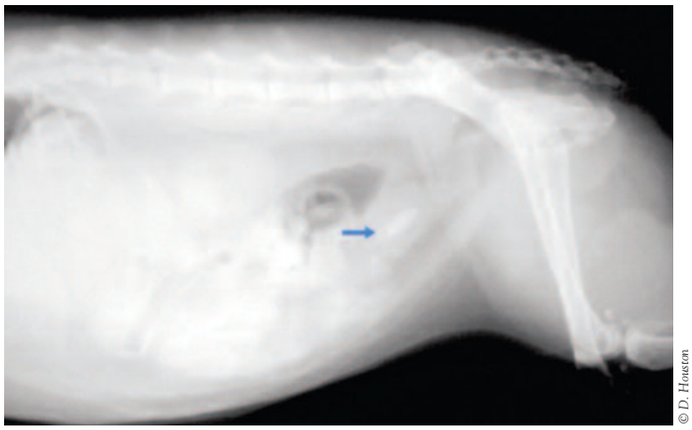


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Figure 29A - Lateral radiograph of the abdomen of a cat. *The arrow points to a large, single urolith.*

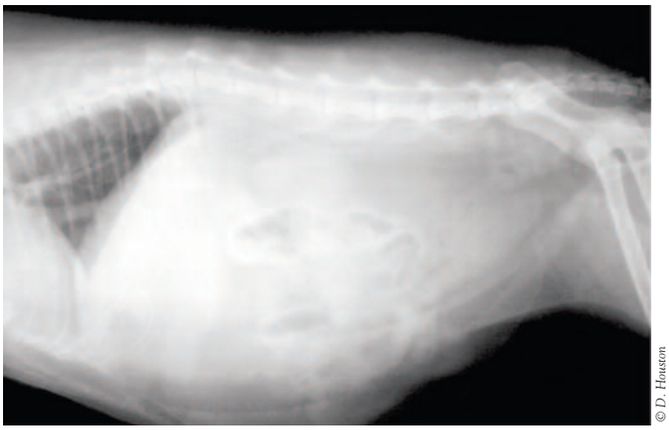

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Figure 29B - Lateral radiograph of the abdomen of a cat four weeks after institution of a struvite dissolution diet. *The previously noted urolith (Figure 29A) has completely dissolved.*

Antibiotic therapy should be based on culture and sensitivity determination of urine obtained by cystocentesis. Antibiotic therapy should be continued for one month following radiographic resolution of the urolith/s, as viable bacteria may remain in the urolith and uroliths may be too small or too lucent to see on radiographs post dissolution.

Calculolytic diets to dissolve struvite uroliths

Pure struvite uroliths can be dissolved by the administration of a diet that promotes an increased urine volume and a urine pH less than 6.3 *(Osborne et al, 1990a; Houston et al, 2004)*. The diet should have a controlled magnesium level and create an RSS value less than one (undersaturated zone). The diet should contain adequate quantities of sodium to promote water intake and the formation of dilute urine. Sterile struvite uroliths do not need adjunctive antibiotic therapy.

The efficacy of a canned, magnesium-restricted, urine acidifying, salt-supplemented diet designed to dissolve struvite urolithiasis was shown in 1990 *(Osborne et al, 1990a)*. More recently, the efficacy of a canned and dry moderately magnesium restricted diet specifically designed to promote the formation of acidic urine, with a RSS value less than one for the dissolution of feline struvite urolithiasis has been reported by *Houston et al* (2004). In this study of 30 cats, the mean time required for dissolution of struvite uroliths was 26 days on the canned diet and 34 days on the dry diet **(Figure 29)**.

It is recommended that dissolution therapy should continue for 1 month after radiographic documentation of struvite dissolution. If the urolith does not dissolve, the wrong mineral type or a complex mineral type may be involved.

Prevention of recurrence

The recurrence rate for struvite uroliths has been reported as 2.7% with a mean recurrence time of 20 months *(Albasan et al, 2006)*. Therefore, following dissolution or mechanical removal of struvite uroliths, a diet designed to help prevent recurrence is recommended. The diet should have a RSS in the undersaturated to metastable range, a urine pH less than 6.5 and should either be high in moisture (canned, pouch, or tray product) or designed to encourage diuresis (enhanced with sodium chloride).

Drug therapy

Urinary acidifying agents such as ammonium chloride or DL methionine are not necessary provided an appropriate urine acidifying diet is used.

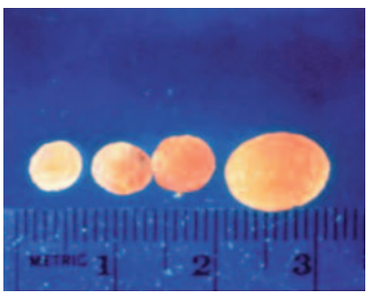

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Figure 30 - Four struvite uroliths removed from the bladder of a cat. *Typical round to wafer or disc-shaped struvite uroliths.*

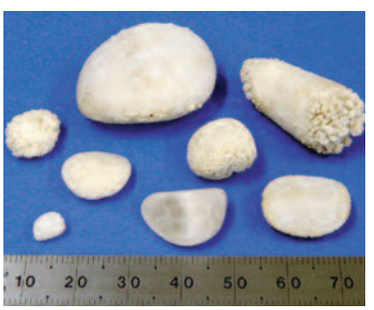

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Figure 31 - A collection of feline struvite uroliths showing variability in appearance.

Monitoring

The efficacy of therapy should be monitored with urinalysis (pH, urine specific gravity, sediment examination) at two weeks, four weeks and then every three to six months. Not all cats with uroliths shed crystals, therefore abdominal radiography should be obtained every three to six months to monitor for early urolith recurrence.

> Calcium oxalate (Figure 32)

Risk factors

The mean age at diagnosis of calcium oxalate urolithiasis in cats is 7.8 years, with a range of 2-18 years. The risk for calcium oxalate urolith formation increases with age. One study reported a bimodal age distribution peaking at 5 and 12 years. The highest risk for developing calcium oxalate uroliths appears to be from 7-10 year of age. *Smith et al* (1998), reported that senior cats (mean age 10.6 ± 1.3 years) produced urine that had significantly lower struvite RSS values (0.72 ± 0.58 vs. 4.98 ± 4.03) and significantly higher calcium oxalate RSS values (3.45 ± 1.62 vs. 0.91 ± 0.87) when compared to a group of younger (4.1 ± 1.0 years) cats. The senior cats had a significantly lower urine pH, compared to the younger cats (6.1 ± 0.2 vs. 6.4 ± 0.2, respectively). The decrease in urine pH in the senior cats may partially explain the increased risk for forming calcium oxalate uroliths with age *(Smith et al, 1998)*.

Genetic and gender differences, inactivity, obesity, and environment have been associated with an increased risk for developing calcium oxalate uroliths *(Lekcharoensuk et al, 2001b)*. Male cats (55%) are more commonly affected and are 1.5 times more likely to develop calcium oxalate uroliths compared to female cats. The Burmese, Himalayan, and Persian breeds have an increased risk of developing calcium oxalate urolithiasis, suggesting that genetic factors may contribute to the formation of calcium oxalate uroliths. Indoor housing has been reported as a risk factor for calcium oxalate urolithiasis *(Kirk et al, 1995; Jones et al, 1997; Gerber et al, 2005)*.

In humans, hyperoxaluria occurs as a result of at least two types of inherited errors of metabolism, both resulting in increased oxalate production and recurrent calcium oxalate urolithiasis *(Williams & Wilson, 1990)*. Inherited primary hyperoxaluria (L-glyceric aciduria), a deficiency of hepatic d-glycerate dehydrogenase, an enzyme required for metabolism of oxalic acid precursors, has been reported in cats but the clinical manifestations of this metabolic disorder have been related to weakness and acute onset of renal failure, not calcium oxalate urolithiasis *(McKerrell et al, 1989; De Lorenzi et al, 2005)*.

The explanation for the increased risk of calcium oxalate uroliths in cats from 1984 to 2002 is not clear although the widespread use of severely magnesium-restricted, urine-acidifying diets to control struvite uroliths has been implicated *(Kirk et al, 1995; McClain et al, 1995; Thumachai et al, 1996; Osborne et al, 1996c; Lekcharoensuk et al, 2000; 2001a,b)*. However, many cats are fed acidifying diets and yet few appear to develop hypercalcemia, metabolic acidosis, and calcium oxalate urolithiasis. Therefore additional factors such as gastrointestinal hyperabsorption or increased renal excretion of calcium and/or oxalate may be important in susceptible cats.

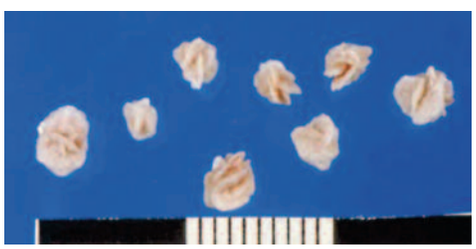
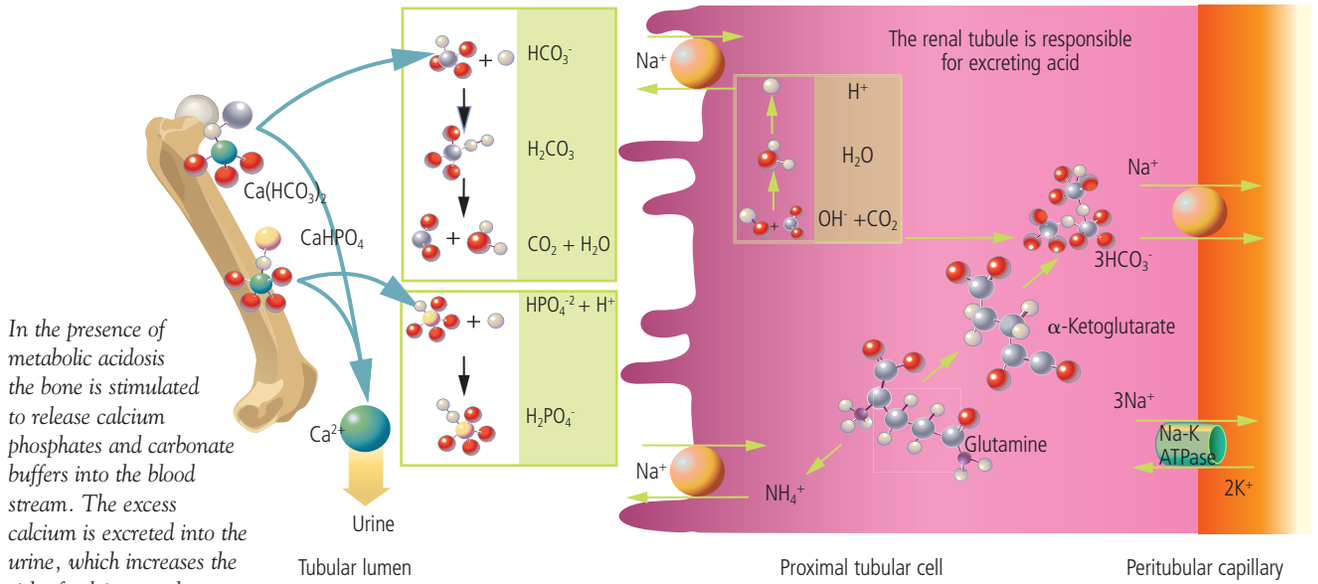


Figure 32 - Typical appearance of feline calcium oxalate uroliths.

Acidosis

Lekcharoensuk et al (2000) reported that cats fed diets formulated to produce a urine pH between 5.99 and 6.15 were three times as likely to develop calcium oxalate uroliths. Persistent aciduria may be associated with low-grade metabolic acidosis, which promotes bone mobilization of carbonate and phosphorus to buffer hydrogen ions **(Figure 33)**. Simultaneous mobilization of calcium coupled with inhibition of renal tubular reabsorption of calcium, results in increased urinary excretion of calcium. Increased urinary calcium excretion has been reported in clinically normal cats fed diets supplemented with urinary acidifiers *(Fettman et al, 1992)*. In five cats with hypercalcemia and calcium oxalate uroliths, discontinuation of the acidifying diets or urinary acidifiers was associated with normalization of serum calcium concentration *(McClain et al, 1999)*.

FIGURE 33 - THE EFFECT OF METABOLIC ACIDOSIS ON URINARY CALCIUM EXCRETION

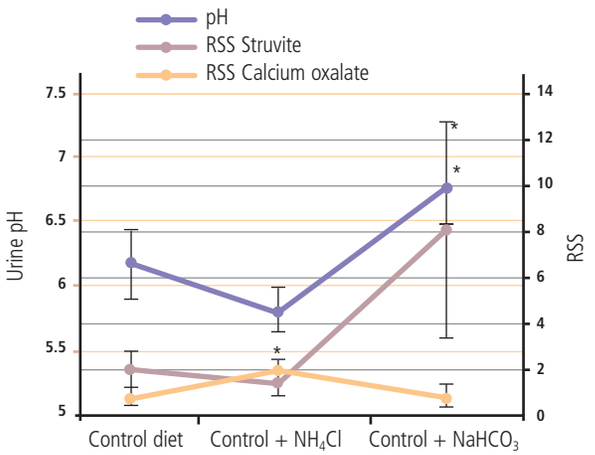


In the presence of metabolic acidosis the bone is stimulated to release calcium phosphates and carbonate buffers into the blood stream. The excess calcium is excreted into the urine, which increases the risk of calcium oxalate.

In one study on cats, the addition of an acidifier to a canned food was associated with a small but significant increase in calcium oxalate RSS. However, this higher RSS was still well below the formation product of 12 *(Stevenson et al, 2000)*. Furthermore, this study demonstrated that it is possible to formulate a very acidifying diet (mean urine pH=5.8) that will both minimize struvite and calcium oxalate crystallization **(Figure 34)**. When comparing urinary pH and calcium oxalate RSS values associated with various commercial and experimental feline diets, urinary pH appears to be a very poor predictor of calcium oxalate RSS **(Figure 35)** *(Tournier et al, 2006b)*.

FIGURE 34 - INFLUENCE OF URINARY PH ON CALCIUM OXALATE AND STRUVITE RSS

(Adapted from Stevenson et al, 2000)



$*p < 0.05$

Mean ± SE urine pH, calcium oxalate and struvite RSS in six cats fed a control diet (C), the control diet with NH_4Cl or the control diet with $NaHCO_3$. Urine pH does significantly affect both RSS CaOx (NH_4Cl diet) and RSS Struvite ($NaHCO_3$ diet). However, even increased, the RSS CaOx is still well below the formation product.

Calcium

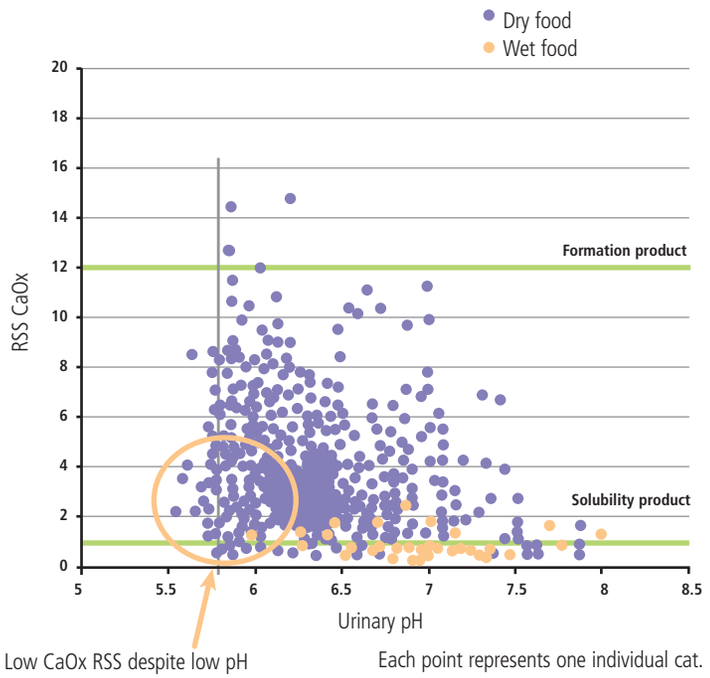
Hypercalciuria was a consistent abnormality in ten cats with calcium oxalate uroliths *(Lulich et al, 2004)*. Increased intestinal absorption of calcium may occur due to excess dietary calcium, excess vitamin D, or hypophosphatemia. Increased renal excretion of calcium may occur with decreased renal tubular reabsorption (furosemide and corticosteroids), or increased mobilization of calcium from body stores (acidosis, hyperparathyroidism, hyperthyroidism, excessive vitamin D) *(Ling et al, 1990; Osborne, 1995a; 1996b; 2000)*.

Protein

Diets high in animal protein have been associated with acidosis, increased urinary calcium and oxalate excretion, and decreased urinary citric acid excretion in humans *(Holmes et al, 2001; Borghi et al, 2002; Pietrow & Karellas, 2006)*. Consumption of animal protein by both healthy cats and cats with calcium oxalate urolithiasis is associated with increased water consumption, urine volume, and urinary phosphorus excretion, while calcium excretion is not increased *(Funaba et al, 1996; Lekcharoensuk et al, 2001; Lulich at al 2004)*. High protein diets (105-138 g/1000 kcal) were less than half as likely to be associated with calcium oxalate urolith formation as diets low in protein (52 - 80 g/1000 kcal) *(Lekcharoensuk et al, 2001b)*. A case-control study reported that cats fed diets low in moisture and low in protein had an increased risk of calcium oxalate urolithiasis *(Lekcharoensuk et al,*

FIGURE 35 - URINE PH IS A POOR PREDICTOR OF THE RISK OF CALCIUM OXALATE IN FELINE URINE

Data from 125 individual diets (from Tournier et al, 2006b)



2001b). Protein type has also been shown to influence urinary oxalate excretion in cats *(Zentek & Schultz, 2004)*.

Water consumption

Intravascular volume depletion and concentration of urine volume increases the risk of urine supersaturation with calcium and oxalate. Cats fed diets high in moisture content are about one third as likely to develop calcium oxalate uroliths compared to cats fed diets low in moisture.

Oxalate

Excessive dietary oxalate (e.g., broccoli, spinach, rhubarb, nuts, strawberries) will increase the renal clearance of oxalate and the risk of urolithiasis in humans and such foods are to be avoided in pets *(Lulich et al, 1994; Holmes et al, 2001)*.

Vitamin C

In humans, although controversial, calcium oxalate uroliths have been associated with excessive consumption of vitamin C and low levels of vitamin B_6 *(Hughes et al, 1981; Mitwalli, 1989; Curhan et al, 1999)*. Vitamin C is metabolized to oxalic acid and excreted in urine. The effect of dietary vitamin C supplement on urinary oxalate concentration has been studied in 48 adult American Domestic Short Hair cats *(Yu et al, 2005)*. Cats were fed a nutritionally complete and balanced dry control food for two weeks before they were fed for four weeks, one of four diets containing 40 mg/kg, 78 mg/kg, 106 mg/kg, or 193 mg/kg of vitamin C, respectively. Vitamin C supplementation up to 193 mg/kg did not affect urinary oxalate concentration in the healthy cats.

Vitamin B_6

Vitamin B_6 increases the transamination of glyoxylate, an important precursor of oxalic acid, to glycine. Therefore pyridoxine deficiency increases the endogenous production and subsequent excretion of oxalate. Experimentally induced vitamin B_6 deficiency resulting in increased urinary oxalate concentrations and oxalate nephrocalcinosis has been reported in kittens *(Bai et al, 1989)*. However, a naturally occurring form of this syndrome has not yet been reported. Supplementation with vitamin B_6 does not decrease urinary oxalic acid excretion compared with a diet containing adequate levels of vitamin B_6 *(Wrigglesworth et al, 1999)*. Consequently, the ability of supplemental vitamin B_6 to reduce urinary oxalic acid excretion in cats with calcium oxalate uroliths consuming diets with adequate quantities of vitamin B_6 is unlikely.

Citrate

Urinary citrate deficiency has been suggested to increase the risk of calcium oxalate in humans by increasing the availability of calcium ions to bind with oxalate *(Allie-Hamdulay & Rodgers, 2005; Pietrow & Karellas, 2006)*. Citrate deficiency may be an inherited defect or be secondary to acidosis, which promotes the renal tubular utilization of citrate. If consumption of dietary acid precursors is associated with hypocitraturia in cats, the risk of calcium oxalate uroliths may increase as citrate is an inhibitor of calcium oxalate urolith formation *(Lekcharoensuk et al, 2001b)*.

Magnesium

Magnesium has been reported to be an inhibitor of calcium oxalate urolithiasis in other species *(Johansson et al, 1980)*. In cats, diets with low magnesium content (0.09-0.18 g/1000 kcal) are asso-

ciated with an increased risk of calcium oxalate urolith formation, compared with diets with moderate magnesium content (0.19-0.35 g/1000 kcal) *(Lekcharoensuk et al, 2001b)*. Conversely, diets with magnesium contents more than 0.36 g/1000 kcal were associated with an increased risk of calcium oxalate urolithiasis *(Lekcharoensuk et al, 2001b)*. Magnesium contributes to increased urinary calcium loss by increasing blood-ionized calcium concentration and suppressing PTH secretion.

Phosphate

Hypophosphatemia may increase the risk of calcium oxalate urolithiasis in cats. The risk of calcium oxalate urolith formation was five times higher in cats fed a diet with 0.85-1.76 g/1000 kcal of phosphorus compared with a diet containing 1.77-3.16 g/1000 kcal of phosphorus (Lekcharoensuk et al, 2001b). Hypophosphatemia will result in the activation of Vitamin D_3 to calcitriol by 1-alpha-hydroxylase in the kidney and cause increased intestinal absorption and renal excretion of calcium. In addition, urinary pyrophosphate has been suggested to be an inhibitor of calcium oxalate urolith formation (*Osborne et al, 1995b; Reed et al, 2000b,c)*. Conversely, diets higher in phosphorus (>3.17 g/1000 kcal) were associated with an increased risk of calcium oxalate urolith formation compared with diets containing moderate levels (1.77-3.16 g/1000 kcal) *(Lekcharoensuk et al, 2001b)*.

Sodium

Supplemental sodium chloride has long been suggested to increase urinary calcium excretion in humans. Similar observations have been made in cats. The link between dietary Na and urinary Ca excretion led to the assumption that high salt diets could promote calcium oxalate formation in cats, and thus lead to the recommendation that diets designed for the management of FLUTD should be low in sodium. However, although increased sodium intake increases calcium excretion, calcium concentration does not increase because of the concomitant increase in urine volume and a significant decrease in CaOx RSS is observed (see above, Effect of dietary sodium on urinary calcium excretion). Furthermore, a recent epidemiological study found that increasing dietary sodium reduces the risk of calcium oxalate uroliths in cats *(Lekcharoensuk et al, 2001b)*.

Potassium

Diets low in potassium have been shown to contribute to the risk for calcium oxalate uroliths *(Lekcharoensuk et al, 2001b)*. Potassium-rich diets may be protective against calcium oxalate urolith formation by altering urinary calcium excretion. This has been shown to be true in humans *(Lemann et al, 1991)*.

Management and prevention of recurrence

Calcium oxalate uroliths do not respond to medical dissolution. Consequently, cystouroliths must be mechanically removed by voiding urohydropropulsion or surgery. Once removed, preventive measures are indicated as the risk of recurrence is high.

Recurrence rates have been reported as 10.9% with a mean recurrence time of 20 months. The recurrence rate was 1.8 times higher in male compared to female cats *(Albasan et al, 2006)*. Medical protocols are therefore essential to reduce urolith recurrence following removal.

Eliminate risk factors

If the cat is hypercalcemic, a complete medical work up is indicated to identify and treat the underlying cause. In many cases, an underlying cause for the hypercalcemia can not be determined.

If the cat is normocalcemic, risk factors for urolithiasis should be identified and controlled. Dry acidifying diets that have not been formulated to increase urine production and drugs that promote excessive urinary calcium excretion (urinary acidifiers, furosemide, etc.) should be avoided. No treats or dietary supplements containing calcium, vitamin D or excessive amounts of vitamin C should be given, as these may promote increased excretion of calcium and/or oxalate *(Osborne et al, 1995a)*.

A collection of feline calcium oxalate uroliths indicating variability in appearance. *Most often, calcium oxalate dehydrate has a speculated appearance (bottom right corner); calcium oxalate monohydrate is often round (bottom left corner).*

Dietary modification

Crystallization of calcium oxalate, the first step in the formation of this urolith cannot occur unless the urine is supersaturated with these crystalloids. Therefore, diets promoting the production of urine that is metastable or undersaturated with calcium oxalate should help prevent reoccurrence. The diet should produce an RSS value significantly less than 12 (ideally less than 5). Augmenting water intake remains a major factor in managing and preventing calcium oxalate urolithiasis (see above: Stimulate diuresis)

Calcium and oxalate

Studies have clearly shown that the concentrations of dietary calcium and dietary oxalate influence the urinary calcium oxalate RSS *(Smith et al, 1998; Markwell et al, 1998a; 1999a,b; Stevenson et al, 2000)*. Excessive dietary calcium and dietary oxalate should be avoided but calcium oxalate preventive diets should not be calcium or oxalate restricted to any significant degree. Reducing consumption of either one of these constituents could increase the availability of the other constituent for intestinal absorption. In one study of ten cats, reduction in dietary calcium was not associated with increased urinary oxalic acid concentration *(Lulich et al, 2004)* but in other studies *(Lekcharoensuk et al, 2001b)*, a decreased risk of calcium oxalate urolithiasis was observed in cats fed diets containing moderate quantities of dietary calcium.

Phosphorus, Magnesium, Potassium

Dietary phosphorus should not be restricted or supplemented *(Lekchareonesuk et al, 2001b)*. The severe phosphate restriction may increase urinary calcium excretion, which contributes to urolith formation. Low protein/renal diets are not recommended because they are the lowest phosphorus containing diets.

As both dietary magnesium restriction and magnesium supplementation have been associated with an increased risk of calcium oxalate urolithiasis in cats; diets should neither be severely restricted nor supplemented with magnesium *(Osborne et al, 1995a; Lekcharoensuk et al, 2001b)*.

Urinary pH

Recent work in our facility suggests that urine pH is not a good predictor of calcium oxalate saturation in healthy cats **(Figure 35)**. . Even though metabolic acidosis will increase urinary calcium concentration *(Kirk et al, 1995; McClain et al, 1995; Thumachai et al, 1996; Lekcharoensuk et al, 2000; 2001)*, it is possible to formulate a diet that will induce a urine pH between 5.8-6.2 and still induce a RSS CaOx well below 5, thus allowing to prevent both struvite and calcium oxalate crystal formation.

A collection of feline calcium oxalate uroliths. *The "Jackstone" like appearance may easily be mistaken for a silica urolith on radiograph.*

Drug therapy and monitoring

Adjunct medical therapies with citrate, thiazide diuretics, and vitamin B_6 have been recommended in some cases of persistent calcium oxalate crystalluria or recurrent urolithiasis. Potassium citrate has been useful in humans to prevent recurrent calcium oxalate urolithiasis, via its ability to form soluble salts with calcium *(Pietrow & Karellas, 2006)*. Oral potassium citrate increases the urine pH and may be of use in cases where the urine pH is more acidic than desired, a state that could contribute to hypocitraturia *(Osborne et al, 1995b; Lekcharoensuk et al, 2001b)*.

Hydrochlorothiazide diuretics are used to treat people with calcium oxalate urolithiasis. Hydrochlorothiazide has been shown to decrease the calcium oxalate RSS in healthy adult cats *(Hezel et al, 2006)*. However hydrochlorothiazide administration was associated with increased excretion of potassium, sodium, magnesium, phosphorus and chloride, which could result in whole body depletion with long term administration.

The efficacy and safety of hydrochlorothiazide have not evaluated in cats with calcium oxalate uroliths, hence its use can not be recommended at this time.

Efficacy of therapy should be monitored with urinalysis (pH, urine specific gravity and sediment examination) at two weeks, four weeks and then every three to six months. As not all cats with calcium oxalate uroliths shed crystals, abdominal radiography should be completed every three to six months to reveal urolith recurrence at a time when the uroliths are small enough that voiding urohydropropulsion may be possible.

Managing renal and ureteral uroliths

Controversy exists as how to most effectively manage renal and ureteral uroliths. *Kyles et al* (2005) reported that 92% of cats with ureterolithiasis were azotemic at the time of presentation, 67% of cats had multiple uroliths, and 63% were affected bilaterally. The high probability of bilateral involvement, concurrent renal insufficiency, and likelihood of reoccurrence limit nephrectomy as a surgical option. Nephrotomy results in the unavoidable destruction of nephrons, hence, this surgery is not recommended unless it is clearly established that the renal uroliths are causing clinically significant disease. Ureterotomy may be indicated for those cats with progressive hydronephrosis and an identifiable ureterolith. Post-operative complications include uroabdomen and ureteral stricture. Alternatively, partially obstructing uroliths can be managed conservatively. The ureterolith will pass into the bladder in 30% of cats managed conservatively *(Kyles et al, 2005)*. Although commonly used in human medicine, lithotripsy has not been established as a routine procedure in the cat.

> Calcium phosphate

Recognition and management of underlying contributing conditions is the first and most important step in the prevention of calcium phosphate urolithiasis. The cat should be assessed for evidence of primary hyperparathyroidism, hypercalcemia, excessive urine concentrations of calcium and/or phosphate, and an inappropriately alkaline urine pH (>7.5). There may also be a previous history of dietary therapy and administration of alkalinizing agents to prevent another urolith type. If a specific underlying disorder is not diagnosed, calcium phosphate uroliths are generally managed similar to strategies used for calcium oxalate urolithiasis. One should, however, be very careful to avoid excessive urine alkalinization, which may occur with some diets used for the prevention of calcium oxalate uroliths.

> Urate (Figure 36)

Risk factors

Urate uroliths are the third most common type of urolith reported in cats. They are composed of uric acid and the monobasic ammonium salt of uric acid (ammonium acid urate). Compared to struvite and calcium oxalate, the prevalence is less than six percent *(Osborne et al, 2000; Houston et al, 2004; 2006)* and this has not changed significantly in the last two decades. In Canada, ten of 321 (3.1%) ammonium urate submissions were from Siamese cats and nine of 321 (2.8%) were from Egyptian Maus *(Houston et al, 2006)*.

Urate uroliths may occur in cats with portosystemic shunts or any form of severe hepatic dysfunction. This may be associated with reduced hepatic conversion of ammonia to urea resulting in hyperammonemia. Urate uroliths in cats with portosystemic shunts often contain struvite. Urate uroliths may also occur:

- in cats with urinary tract infections that result in increased urinary ammonia concentrations,
- in cats with metabolic acidosis and highly acidic urine,
- and when cats are fed diets high in purines, such as liver or other organ meats *(Osborne et al, 1992a; Ling 1995; Ling & Sorenson, 1995)*.

In the majority of cases, the exact pathogenesis remains unknown *(Cannon et al, 2007)*.

Figure 36 *- Urate urolith.*

Treatment

Urate uroliths may be amenable to dietary dissolution, however, there are no published clinical trials on the efficacy of diet for the medical dissolution of feline urate uroliths.

The dietary strategy aims at decreasing the purine content of the diet. As with all urolith types, encouraging water intake and urine dilution by feeding a moist (canned, pouch, tray) diet or adding supplemental water or sodium to the food can help to lower urinary saturation.

Alkalinization of urine

Alkaline urine contains low levels of ammonia and ammonium ions, and thus alkalinizing the urine will decrease the risk of ammonium urate urolithiasis. Low protein, vegetable based diets have an alkalinizing effect but additional potassium citrate may be needed. The dose should be individualized to maintain a urine pH in the range of 6.8-7.2. Alkalinizing the urine above 7.5 should be avoided as this may promote formation of secondary calcium phosphate crystals. If a vegetable based diet is used in a cat, care must be taken to ensure it is adequately balanced to meet the unique needs of the cat.

Xanthine oxidase inhibitors

Allopurinol, an inhibitor of xanthine oxidase, the enzyme responsible for catalyzing the conversion of xanthine and hypoxanthine to uric acid has been used in other species to help lower urinary urate excretion. Although a dosage of 9 mg/kg PO per day has been suggested for cats *(Plumb, 2002)*, the efficacy and potential toxicity of allopurinol in cats is unknown and consequently, it's use in cats is not recommended.

Monitoring

During dissolution, the size of the urolith(s) should be monitored by survey and/or double contrast radiography or ultrasonography every four to six weeks. Following complete dissolution, ultrasound examination (or double contrast cystography) is recommended at least every two months for one year as the risk of recurrence is high. The efficacy of preventative therapy should be also be monitored with urinalysis (pH, urine specific gravity, sediment examination) every three to six months.

> Cystine (Figure 37)

Risk factors

Cystine uroliths occur in cats with cystinuria, an inborn error of metabolism characterized by a defective proximal tubular reabsorption of cystine and other amino acids (ornithine, lysine, arginine) *(DiBartola et al, 1991; Osborne et al, 1992a; Ling, 1995; Osborne et al, 1996)*. No obvious gender or breed predisposition has been reported but the Siamese breed may be at risk *(Ling et al, 1990; Osborne et al, 2000; Cannon, 2007)*. Most cats are middle to older aged *(Kruger et al, 1991)*.

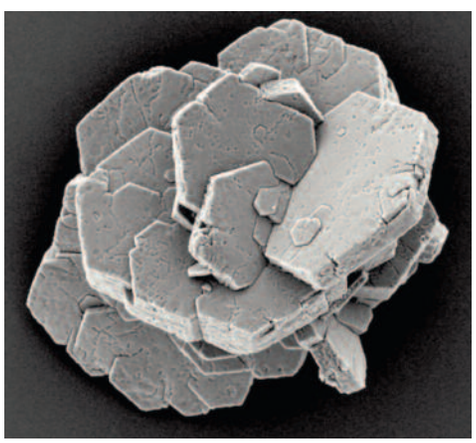


Figure 37 *- Scanning electron microscope image of a cystine urolith from a cat.*

Management

Medical protocols that consistently promote the dissolution of cystine uroliths in cats have not yet been developed *(Osborne et al, 2000)*. Small uroliths may be removed by voiding urohydropulsion *(Lulich et al, 19993b)*. Cystotomy is required to remove larger uroliths.

If medical dissolution is attempted, the aim of therapy is to reduce the concentration of cystine in the urine and to increase cystine solubility. This usually requires dietary modification with a methionine-cystine reduced protein diet in combination with a thiol-containing drug.

Thiol-containing drugs

These drugs react with cystine by a thiol disulfide exchange reaction, resulting in the formation of a complex that is more soluble in urine than cystine. N-2-mercaptopropionyl-glycine (2-MPG) is recommended at a dosage of 12-20 mg/kg q 12 hours *(Osborne et al, 2000)*.

Alkalinization of urine

The solubility of cystine is pH dependent, being markedly more soluble in alkaline urine. Urine alkalinization may be achieved using a diet that contains potassium citrate or additional potassium citrate may be administered.

Monitoring

During dissolution, the size of the urolith(s) should be monitored by survey and double contrast radiography or ultrasonography every four to six weeks. Following complete dissolution, ultrasound examination (or double contrast cystography) is recommended at least every two months for one year as risk of recurrence is high. Efficacy of therapy should be also be monitored with urinalysis (pH, urine specific gravity, sediment examination) every two to three months.

> Xanthine (Figure 38)

Xanthine uroliths are rare and may be due to an inborn error of purine metabolism or arise secondary to the administration of allopurinol. In most cases, no identifying risk factors are observed. There is no apparent breed, age or sex predisposition reported *(Osborne et al, 1992a; 1996b; White et al, 1997)*.

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Figure 38 - Xanthine urolith (scale: 0.1 mm markings). *Small xanthine calculi from a 9 month male siamese cross cat. The pale color is atypical; usually they are green or yellow.*

The dietary strategy aims at decreasing the purine content of the diet. As with all urolith types, encouraging water intake and urine dilution by feeding a moist (canned, pouch, tray) diet or adding supplemental water or sodium to the food can help to lower urinary saturation. Allopurinol therapy must be discontinued in the management of urate urolithiasis as it is a contributing factor to xanthine urolith formation.

> Silica (Figure 39)

Silica uroliths are uncommon. Based on limited numbers, there is no breed predisposition. In Canada, males outnumbered females in submission *(Houston et al, 2006)*. The pathogenesis, at least in dogs, may involve consumption of an absorbable form of silica in various foods, resulting in urinary silica hyperexcretion. There may be some relationship to the increased use of plant-derived ingredients such as fibers and bran in pet foods *(Osborne et al, 1995a,b)*.

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Figure 39 *- Silica urolith.*

Silica uroliths may be an incidental findings in cats. Surgical removal is indicated if clinical signs of FLUTD are thought to be due to the urolith. Because the initiating and precipitating causes of silica urolithiasis are unknown, only nonspecific dietary recommendations can be made. Empiric recommendations are to change the diet to one with high quality protein and if possible, reduced quantities of plant ingredients. Increased water intake and urine dilution is to be encouraged.

> Miscellaneous uroliths

Potassium magnesium pyrophosphate uroliths have been reported in four Persian cats *(Frank et al, 2002)*. In Canada, a total of 15 potassium magnesium pyrophosphate uroliths have been analyzed at the Canadian Veterinary Urolith Center. Two thirds were identified in male cats. The majority occurred in domestic cats (66.7%). There was one male and one female Himalayan, one male and one female Persian, and one male Maine Coon cat. There were an additional nine uroliths with a nidus of either calcium oxalate (eight) or struvite (one) surrounded by pyrophosphate uroliths or shells. Although the etiology is not definitively known, it is postulated that it is related to some temporary or permanent enzyme dysfunction causing pyrophosphate supersaturation of the urine, which leads to crystallization of the urolith *(Frank et al, 2002)*.

Dried solidified blood uroliths **(Figure 40)** have been reported in cats in North America *(Westropp et al, 2006)*. Their etiology remains unknown. These uroliths usually do not contain any mineral material and a large number are radio-transparent.

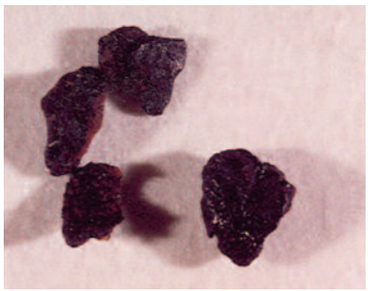

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Figure 40 - A collection of dried solidified blood uroliths from the bladder of a cat.

Because the initiating and precipitating causes of both potassium magnesium pyrophosphate uroliths and dried solidified blood uroliths are unknown, only nonspecific dietary recommendations can be made. Empiric recommendations are to change the diet to one that is highly digestible and low in fiber with high quality protein. Increased water intake and urine dilution is to be encouraged.

> Compound uroliths

Compound uroliths consist of a nidus of one mineral type and a urolith or shell of another mineral type **(Figure 41)**. They form because factors promoting precipitation of one type of urolith supersede earlier factors promoting precipitation of another mineral type. Some mineral types may also function as a nidus for the deposition of another mineral type; for instance, all urolith types predispose to urinary tract infections, which in turn, may result in secondary struvite precipitation *(Osborne et al, 2000)*.

The possibility of compound uroliths highlights the need to submit uroliths for quantitative analysis so that the appropriate dietary and medical strategy can be implemented. The dietary strategy aims at managing the factors that lead to the formation of the nidus. As with all urolith types, encouraging water intake and urine dilution by feeding a moist (canned, pouch, tray) diet or adding supplemental water or sodium to the food can help to lower urinary saturation.

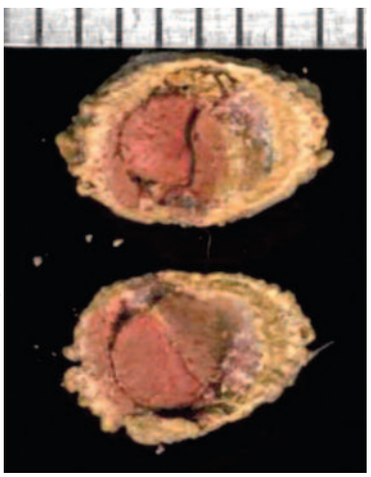

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Figure 41 - Complex urolith removed from a cat. *The urolith was submitted for quantitative analysis: once opened, the nidus was analyzed as ammonium acid urate. The shell was determined to be struvite.*

Conclusion

Encouraging water intake to enhance urine volume and diuresis is paramount for the management of all cats with clinical signs of lower urinary tract disease. For FIC, urine dilution decreases noxious, irritating substances in the bladder. For urethral plugs, urine dilution and enhanced urine volume will also help decrease the concentration of proteinaceous material and urinary tract debris. For urolithiasis, urine dilution enhances urine volume for a given solute load, reduces saturation, and decreases the concentrations of crystalloids. In addition, increasing urine volume may influence crystal transit time through the urinary tract, thus reducing the potential for crystal growth.

Dietary modification is an important part of the management regimen for cats with urolithiasis, regardless of the cause. Specific dietary recommendations for individual uroliths are dependent on the mineral composition of the urolith. For cats with struvite urolithiasis, control of magnesium and reduction of urine pH through dietary manipulation are necessary to achieve urine which is undersaturated with struvite. For cats with calcium oxalate urolithiasis, attention is paid to the amount of calcium and oxalate precursors in the diet and the goal is to achieve an RSS in the metastable range. Manipulating urinary pH is not effective for the management of calcium oxalate uroliths. For metabolic uroliths (cystine, xanthine, urate), reduced quantities of dietary protein are recommended and urine pH is adjusted to be in the neutral to alkaline range.

Frequently asked questions about nutritional management of feline lower urinary tract disorders

Q	A
A cat presents with hematuria and inappropriate urination. There are no bacteria seen on the urinalysis. Should I treat the cat with antibiotics and see if he responds to therapy or should I recommend radiographs or other diagnostic procedures?	Urinary tract infections (UTIs) are very uncommon (<1%) in healthy cats and the routine use of antibiotics is not recommended. Idiopathic cystitis or urolithiasis is more common than UTIs in cats and a radiograph is indicated. Struvite and calcium oxalate uroliths are the two most common uroliths in cats and they are both radiodense. Note: urate and cystine stones are usually radiolucent, and require positive contrast studies or ultrasound for determination.
If I see a urolith on a radiograph, is it most likely to be struvite or calcium oxalate?	In some regions of the world, struvite predominates in cats; in other regions, calcium oxalate uroliths are more common. Therefore, rather than predict what the urolith is, it is appropriate to retrieve a urolith and perform quantitative analysis. The urolith can be retrieved via free catch using an aquarium net, via catheter assistance, voiding urohydropropulsion, cystoscopy or cystotomy. Urine pH and sediment examination may or may not be helpful as crystals may not be passed at all or the crystals that are present could be different than the underlying urolith that is present. If struvite is suspected, dissolution therapy may be attempted. Failure to dissolve the uroliths within six weeks suggests the urolith is of a different mineral composition and surgical removal is indicated.
Are kidney stones in cats more likely to be struvite or calcium oxalate?	In cats, approximately 70% of nephroliths are calcium oxalate. Calcium oxalate nepholiths are present in up to 50% of cats with renal disease. Therefore, all cats that have renal disease should have abdominal radiographs. It is important to recognize if nephroliths are present and to monitor for obstruction and a decline in renal function.
How should nephroliths and ureteroliths be managed in cats?	If the nephroliths are causing complete obstruction or progressive deterioration in renal function, surgical removal is indicated. However, because of the unavoidable destruction of nephrons during nephrotomy, surgical removal is not recommended unless it can be established that the uroliths are the cause of clinically significant disease. If not, the patient should be monitored for indications of disease progression or ureteral obstruction. In many cases, ureteroliths will migrate into the bladder so it is appropriate to obtain serial radiographs to monitor for urolith movement.
How often should the cat be reexamined after a urolith has been removed? What diagnostic tests are recommended to monitor the patient?	Because many uroliths have a high risk of recurrence, it is recommended to obtain radiographs every three to six months. For metabolic uroliths (urate, cystine), contrast radiography or ultrasound examination may be necessary as these stones are typically radiolucent. Urine pH and urine specific gravity should be performed every three months to ensure owner compliance and diet efficacy.

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Focus on:

Sodium

After calcium and potassium, sodium is the most abundant ion in the body. It accounts for around 0.13% of the body weight of a mammal. Extracellular sodium is found in the skeleton (43% of total sodium), interstitial fluids (29%) and plasma (12%). The remaining sodium is mainly found inside the cells.

Sodium plays several essential roles in cell function:

- it maintains the osmotic pressure balance between the intra- and extracellular environment and regulates the volume of extracellular fluids. As a water balance regulator it has an important role in the development of thirst and urine elimination;
- it intervenes in acid-base balance;
- it participates in the transmission of nerve impulses.

The digestive absorption of sodium is general very important. A constant sodium level is maintained in the body by regulating renal and intestinal secretion.

When it comes to determining the salt content in different foods, it is important to measure carefully.

Publications dealing with the influence of sodium (Na) on the physiology do not always express the sodium concentration of foods in the same way. Before interpreting the results, it is advisable to distinguish the values in:
- mg or mmol of Na per kg of weight
- mg or mmol of Na per kg of food
- % of dry matter of the food.

The sodium values are sometimes given through the quantity of sodium chloride (NaCl) added. The units must therefore be taken into account before comparing values.

Calculating the equivalences between mg and mmol of sodium

- The molecular weight of NaCl is 58.45 g/mol.
- In 1 Mole of NaCl, the sodium ions weigh 23 g and the chloride ions weigh 35.45 g.
- In 1 mmol of NaCl, the sodium ions weigh 23 mg and the chloride ions weigh 35.45 mg.
- A factor of 23 is therefore used for conversion.

Example 1:

10 mmol of sodium is equivalent to:
23 x 10 = 230 mg of Na

Example 2:

10 mg of sodium is equivalent to:
10 / 23 = 0.43 mmol of Na

Do not confuse the sodium chloride (NaCl) and sodium (Na) contents in a food

- In 1 mole of NaCl, the sodium ions account for 39.3% of the total and the chloride ions around 60.7%.
- A factor of 0.393 is used for conversion.

Example:

1% of sodium in a food corresponds to: 1/0.393 < 2.54% of NaCl.

When the sodium source is another sodium salt, the calculation is done in the same way, based on the percentage of sodium in each salt:
- Sodium carbonate contains 37% of sodium.
- Sodium bicarbonate contains 27% of sodium.
- Sodium phosphate contains 16% of sodium.

Cats do not sweat, so they are not exposed to major losses caused by sweating, even in the event of intense effort or high temperatures.

The dissolution kinetics of feline struvite stones in urine *in vitro* depends on the urine struvite relative supersaturation

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Introduction

Relative supersaturation (RSS) is a method that enables measurement of the potential for crystals to form or dissolve in urine, based on composition **(Figure 1)**. This technique has been validated in cats *(Robertson et al, 2002)*. The aim of this study was to assess whether struvite RSS is a good predictor of the in vitro struvite (ammonium magnesium phosphate) dissolution kinetics in cat urine.

FIGURE 1 - EVALUATION OF THE PROBABILITY OF STRUVITE STONE FORMATION BASED ON URINE SATURATION

Materials and methods

Animals and diets

Three commercial complete dry expanded diets (A, B, C) were fed successively to 7 Chartreux cats (4 neutered males, 3 females, 6.0 ± 2.8 yrs, 5.9 ± 1.3 kg) for 2 weeks. Diets B and C were specifically formulated to dissolve struvite uroliths (low urine acid pH and RSS).

Parameters

Urinary volume, pH, specific gravity and concentrations of 10 solutes (Ca, Mg, Na, K, NH_4+, phosphate, citrate, sulfate, oxalate, uric acid) were measured in pooled urine for each diet collected during the last 7 days of each study period **(Table 1)**.

Based on these data, the RSS for struvite was calculated using the SUPERSAT™ software *(Robertson et al, 2002)*.

Selection of struvite stones and preparation of urine samples

Three groups of feline struvite stones were selected on the basis of homogeneity of shape and weight (mean weight: 0.201 ± 0.010 g). For each diet, the pooled urine from all 7 cats was aliquoted in bottles, based on the mean daily volume of urine produced by the cats. The bottles were stored at -20°C pending the study.

TABLE 1 - URINE PROPERTIES FOR EACH DIET

	Diet A	Diet B	Diet C
Mean urine volume (mL/cat/day)	65.0	92.7	118.2
Urinary pH	7.34	6.27	6.18
Urinary specific gravity	1060	1048	1046
Struvite RSS	7.30	0.45	0.19

In vitro dissolution procedure

On day 0 and for each diet, a bottle of urine was defrosted and one group of struvite stones was placed in the urine **(Figure 2a)**. The bottle was then placed in a water bath at 38°C for 24 hours (with a shaking mode during 9 hours to simulate cat activity) **(2B)**. At the end of the 24 hour period, the urine was filtered to collect the stones **(2C)**.

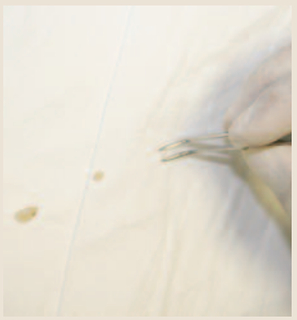
The stones were lightly dried on absorbent paper **(2D)** and weighed **(2E)**. A new urine bottle was then defrosted and the process repeated until complete dissolution of the stones was achieved **(Figure 3)**.

FIGURE 2 - *IN VITRO* STRUVITE STONE DISSOLUTION PROTOCOL

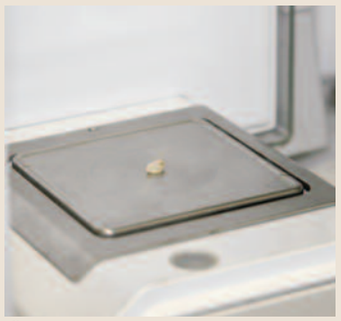
2A

2B

2C

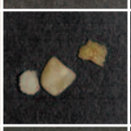
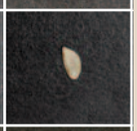
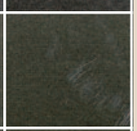
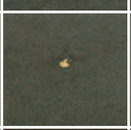


2D



2E

FIGURE 3 - APPEARANCE OF STRUVITE STONES DURING DISSOLUTION

	Diet A	Diet B	Diet C
Day 0			
D2			
D4			
D6			
D8			
D10			
D12			
D14			
D16			
D18			
D20			
D22			
D24			

Discussion and conclusion

With saturated urine (diet A - RSS = 7.3), little dissolution was observed over the duration of the study **(Figure 4)** possibly due to the abrasion of the stones during agitation.

When the RSS is < 1 (undersaturation zone), urine dissolves struvite stones efficiently **(Figure 4)** and the lower the RSS, the faster the dissolution kinetics **(Table 2)**. RSS is thus a good predictor of the potential of urine to dissolve struvite.

FIGURE 4 - DISSOLUTION KINETICS OF STRUVITE STONES FOR EACH DIET

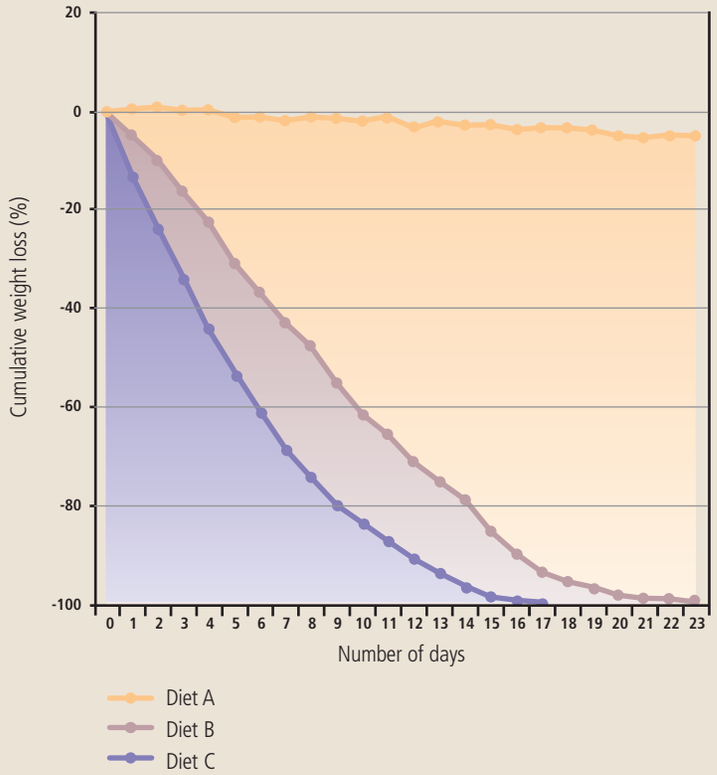


TABLE 2 – DISSOLUTION SPEED OF STRUVITE STONES FOR EACH DIET

	Diet A	Diet B	Diet C
Struvite RSS	7.30	0.45	0.19
Number of days before complete dissolution	-	23	17
Dissolution speed (mg/day)	0.01	8.52	11.59

Reference

Robertson WG, Jones JS, Heaton MA, et al. Predicting the crystallisation potential of urine from cats and dogs with respect to calcium oxalate and magnesium ammonium phosphate (struvite). J Nutr *2002; 132: 1637s-1641s.*

Heart

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Acquired cardiovascular diseases in cats: the influence of nutrition

ABBREVIATIONS USED IN THIS CHAPTER

ACEI: angiotensin-converting enzyme inhibitors
BID: twice daily
BP: blood pressure
CKD: chronic kidney disease
DCM: dilated cardiomyopathy
DMB: dry matter basis
HCM: hypertrophic cardiomyopathy
HR: heart rate
ME: metabolizable energy
NRC: National Research Council
RAAS: renin-angiotensin-aldosterone system
RCM: restrictive cardiomyopathy
SH: systemic hypertension
SID: once daily
TID: three times a day
TPR: total peripheral resistance

Acquired cardiovascular diseases in cats: the influence of nutrition

Valérie CHETBOUL

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A qualified veterinarian since 1984 with a degree from the Alfort National Veterinary School (France), Professor Valérie Chetboul has taken training courses, obtained diplomas and carried out research projects in her favourite field, cardiology, in both Europe and the United States. In 1986, in collaboration with Professor Pouchelon, she opened the first echocardiography clinic for domestic carnivores. The growth of her field of specialization is illustrated by the creation of the Alfort Cardiology Unit and the first French Holter veterinary center (2000) and by an active collaboration with a cardiovascular surgical research unit in Paris (2002). Her involvement in the field of cardiovascular research was translated into her participation in the establishment of a National Health and Medical Research Institute center on the Alfort National Veterinary School campus (2005), attached to the University of Paris XII and dedicated to cardiology. She has published numerous articles in scientific referred journals with an international readership and has written several works, among which an 'An Echo-Doppler Colour Atlas of Dogs and Cats', which in 2002 earned her the Groulade Prize by the Veterinary Academy of France. She was editor-in-chief of the Journal of Veterinary Cardiology (2002-2006) and she is still editor of this journal. She has also given numerous papers at different international conferences, both in human and veterinary medicine. Her competence has been recognized by her peers, who in 2001 granted her the prestigious Award of the American College of Veterinary Internal Medicine.

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Vincent Biourge graduated from the Faculty of Veterinary Medicine of the University of Liège (Belgium) in 1985. He stayed as an assistant in the nutrition department for 2 more years before moving to the Veterinary Hospital of the University of Pennsylvania (Philadelphia, USA) and to the Veterinary Medical Teaching Hospital of the University of California (Davis, USA) as a PhD/resident in clinical nutrition. In 1993, he was awarded his PhD in Nutrition from the University of California and became a Diplomate of the American College of Veterinary Nutrition (ACVN). In 1994, he joined the Research Center of Royal Canin in Aimargues (France) as head of scientific communication and then as manager of the nutritional research program. Vincent is now Scientific Director of Health Nutrition at the Research Center of Royal Canin. He has published more than 30 papers, and regularly present scientific papers as well as guest lectures at International Veterinary Medicine and Nutrition meetings. He is also a Diplomate of the European College of Veterinary Comparative Nutrition (ECVCN).

Diet has a major impact on the etiology and the therapy of feline cardiovascular diseases. As in humans and dogs, sodium intake in the diet can help modify cardiovascular function. More specifically, cats are dependent on a diet that provides sufficient taurine. Contrary to dogs, taurine is an essential amino acid for cats. The synthesis of bile acids in the cat is exclusively dependent on taurine, and the hepatic activity of the enzymes responsible for its synthesis from the sulfur amino acids, methionine and cysteine is extremely weak.

Introduction

Essentially, acquired cardiovascular disease in cats is due to either systemic hypertension (SH) or a cardiomyopathy (including more specifically taurine deficiency). This chapter will review separately and successively each of these pathological entities. An epidemiological, etiological, pathophysiological and diagnostic review will be conducted for and the potential etiological or therapeutic influence of the diet will be considered. While cardiomyopathies (especially hypertrophic forms) are the most commonly found cardiopathies in practice, it would appear justified to first consider SH, due to the key role dietary sodium plays in the development of cardiovascular diseases in general. Additional points of the nutritional management of cardiopathies will be handled in the third part of this chapter.

1 - Systemic hypertension in cats

SH is defined as the chronic systolic and/or diastolic increase in systemic blood pressure (BP). It is now a well-recognized clinical phenomenon in domestic carnivores, especially cats older than ten years *(Chetboul et al, 2003; Brown, 2006; Brown et al, 2007)*. Most clinicians consider a diagnosis of SH in cats when the systolic BP and diastolic BP is at least 160 and 100 mmHg respectively, measured in a calm animal and according to current recommendations *(Stepien, 2004; Brown et al, 2007)*.

► Etiology and pathogenesis

BP is the lateral force the blood exercises on each surface unit of the arterial vascular wall *(Guyton & Hall, 1996)*. BP depends on heart rate (HR) and total peripheral resistance (TPR).

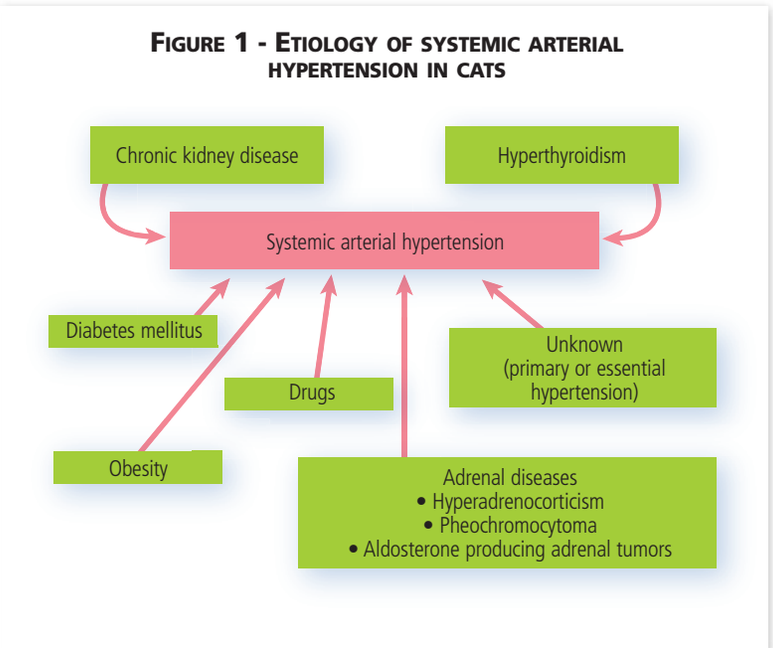
$$BP = HR \times TPR$$

The increase in BP can therefore result in a higher HR (due to an increase in the heart inotropism or blood volume) or a rise in TPR (during vasoconstriction, structural modification of the vessels or blood hyperviscosity). The circumstances that may lead to SH are therefore multiple.

Contrary to humans, in which primary or essential SH is the most common form, feline SH is most often secondary to another disorder **(Figure 1)**, most commonly renal or endocrine dysfunction (hyperthyroidism) *(Kobayashi et al, 1990; Syme et al, 2002; Chetboul et al, 2003)*. Essential SH is rare in the feline species. However, more routine measures of BP in veterinary medicine associated with the aging of the animal population suggest a greater frequency. At the moment it is difficult to establish, but SH may affect up to 18-20% of cats *(Elliott et al, 2001; Maggio et al, 2000)*. Just like in humans, BP tends to rise with age in normal cats *(Samson et al, 2004)*.

The main cause of feline SH **(Figure 1)** is chronic kidney disease (CKD). Studies show that 20-60% of feline renal patients are hypertensive *(Kobayashi et al, 1990; Stiles et al, 1994)*. There are many pathogenic mechanisms linking the kidneys and SH to varying

FIGURE 1 - ETIOLOGY OF SYSTEMIC ARTERIAL HYPERTENSION IN CATS



degrees of sodium and water retention and hyperactivity of the renin-angiotensin-aldosterone system, as evidenced by:
- hormonal alterations (plasma renin activity, aldosteronema, plasma aldosterone/renin ratio)
- histological and immunohistochemical analysis of the kidneys of animal patients *(Taugner et al, 1996; Jensen et al, 1997; Mishina et al, 1998; Pedersen et al, 2003)*.

SH in cats is also a frequent complication of untreated or poorly controlled hyperthyroidism, affecting a highly variable proportion of animals according to the studies. Between 20% and almost 90% of cats with hyperthyroidism are reported to be hypertensive in the literature *(Kobayashi et al, 1990; Stiles et al, 1994)*. The true prevalence of pathologic SH is probably overestimated due to the sensitivity of the cat to stress. SH in cats with hyperthyroidism is most often moderate and reversible with the treatment of the underlying endocrinopathy. The origin of SH in the event of hyperthyroidism *(Feldman & Nelson, 1997)* is multifactorial, including an increase in heart rate induced by the thyroidal hormones, an inotropic and chronotropic action directly and indirectly mediated by the receptors coupled to adenylate cyclase, and hyperactivation of the renin-angiotensin-aldosterone system via stimulation of the β juxta-glomerular receptors that initiate increased synthesis of renin.

Other less common causes of SH in cats include diabetes mellitus or more rarely obesity, hyperadrenocorticism, pheochromocytoma, hyperaldosteronemia, or even drugs such as glucocorticoids, phenylpropanolamine, erythropoietin and cyclosporine A *(Maggio et al, 2000; Chetboul, 2003; Senello et al, 2003; Brown, 2006; Brown et al, 2007)*. Predisposing factors include *(Brown, 2006)* rapid sodium chloride infusion (classic example of a cat with CKD), which may accelerate the expression of subclinical SH or lead to a sharp increase in BP that was initially within the upper limits of normal.

► Role of sodium

> In rodents

An excess in dietary sodium (Na) is well known in some animal species to be directly responsible for SH or at least a predisposing factor to its expression. A diet with a very high salt content [8% Na on a dry matter basis (DMB)]; (by comparison, commercially available diets for cats do not exceed 2% Na DMB) for a period of eight weeks leads to increased BP not only in spontaneously hypertensive rats but also in the initially normotensive Wistar-Kyoto rat *(Yu et al, 1998)*. In the abovementioned rats, these changes were accompanied by the development of interstitial fibrotic lesions in the kidneys (glomeruli, tubules) and the arteries of the left myocardium *(Yu et al, 1998)*. These changes paralleled the increased tissue expression of the gene coding for transforming growth factor-beta 1 (TGFβ1). Likewise, in a murine model of renal failure induced by nephron reduction, it has been shown that excessive sodium intake is accompanied by a rise in systemic BP *(Cowley et al, 1994)*.

The genetic models of SH include the salt-sensitive Dahl rat, which develops SH as well as disproportionate fibrotic and hypertrophic lesions in the arteries and left myocardium after the administration of a salt-enriched diet (2-8% Na DMB) *(Zhao et al, 2000; Siegel et al, 2003; Charron et al, 2005)*.

> In humans

It has been demonstrated that excessive salt intake in humans can also be deleterious and a direct cause of increased BP, although there is great heterogeneity in responses depending on the individual *(Weinberger et al, 1986; 1996; 2001)*. Thus, in people who are said to be sensitive to salt – less than 25% of the normotensive population *(Weinberger et al, 1986, 1996)* – the increase in dietary salt intake (from 230 mg (10 mmol)/day to 34.5 g

(1500 mmol) over a period of 15 days) is accompanied by an abnormally large rise in BP that may exceed 30% of the baseline value *(Luft et al, 1979; Weinberger et al, 1996; 2001)*. This abnormal sensitivity to salt is said to be a mortality factor independent of the BP value *(Weinberger et al, 2001)*. Inversely, in some hypertensive diseases, sodium restriction may help reduce BP in a manner comparable to that of an anti-hypertensive drug *(Weinberger et al, 1986; Luft & Weinberger, 1997)*. The effect on BP of salt intake in humans is however highly variable, depending on various factors including genetic context, age, consumption of other electrolytes or even the concomitant intake of some drugs *(Luft & Weinberger, 1997)*. The genetic predisposition to salt sensitivity is said to play a major role in humans, as demonstrated in African American people or people with non-insulin dependent diabetes mellitus.

> In healthy cats

Compared with humans or rats, there are fewer data on the influence of dietary sodium in the genesis of SH in cats. To the authors' knowledge no case of salt-sensitivity has been truly described comparable to those depicted in humans or rats. In the feline species, it has even been shown that a relatively high sodium level in a normotensive animal is accompanied by an increase in water consumption and urine output *(Devois et al, 2000; Luckschander et al, 2004)*. Thus, in healthy young cats (average age 2.5 years, n=10) the administration of a diet with a moderate sodium chloride (NaCl) content (1.02% Na and 2.02% Cl DMB) for a period of two weeks does not change the systolic BP value (measured with the Doppler method), which remains within reference intervals comparable to what is obtained with a control diet (0.46% Na and 1.33% Cl DMB). In the same study, compared with the control diet, the diet with the higher salt content resulted in only a significant increase in water consumption (in excess of 50%) and urinary osmolarity associated with a reduction in urine density.

While supplementary data (high-salt diet given over a longer period to several animals) are needed to complete the results, the National Research Council (NRC) has estimated that there is now sufficient scientific evidence to conclude that a value of 1.5% Na DMB in a dry food providing 4000 kcal/kg could be considered as being risk-free, in healthy cats *(NRC 2006)*. This level equates to an intake of 3.75 g of sodium per 1000 kcal.

> What about cats whose renal function is impaired?

Six different studies of healthy dogs and cats as well as animals with renal failure (presenting maximum azotemia equivalent to stage III CKD according to the IRIS classification) show no influence of a moderate rise in sodium ingestion (up to 3.2 g of sodium per 1000 kcal of metabolizable energy (ME)) on BP *(Greco et al, 1994; Buranakarl et al, 2004; Luckschander et al, 2004; Kirk et al, 2007)*.

► Pathophysiological consequences

Most of the organic consequences of SH appear for systolic BP values in excess of 180 mmHg *(Brown, 2006)*, more particularly during the sharp rise in pressure (30 mmHg or more in less than 48 hours).

- **The kidneys** are one of the preferred targets of SH *(Brown, 2006)*. Untreated SH can lead to the development of nephroangiosclerotic lesions, which themselves have the potential to accentuate the initial hypertension.

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According to the available scientific information, blood pressure in healthy cats or cats with moderate CKD is not affected by the sodium levels required to stimulate water consumption and urine output in cats.

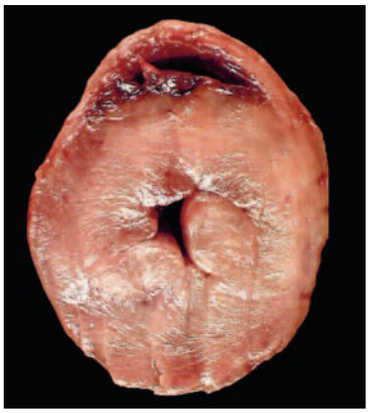

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Figure 2 *- Example of marked symmetrical concentric hypertrophy of the left ventricle in a cat with renal failure and systemic arterial hypertension.*

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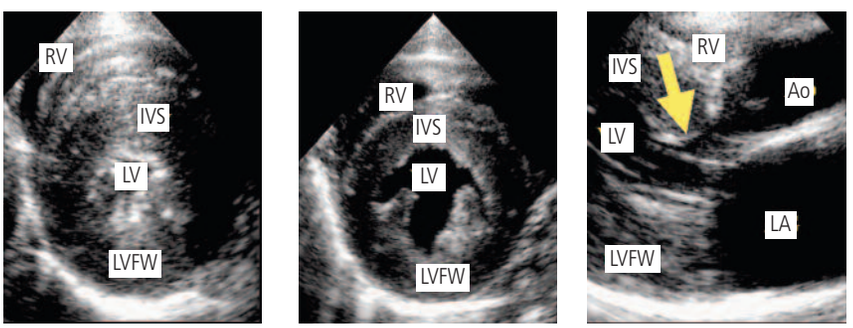
Figure 4 *- Sudden blindness in a cat, caused by hypertensive retinopathy.*

- **The heart**, and specifically the left ventricle, is another main target organ of SH. In a study conducted in association with Toulouse National Veterinary School on 58 hypertensive cats *(Chetboul et al, 2003)*, 85 % presented with an abnormal echocardiograph. In 59% of the cases, the alteration was concentric hypertrophy of the left ventricular wall **(Figures 2 & 3A)**, symmetric or not. There was no correlation between the degree of parietal hypertrophy and blood pressure values nor the age of the animals. Eccentric hypertrophy and septal hypertrophy localized in the subaortic region **(Figures 3B & 3C)** were found in a lower but similar proportion (13% each). Dilatation of the left atrium was associated with the left ventricular remodelings in less than one third of cases (28%). Feline SH has also been shown to accompany modification of the proximal aorta (dilatation, twisting contours) *(Nelson et al, 2002)*.

- **Ocular lesions** are common in hypertensive animals *(Maggio et al, 2000; Chetboul et al, 2003; Samson et al, 2004)*, affecting up to 50% of hypertensive cats and 80% of hypertensive cats with renal failure. These lesions mainly correspond to alterations in the vascularization of the fundus termed 'hypertensive retinitis' **(Figure 4)**: abnormal twisting and dilatation of blood vessels in the retina, localized or diffuse preretinal or retinal hemorrhages, and partial or total detachment of the retina potentially leading to permanent blindness in the absence of early treatment. SH may also cause hyphema, anterior uveitis due to vasculopathy of the ciliary bodies or even glaucoma caused by an obstruction of the iridial angle by blood.

- A sharp and marked rise in BP may lead to the appearance of **cerebral lesions** (edema or hemorrhage) classified as hypertensive encephalopathy *(Brown et al, 2005; Brown, 2006)*. Hypertensive encephalopathy causes various nervous problems ranging from simple behavioral modifications (hypernervosity, anxiety, complaining mewing), ataxia and disorientation, to more serious signs (torpor **(Figure 5)**, convulsions or coma). For reasons that are not yet apparent, cats suffer from hypertensive encephalopathy more often than dogs.

FIGURE 3 - THE THREE MAIN TYPES OF LEFT VENTRICULAR REMODELING ASSOCIATED WITH SYSTEMIC ARTERIAL HYPERTENSION IN CATS



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3A - *Concentric hypertrophy.*

3B - *Eccentric hypertrophy.*

3C - *Localized hypertrophy.*

2D echocardiographic image, right parasternal route, images taken at the end of the diastole, transventricular short axis views (3A and 3B) and long-axis 5-chamber view (3C).

Symmetrical parietal hypertrophy is concentric in the animal in Figure 3A and eccentric in the animal in Figure 3B with very reduced and normal left ventricular diameter respectively. Note the large deformation of the localized interventricular septum in the subaortic region in Figure 3C (marked).

LVFW: left ventricular free wall
IVS: interventricular septum
RV: right ventricule
LV: left ventricule
Ao: aorta
LA: left atrium

► Diagnosis

> Diagnostic step n°1: suspicion

In practice, SH must be suspected when the cat has a disorder that is a known cause of SH (especially CKD or hyperthyroidism). Other suspicious circumstances include:
a) when one or more (physical or functional) symptoms are suggestive of SH **(Table 1)**.
b) identification of left cardiomegaly or left ventricular remodeling by radiograph or ultrasound imaging, respectively.

The diagnosis of SH can also be established during the routine measurement of BP despite the absence of other signs based on clinical observation, etiology, radiograph or ultrasound. However, an increase in BP alone, should be carefully interpreted (do not hesitate to repeat the BP measurement in the absence of clinical signs or biochemical modifications).

> Diagnostic step n°2: confirmation via BP measurement

The Doppler method **(Figures 6 & 7)** is currently recommended by the majority of authors due to its speed and simplicity compared with oscillometry *(Jepson et al, 2005)*. In addition, the Doppler method is strongly correlated with the values obtained by the gold standard reference method of direct catheterization *(Binns et al, 1995)*. The only drawback of this technique is the occasional difficulty determining the diastolic BP value, which is negated by experienced operators. Several rules must however be followed to ensure that the values measured are as repeatable and reproducible as possible and to limit anxiety-induced hypertension ("white coat effect"), which can lead to the erroneous diagnosis of pathological SH.

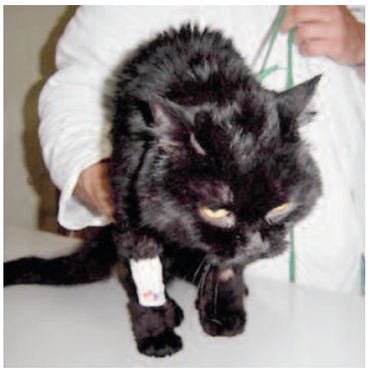

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***Figure 5** - Exhaustion and torpor in a cat with systolic arterial hypertension (systolic arterial pressure = 290 mmHg).*

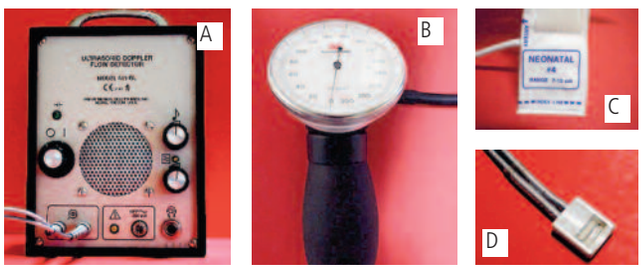

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Figure 6 - Example of equipment used to measure blood pressure by the Doppler method. *6A: machine - 6B: manometer - 6C: occlusive cuff - 6D: transducer (8-10 MHz).*

FIGURE 7 - BLOOD PRESSURE MEASUREMENT BY THE DOPPLER METHOD IN A CAT

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7A: Positioning of the cuff at the base of the tail and distal application of gel.

7B: Inflation of the cuff after location of the blood flow. The animal is lying on its sternum (measurement taken at heart level).

TABLE 1 - COMPARATIVE DISTRIBUTION OF CLINICAL SIGNS IN HYPERTENSIVE CATS (N=58) AND NORMOTENSIVE CATS (N=113). ALL ANIMALS WERE REFERRED WITH SUSPECTED SYSTEMIC ARTERIAL HYPERTENSION

(Chetboul et al, 2003)

Clinical signs	Hypertensive cats (n=58)	Normotensive cats (n=113)
Heart murmur	62%	72%
Polyuria-polydipsia	53%*	29%
Retinal lesions (detachment, hemorrhage)	48%**	3%
Anorexia- fatigue	45%	71%
Gallop rhythm	16%**	0%
Vomiting	15%	16%
Nervous symptoms	13%	13%
Dyspnea – Coughing	12%	17%
Weight loss	12%	14%
Other	1%	17%

*The most specific symptoms (albeit not pathognomonic) of SH were retinal lesions**, galloping sound** and polyuria-polydipsia*, the only ones to be significantly more common in hypertensive cats than in normotensive cats (**: $p<0.001$; *: $p<0.01$).*

Rules to be followed to measure blood pressure in cats

(Stepien et al, 2004; Snyder et al, 2006; Brown et al, ACVIM consensus statement, 2007)

1) The following recommendations help limit "white coat hypertension" and avoid erroneous diagnosis of pathological hypertension.

- Conduct the test in a separate room that is calm, in the presence of the owner.
- Wait until the heart rate is stable or the cat calms down before conducting a test or registering the results.
- Eliminate the first BP values, then take 3-5 additional measures, if possible at 30-60 seconds intervals to calculate the average.
- Do not hesitate to repeat the test within 48 hours, in the event of clinical or etiological suspicion, or 15-30 days, in less urgent circumstances in borderline cases (cat showing stress and BP values above the upper limits: 160 mmHg in systole, 100 mmHg in diastole).

2) The following rules help increase the reliability of the technique.

- The same people, trained in the technique and the use of the equipment should always conduct BP tests at any given clinic or in any given team.
- The ambient temperature in the room should not be too low, to avoid the appearance of peripheral vasoconstriction, which could cause the BP value to be higher than expected or even make it difficult to get a measurement.
- Use the appropriate cuff (if it is too small BP may be overestimated; if it is too big the BP may be underestimated).
- The average BP value, the name of the tester, the test site and the number of measurements taken should be noted, to ensure maximum rigor in longitudinal monitoring.

Table 2 - Common hypertensive agents recommended for cats with systemic arterial hypertension

Classes	Substances	Doses
Diuretic	Hydrochlorothiazide	1-3 mg/kg BID
Calcium inhibitor	Amlodipine: highly effective in cats	0.625-1.25 mg/cat/day (or 0.18-0.3 mg/kg PO SID)
Angiotensin conversion enzyme inhibitors *(in the event of very moderate SH with proteinuria, or if nephroprotective effect is desired or in association with amlodipine (if amlodipine alone does not work)*	Benazepril Enalapril Imidapril Ramipril	0.25-0.5 mg/kg/day SID PO 0.25-0.5 mg/kg SID to BID PO 0.5 mg/kg/day SID PO 0.125 mg/kg/day (up to 0.25 mg/kg if necessary) SID PO
β-blockers	Propranolol Atenolol	0.1-1 mg/kg 2-3 x/day PO or 2.5-5 mg/cat BID to TID PO or 6.25-12.5 mg/cat SID to BID PO
Other	Spironolactone	1-2 mg/kg/day PO (little documented in cats)

By far the best anti-hypertensive documented in the feline species is amlodipine.
PO: per os
The use of these agents in cats can be restricted according to the licence applicable in each country.

> Diagnostic step n°3: determination of the cause

When SH is identified in a cat the veterinarian must begin with a simple blood test (urea, creatinine and T_4 measurement) to confirm or rule out CKD and hyperthyroidism. If the results are normal, a complete medical evaluation must be conducted before concluding primary SH. This examination includes a CBC, biochemical profile, urine analysis and even an abdominal ultrasound to check for an adrenal mass. Finally, it also advised to analyse the urine protein to creatinine ratio (UPC) as proteinuria can be a negative pronostic factor *(Jepson et al, 2007)*.

► Medical treatment

Anti-hypertensive drugs that can be administered to cats are listed in **Table 2**. Amlodipine besylate is by far the anti-hypertensive of choice in cats. It is a documented drug in the species with efficacy in most cases without the additional need of other anti-hypertensive treatments *(Henik et al, 1997; Elliott et al, 2001; Snyder et al, 2001; Tissier et al, 2005)*. Amlodipine is a long-action calcium inhibitor of the dihydropyridine group that acts against the opening of the voltage-dependant slow calcium channels. Its long action (contrary to that of nifedipine) limits the secondary effects of sudden hypotension (tachycardia, exhaustion, malaises). Amlodipine also has few negative effects on inotropism and conduction. Amlodipine is not recommended in cats with hepatic failure.

Treatment of the primary disorder, when known, is a priority. In cats with hyperthyroidism, normalization of BP may be achieved in association with the restoration of euthyroidism without use of anti-hypertensives *(Snyder & Cooke, 2006)*. In an emergency (sudden blindness or major tachyarrhythmia), it will be necessary to quickly reduce BP with the administration of amlodipine (calcium inhibitor) or β blockers (propranolol, atenolol), which have the advantage of directly targeting the action sites of thyroidal hormones on the cardiovascular system **(Table 2)**.

► Adapting the sodium content in food

Based on the data on excess dietary sodium from animal SH models or human medicine (see above), it is often accepted that the ingestion of sodium must be severely reduced in hypertensive cats. While excessive and sudden sodium intake (1.3%/DMB or more) must be avoided in the event of feline SH *(Snyder & Cooke, 2006)*, no study has yet shown the benefit of sodium restriction in cats in terms of blood pressure values or life expectancy.

Contrary to preconceived ideas, too low an intake of dietary sodium in cats can be rather harmful, as shown by *Buranakarl et al (2004)*. For one week, three groups of cats were given the same dry food differentiated only by sodium content: 0.34%, 0.65% and 1.27% as fed, (0.5 g, 1.4 g and 2.8 g per 1000 kcal, respectively). One group of healthy cats (control group, n=7) was compared with two groups of cats with experimental renal disease by renal infarct (ligature of the branches of the renal artery) associated either with contralateral nephrectomy ('remnant kidney (RK) model', n=7) or contralateral 'wrapping' (wrapping or WA model, n=7).

In the two groups of cats with renal failure, in spite of the prescription of amlodipine (0.25 mg/kg/24 hours PO) systemic, systolic, diastolic and average BP (measured by radiotelemetry) were higher than in the control group, significantly in the RK group and to a lesser degree in the WA group. However, no influence of dietary sodium was observed in the three groups of cats, on heart rate, blood pressure variability (shown by a retained baroreflex also in sick animals) or the systemic BP value (systolic, diastolic and mean). In other terms, and contrary to the data published in rats *(Cowley et al, 1994)*, the high sodium diet characterized by 2.8 g Na/1000 kcal was not responsible for a rise in BP in either the healthy control cats, which concurs with the data obtained for healthy dogs *(Krieger et al, 1990; Greco et al, 1994)* or cats with renal failure. Likewise, the lower sodium diet did not induce a lower systemic BP in the two groups of sick cats nor in the control group. This latter diet was shown to have no beneficial anti-hypertensive protector effect in cats with renal disease.

In the same study *(Buranakarl et al, 2004)*, the lowest sodium intake (0.5 g/1000 kcal) was also associated with:

- a significant reduction in the glomerular filtration rate in control cats compared with the values obtained in the same group with the other two diets. The same observation was made in the WA group;

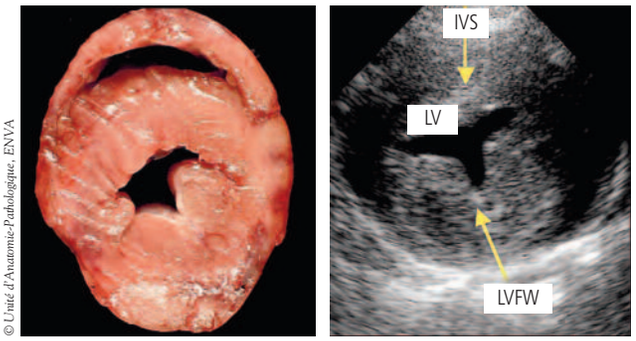
- activation of the renin-angiotensin-aldosterone system (RAAS) in cats with renal disease which was greater in the WA group than in the RK group. This activation was characterized by aldosteronemia and a higher serum aldosterone/renin ratio compared with the control group. These hormonal modifications were reduced with NaCl supplementation. This diet was also associated with an increase in the arginine-vasopressin plasma concentration in the RK group;

- hypokalemia in healthy cats and even more in cats with renal disease, associated with an increase in the excreted potassium fraction (very marked in the WA model) linked to a large degree to hyperaldosteronism, which is potentially harmful (risk of hypokalemic nephropathy and progressive renal lesions).

© Malik

This cat shows a typical posture signifying general muscle weakness, with drooping of head and neck, that may be encountered with severe hypokalemia in patients with CKD, as well as in hypokalemia due another cause.

Figure 8 - Example of hypertrophic cardiomyopathy in a cat



© Unité d'Anatomie-Pathologique, ENVA

8A: Marked systemic concentric hypertrophy of the left ventricle visually similar to that of Figure 3A.

8B: The concentric hypertrophy in Figure 8A was initially identified on echocardiographicexamination (2D, right parasternal route, image obtained at the end of diastole, transventricular short axis view).

LVFW: left ventricular free wall; IVS: interventricular septum; LV: left ventricular cavity.

To summarize, the data presented above demonstrate that major restriction of sodium is not recommended in hypertensive cats or in cats with CKD that have hypertensive tendencies. Excessive restriction risks stimulating the renin-angiotensin-aldosterone system, a pressure system par excellence. This aggravates the reduction in the glomerular filtration rate and favors hypokalemia due to increased kaliuresis. The same recommendation applies to healthy cats.

Lastly the prescription of a low calorie diet has not been shown to have a hypotensive effect in obese cats *(Snyder & Cooke, 2006)*, although few data are available on this subject.

2 - Feline cardiomyopathies

Cardiomyopathy designates all the disorders of the myocardium not secondary to a disease of another part of the cardiovascular system (valvular disease, alteration of the pericardium or the conducting system). These disorders are described as primary when their cause is undetermined or poorly identified. They are secondary when their origin is identified (hormonal, dietary, toxic, infectious or infiltrative cause). The importance of cardiomyopathies in cats is linked to the fact that they represent more than 90% of acquired cardiopathies in this species and are found in around 10% of cats at post mortem *(Fox, 1999)*.

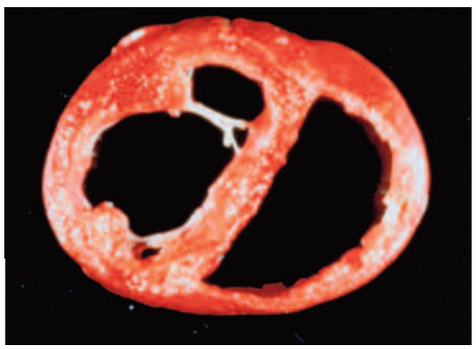


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***Figure 9** - Example of taurine deficiency dilated cardiomyopathy.*

► Classification – Main characteristics

Cardiomyopathies are very heterogenous and can be classified according to different criteria. The most commonly used classification in practice is one that combines morphological, functional and lesional characteristics. There are four main groups of cardiomyopathy: hypertrophic (HCM), dilated (DCM), restrictive (RCM) and 'unclassified' also known as intermediate.

- **Hypertrophic forms (Figure 8)** are characterized by myocardial hypertrophy, most often of the free wall of the left ventricle and/or the interventricular septum. This hypertrophy may be symmetrical, asymmetrical or localized in the subaortic region, at the mainstays or the apex, which is described as segmentary hypertrophy *(Fox, 2003; Häggström, 2003)*. HCM includes the primary forms, some of which have been shown to be genetically determined. These are handled in the next section. There are also secondary HCM, especially associated with hyperthyroidism, SH (see chapter 2), acromegaly and inflammatory or cancerous myocardial infiltration (particularly lymphoma).

- **Dilated forms** are rare compared with hypertrophic forms. They may be primary or secondary. Secondary forms are either due to the cardiotoxicity of adriamycin (now uncommon), a sequela of myocarditis or taurine deficiency. Taurine deficiency cardiomyopathy **(Figure 9)**, which is now very rare due to the supplementation of taurine in commercial foods, is discussed further in the text *(Pion et al, 1992 a,b)*. DCM is characterized by a drop in inotropism concerning the left ventricle only or both ventricles simultaneously. Dilated cardiomyopathies that affect only the right heart have also been described *(Fox et al, 2000)*.

- **Restrictive forms**, of varying phenotypical expression, are characterized by a diastolic myocardial dysfunction caused by endocardial fibrosis or most often major endomyocardial fibrosis. The ori-

gin of these restrictive forms remains unclear *(Fox, 2004)*. Fibrosis may be cicatricial, secondary to an immune process, a viral infection or inflammation.

- **Intermediate cardiomyopathies** cover all myocardial modifications not strictly dilated, hypertrophic or restrictive. They include primary cardiomyopathies associating hypertrophy and dilatation as well as various infiltrations (e.g. myocardial mineralization in the event of hypervitaminosis D or hyperparathyroidism).

One study *(Gouni et al, 2006)* has been conducted on acquired feline cardiovascular diseases (primary cardiomyopathies, SH and degenerative valve lesions) diagnosed by echo Doppler at the Cardiology Unit at Alfort (UCA) between 2001 and 2005. Primary HCM was by far the most common disease among the 305 cats in the study (197/305 or 65% of cases), representing more than 85% of all primary cardiomyopathies. The second cardiomyopathy was RCM, followed by DCM and 'unclassified' cardiomyopathies, accounting for only 9%, 2% and 1.3% of all 305 cardiopathies respectively.

► Current knowledge on primary hypertrophic cardiomyopathy

> Genetic determinism

Breed predispositions to HCM have been described, especially the Maine Coon, American Shorthair and Persian. HCM on the other hand is fairly rare in the Siamese, Burmese and Abyssinian *(Kittleson et al, 1998)*. A hereditary form of the disease was recently proven in a colony of Maine Coon cats in the United States *(Meurs et al, 2005)*. The mutation is in the gene coding for myosin binding protein C (MYBPC3) and the described mode of transmission is dominant autosomal with variable expression. A different mutation of the same gene was recently found in the Ragdoll *(Meurs et al, 2007)*.

The Maine Coon is predisposed to primary hypertrophic cardiomyopathy.

© Y. Lanceau/RC/Maine Coon

Sex is also a factor in the expression of HCM. Most cats (up to 90% according to the studies) affected by HCM are toms. Age on the other hand does not appear to have so great an influence on the disease, which can affect cats aged 3 months to 17 years, with an average between 4 and 7 years *(Fox, 2000)*.

> Pathophysiological consequences

Left myocardial hypertrophy characterizing HCM mainly causes alteration of the diastolic function, at least initially, both at the very start of diastole (relaxation phase or active phase necessitating energy) and in the second and final phase of diastole (compliance phase). Due to myocardial hypertrophy and especially the fibrotic lesions frequently associated with HCM, the elasticity of the myocardium is reduced and the compliance phase is altered. Furthermore, due to coronary alterations and myocardial ischemia connected with a "relative" reduction in the coronary/myocardial mass ratio, the relaxation phase is also altered.

This diastolic myocardial dysfunction leads eventually to dilatation of the left atrium because of the problems of diastolic emptying of the atrium, followed by the development of left heart failure and finally to the terminal phase of overall heart failure. Left atrial dilatation is frequently accentuated by the presence of mitral layers that cause mitral systolic reflux, which in turn is aggravated by the abnormal movement of the mitral layers – mitral anterior systolic motion – accompanying the obstructive hypertrophies (the extremity of the mitral layers move in the left ventricular outflow tract during systole).

Recent studies using modern ultrasound imaging technology (tissue Doppler imaging (TDI)) have shown that systolic dysfunction associated with diastolic dysfunction occurs much earlier than previously thought. This may contribute to the earlier development of congestive heart failure *(Carlos Sampedrano et al, 2006; Chetboul et al, 2006a b)*.

Arterial thromboembolism, defined as the partial or total obliteration of an artery by a distally formed blood clot, constitutes another potential complication of HCM. According to a retrospective study of 100 cases of arterial thromboembolism in cats, the most common cause of this complication is HCM *(Laste & Harpster, 1995)*. The primary thrombus forms most often in the left atrium (especially during atrial dilatation), sometimes in the left ventricle and much less frequently in the right cavities unless they are dilated themselves *(Laste & Harpster, 1995; Smith et al, 2003)*. In the majority of cases (on average 90%), the embolized thrombus ends in the aortic trifurcation, causing ischemic neuropathy of the two posterior limbs. Other localizations are sometimes observed (brachial, cerebral, mesenteric, pulmonary and renal arteries). Congestive heart failure and cardiac arrhythmias *(Smith et al, 2003)* are commonly associated with arterial thromboembolism (more than 40% of cases for each).

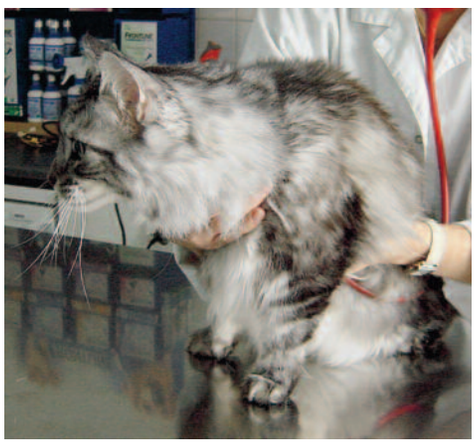


Figure 10 *- Auscultation (here a Maine Coon) is a fundamental part of the clinical cardiovascular examination, even in asymptomatic animals.*

Fatty acid metabolism

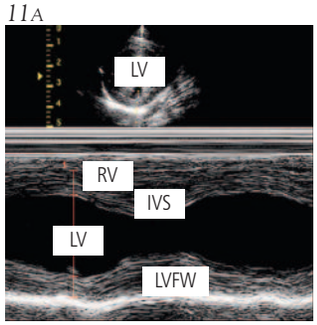
Fatty acids (FA) are the heart's main source of energy. Abnormalities in the metabolism of FA are sometimes associated with some cardiopathies, including some forms of HCM in humans *(Kelly & Strauss, 1994)*. A deficiency of CD36 has been described in human DCM. CD36 is a FA transporter that helps provide energy to the myocardium *(Okamoto et al, 1998; Watanabe et al, 1998; Nakata et al, 1999; Hirooka et al, 2000)*.

In spontaneously hypertensive rats, in which SH is associated with insulin resistance and dyslipidemia, the administration of short- and medium-chain fatty acids (SMCFA) at 21.5 g/100 g diet permits restoration of normoglycemia and limits the consequences of hyperinsulinemia and cardiac hypertrophy *(Hajri et al, 2001)*. These results suggest that insufficient provisioning of energy to the myocardial cells could contribute to the development of HCM.

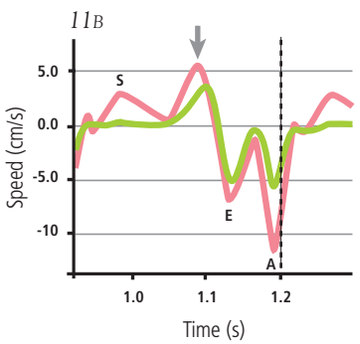
Additional studies will be needed to confirm the positive role of SMCFA in cats with HCM.

FIGURE 11 - EARLY SCREENING FOR HYPERTROPHIC CARDIOMYOPATHY IN A MAINE COON USING ECHOCARDIOGRAPHY
(Chetboul et al, 2006b).

11A



11B



The conventional echocardiograph image, especially in M mode (11A), fails to show any anomaly. Tissue Doppler imaging on the other hand (11B) (2D color mode) shows major diastolic dysfunction characterized by abnormal inversion of E and A waves (normally E/A>1), with the presence of a post-systolic contraction (marked). The left and septal myocardial walls hypertrophied one year later.
LVFW: left ventricular free wall
IVS: interventricular septum
RV: right ventricular cavity
LV: left ventricular cavity

> Diagnosis

The first step in the diagnosis of HCM is a careful clinical examination, with special attention for auscultatory abnormalities **(Figure 10)**: tachyarrhythmia, systolic murmur in the left apex, often also audible in the sternal region, systolic murmur in the left basal region during sub-valvular aortic obstruction, and a gallop rhythm. However, the absence of a heart murmur does not exclude the presence of HCM, as around 40% of cats are exempt *(Rush et al, 2002)*. Almost half of cats with HCM have congestive heart failure characterized by restrictive dyspnea (pulmonary edema and pleural effusion), ascites or much more rarely coughing. Syncope is a rare expression of the disease, found in less than 5% of cases *(Rush et al, 2002)*.

An echocardiographic examination permits the direct confirmation of myocardial hypertrophy (precise quantification and location) as well as its consequences for the cavities (dilatation of the left atrium) and hemodynamics (subvalvular aortic obstruction, pulmonary arterial hypertension). An earlier diagnosis of HCM can be obtained by tissue Doppler imaging **(Figure 11)**, which may sometimes reveal a diastolic or systo-diastolic myocardial dysfunction even before parietal hypertrophy is detectable by conventional ultrasound imaging *(Chetboul et al, 2005; Chetboul et al, 2006a, b)*. This technique can be especially useful for

animals destined for breeding or 'doubtful' cases, whose myocardial walls are at the higher end of the thickness limit.

A DNA test is now available to look for the gene mutation in the Maine Coon coding for MYBPC3. This test enables differentiation of wild homozygote animals from heterozygote animals or animals with mutated homozygotes. However, this genetic status does not predict myocardial disease (presence or absence, quantitative importance). Data collected over more than two years (unpublished UCA data) from complete clinical, ultrasound and TDI data in Maine Coons (more than 100) show that some heterozygote animals may remain asymptomatic for many years, when they undergo conventional ultrasound examinations or even normal TDI. Conversely, some rare cats genetically tested 'normal' (wild homozygotes) can present signs of HCM in an ultrasound examination and/or TDI, implying that HCM is not linked to a single gene, at least in this breed. In practice, if owners have the resources, the ideal scenario is a precautionary DNA test together with ultrasound imaging.

> Prognosis and therapeutic principles

HCM is a serious cardiopathy due to the potential complications, which include congestive heart disease (46% of cases), arterial thromboembolic accidents (16.5%) and arrhythmia potentially causing sudden death *(Rush et al, 2002)*. In a retrospective study by *Rush et al* (2002), which included 260 cats with HCM, the median survival time in animals that survived more than 24 hours was 709 days with a large variability (2-4418 days). Animals whose disease was not clinically expressed had a better survival (median of 1129 days). Conversely, those presenting with an arterial thromboembolic accident had a lower survival rate (median of 184 days). The seriousness of thromboembolic complications in the cat is shown in other studies, including a study by *Smith et al* (2003) that reported a median survival rate of 117 days, and only 77 days if associated with heart failure.

The treatment of HCM is based on the different classes of drugs **(Table 3)**: angiotensin-converting enzyme inhibitors, calcium inhibitors of the benzothiazepine family and beta-blockers. In the event of congestive heart failure, angiotensin-converting enzyme inhibitors will be preferred due to preliminary results of the study by *Fox et al* (Multicenter Feline Chronic Failure Study) *(Fox, 2003)*. Studies are however necessary to improve understanding of the comparative position of each of these classes in the treatment of feline HCM.

► Taurine deficiency cardiomyopathy

Until the end of the 1980s, dilated cardiomyopathy (DCM) was more common than HCM in the feline population *(Fox, 1999)*. Improved knowledge of the taurine requirements of cats has since reduced its incidence considerably.

Taurine was discovered in 1827 as a constituent of ox bile *(Bos taurus)*, which is where the name is derived from. It is a sulfur-containing amino acid.

$$(H^{+}_{3}\,N - CH_2 - CH_2 - SO^{-}_{3})$$

Taurine cannot be linked by peptide bonds and thus cannot be part of a protein. In its free form, it is mainly found in the striated muscles (including the myocardium), the central nervous system, the retina and the liver *(Zelikovic et al, 1989)*. Taurine plays a membrane protection role in the myocardium and regulates contractile function. An inadequate taurine intake can thus cause myocardial dysfunction, which in turn may be complicated by congestive heart failure *(Pion et al, 1992a,b)*.

Table 3 - Categories of therapeutic agents used to treat feline hypertrophic cardiomyopathy

Drugs	Properties	Dose, administration method
ACEI (enalapril, benazepril, ramipril, imidapril)	- Reduction of pre- and post-load resulting in lessening of symptoms of cardiac failure - Anti-ischemic effects via reduction of the post-load (so reduction of systolic constraints of the myocardium) and coronary vasodilatation - Anti-hypertrophy effects and reduction of remodeling	- Benazepril (with amylodipine in the cat with CKD): 0.5 mg/kg (SID) PO (palatable form available) - Imidapril, only ACEI in liquid form: 0.5 mg/kg (SID) PO or directly in the mouth or in the food (very advantageous in cats). Long-term innocuousness documented - Enalapril: 0.5 mg/kg SID to BID PO - Ramipril: 0.125 mg/kg (up to 0.25 mg/kg) SID PO
Calcium inhibitors of the benzothiazepine family (diltiazem)	- Direct improvement in the diastolic function - Moderate chronotrope <0 effect, beneficial for diastolic alteration and ischemia - Anti-ischemic effects via coronary vasodilatation and drop in myocardium's O_2 consumption - Anti-hypertrophic effects - Possible drop in subaortic gradient	Reconditioned diltiazem: - short-action form: 1.75-2.5 mg/kg TID or 7.5 mg/cat TID PO - slow-release form: 5-10 mg/kg/day (SID) PO
β-blockers (atenolol, propranolol)	- Indirect beneficial effect on diastolic alteration and ischemia, mainly via increase in ventricular and coronary refilling time (chronotrope <0) - Indicated in the event of MCH with major tachyarrhythmia or major systolic subaortic gradient - Propranolol not recommended in the event of heart failure due to inhibition of β2 receptors	- Propranolol: 0.1-1 mg/kg BID to TID PO or 2.5-5 mg/cat/day BID to TID (starting with low doses); - Atenolol: 0.2-1 mg/kg SID to BID PO or 6.25-12.5 mg/cat/day SID to BID (starting with low doses).

The use of these agents in cats can be restricted according to the licence applicable in each country.
ACEI: angiotensin-converting enzyme inhibitors

> Genetic determinism

Taurine is primarily synthesized in the liver from sulfur-containing amino acids, methionine and cysteine **(Figure 12)**, and the action of several enzymes, including cysteine dioxygenase and cysteine sulphinic acid decarboxylase. In cats, the biosynthesis of taurine from its precursors is inadequate to cover the needs, as the activity of the hepatic enzymes is very low (especially compared with dogs). A dietary intake of taurine is therefore essential.

Moreover cats waste large amounts of taurine. Indeed, as dogs, they use only taurine for the conjugation of bile acids, whereas humans and rats can also use glycine *(Morris et al, 1987)*. This represents a continual loss of taurine, as a substantial part is not recovered by the entero-hepatic circulation and is lost in the feces **(Figure 13)**.

Why has the cat lost its ability to synthesize a nutrient as essential as taurine? Taurine is one of the most abundant amino acids in animal tissues, so cats are not at risk of taurine deficiency when on their natural diet. Under those circumstances producing taurine is a waste of energy whereas the deamination and desulfurization of cysteine is an alternative metabolic pathway that allows cats to produce energy rather than taurine from sulfur amino acid catabolism.

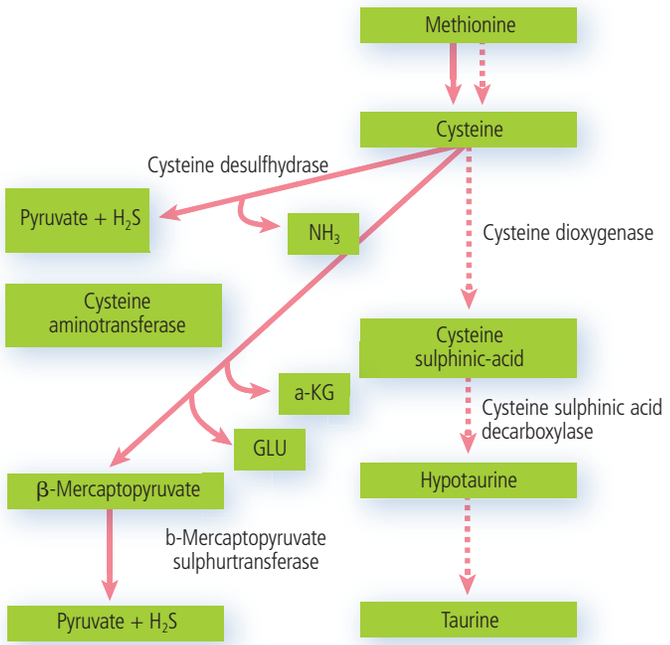
> Pathophysiological consequences of taurine deficiency

When a cat is deficient, the body's taurine concentrations fall in a few days to a few months depending on the tissue: the plasma is affected first, followed by the whole blood, then the muscles and lastly the retina and the nervous tissue *(Pacioretty et al, 2001)*.

The requirement of taurine in cats is a unique example of a nutritional need that varies according to the influence of the diet on the intestinal flora *(Backus et al, 2002)*. The measurement of breath hydrogen in cats (a measure of the level of intestinal fermentations) shows that wet food favors the proliferation of a flora that consumes larger quantities of taurine than the flora associated with dry expanded kibbles *(Morris et al, 1994; Backus et al, 1994; Kim et al, 1996a,b)*. Taurine losses are linked to the level of protein in the diet as well as the heat processing applied in canning. This explains why wet food requires higher levels of taurine supplementation (1.7 g/kg DMB) compared to dry food (1 g/kg DMB).

Figure 12 - General pathway of taurine synthesis in the liver from sulphur amino acids

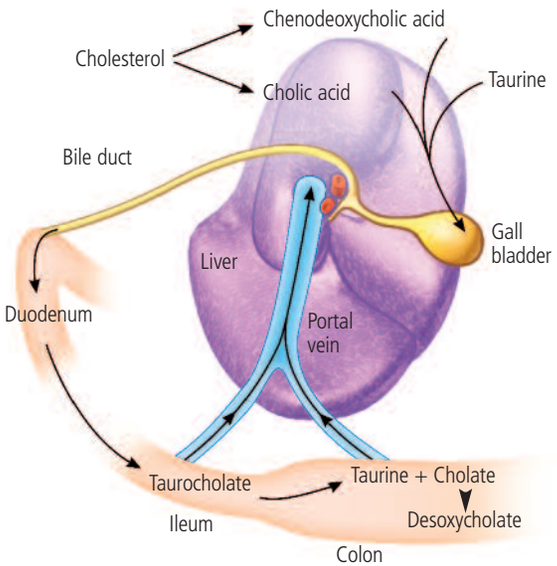
From Morris, 2002



The activities of the enzymes cysteine dioxygenase and cysteinesulphinic acid decarboxylase are low in cats, which severely restricts synthesis of taurine. Cysteine is metabolized to pyruvate, which provides an energy substrate.

Taurine deficiency has been shown to be the main cause of DCM in cats *(Pion et al, 1987)*. If identified in time, this disease can be reversed by the oral administration of taurine. Deficient cats present anatomical abnormalities of the heart but there are no histological lesions that would suggest an organic disease of the cardiac tissue. The pathophysiological mechanisms by which taurine deficiency affects cardiac function remain poorly understood. Taurine affects ionic flow of calcium and sodium in the myocardium and thus plays a role in regulating systolic and diastolic myocardial activity *(Novotny et al, 1991)*. The interaction between taurine and calcium (characterized by the spontaneous release of calcium by the reticulum and increased sensitivity of the myofilaments to calcium) contributes to its positive inotrope effects.

Figure 13 - Enterohepatic circulation of taurine



> Diagnosis

The role of taurine in feline DCM has been known for twenty years *(Pion et al, 1987)*. Clinical signs vary widely depending on the individual. Experimental taurine deficiency often produces the simultaneous appearance of irreversible central retinal degeneration **(Figure 14)** (within six months and inducing total blindness within less than two years) and DCM of varying degrees within two to four years. Not all cats fed taurine deficient diets will develop ultrasonographic or clinical signs of DCM during this time frame.

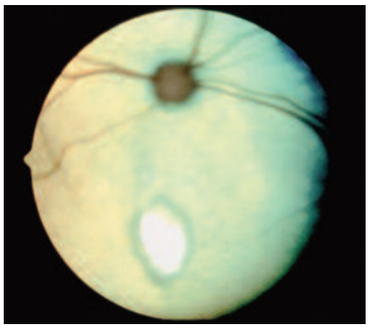


Figure 14 *- Central retinal degeneration in a cat suffering from taurine deficiency.*

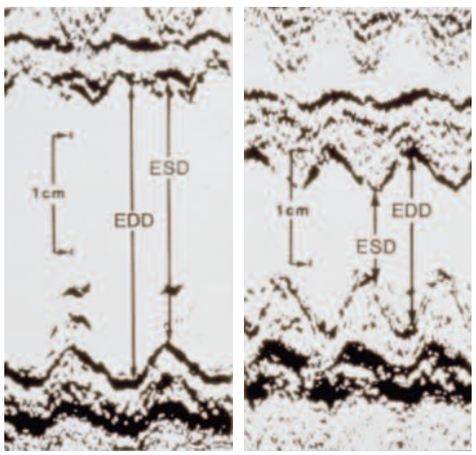


Figure 15 - Echocardiograph of taurine-deficiency associated dilated cardiomyopathy (time-movement mode) before (on the left) and after (on the right) taurine supplementation.
In this patient, the echocardiography shows a reduced shortening fraction and a dilatation of the left cavities (left picture). These alterations are reversible after taurine administration (right picture).

ESD: end systolic diameter of the left ventricle
EDD: end diastolic diameter of the left ventricle

Taurine deficiency also affects reproduction (reduced fertility in both males and females, fetal resorption, abortions and malformations of newborn kittens) as well as poor growth.

When taurine-deficiency DCM develops, owners are often alerted by the sudden appearance of dyspnea caused by the development of congestive heart failure. Echocardiography shows a reduced shortening fraction **(Figure 15)** as well as an increased systolic diameter of the left ventricle. Later on a left ventricular dilatation that is both systolic and diastolic, associated with thinning of the cardiac walls occurs. In well-developed forms, all four heart chambers are dilated.

In healthy cats, the plasma taurine concentration is greater than 50 nmol/mL *(Pacioretty et al, 2001)* but the plasma concentration reflects recent taurine intake only. It is affected by fasting and does not provide any information on the body's reserves. The result may be artificially high in cats with systemic thromboembolism. As white blood cells and platelets contains high levels of taurine, plasma concentration will be affected by hemolysis or poor separation of the buffy coat.

Establishing a conclusive diagnosis of taurine deficiency requires measurement of the whole blood taurine level because it better reflects taurine concentrations in the myocardium and skeletal muscles. In healthy cats, the whole blood taurine concentration should be higher than 250 nmol/mL *(Pacioretty et al, 2001)*. If lower, taurine deficiency is confirmed.

> Treatment

In addition to feeding a diet containing adequate taurine, it is generally recommended to supplement the cat with 250 mg of taurine twice daily *(Freeman, 2000)*. If the cat's heart failure can be controlled initially the prognosis is good and clinical signs should clearly improve within one to two weeks. This delay corresponds to the recovery of a normal plasma concentration. Improvements in radiographic and echocardiographic signs will take at least 3-6 weeks. Even if clinical signs improve rapidly supplementation should be pursued for several months.

Some cases of taurine-deficiency associated DCM do not respond to the administration of taurine. The reason for this remains unclear. Nevertheless, taurine supplementation is still recommended for these 'resistant' animals at 250 mg twice daily *(Freeman, 2000)*.

> Prevention

Prior to 1987 the taurine levels found in commercial wet cat foods were commonly inadequate to maintain plasma and whole blood concentrations. As the role of taurine in the pathogenesis of DCM has been better understood, manufacturers have increased taurine levels in their diets and the incidence of feline DCM is now very low *(Pion et al, 1992a,b)*.

To maintain plasma and whole blood taurine concentrations within the physiological range, feline dry expanded diets must contain at least 1 g taurine/kg DMB and wet diets at least 1.7 g/kg DMB *(NRC 2006)*. Taurine supplementation is very safe and no harmful effect on health has been found, even at doses in excess of 10 g/kg DMB in diets with energy concentrations around 4500 kcal/kg *(NRC, 2006)*.

3 - Nutritional recommendations for the management of feline cardiopathy

While little information is available in the literature on the specific nutritional requirements of cats with cardiac diseases, several general recommendations can be provided by extrapolating from other species and considering the metabolic peculiarities of cats.

► Equate energy density of the diet to the cat's body condition

The body condition score of cats with cardiopathy is highly variable. Maintaining optimal condition in these patients is one of the major goals of dietary treatment.

> Cachexia

Severe weight loss and muscle wasting is less common in cats than in dogs with cardiopathy. *(Freeman, 2000)*. "Cardiac cachexia" does not generally appear until advanced stages of heart failure and can be associated with very rapid muscle atrophy. The myocardium is not protected from general protein catabolism, in addition to lower immune defenses and generalized weakness, "cardiac cachexia" may also contribute to the progression of heart failure.

"Cardiac cachexia" is multifactorial: anorexia,increased energy requirements, metabolic alterations, poor blood perfusion of the tissues, as well as complication of renal failure, either primary or secondary to cardiovascular disease all contribute **(Figure 16)**.

Spontaneous food consumption must thus be encouraged in cats with cachexia, by feeding palatable diets (see below recommendations on protein and sodium levels), presenting frequent small meals and warming wet foods to name a few. In order to reduce the volume of the meals, the energy density of the diet should be increased (e.g. higher fat and lower fiber levels).

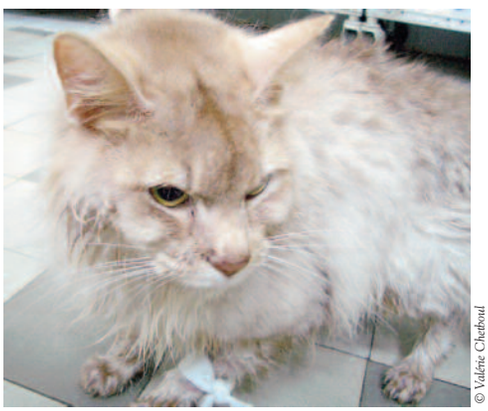
> Overweight cats

Around 35% of the cats presented to veterinarians are overweight *(Lund et al, 2006)*. Whatever the species, obesity is associated with an increased cardiovascular risk. Caloric restriction to induce weight loss in obese cardiac cats is desirable and more so if the cat is exercise intolerant.

Studies in rodents have found that long term energy restriction reduces oxidative stress and protects against several degenerative diseases including cardiomyopathies *(Kemi et al, 2000; Guo et al, 2002)*. To our knowledge, such a study has not been conducted on cats.

► Provide protein and amino acids to fight cachexia and promote food intake

It has long been recommended that animals with heart failure should be fed diets with reduced protein levels to protect renal function, as renal and cardiac diseases are often linked *(McClellan et al, 2004; Nicolle et al, 2007)*. Those recommendations are now clearly outdated (see chapter 7). Moreover cats, because of their true carnivorous nature, have high protein requirements and their metabolism cannot adapt to low protein intakes. Restricting protein simply increases the risk of "cardiac cachexia" and exercise intolerance. Food for cats with cardiac disease must therefore contain at least the minimum protein requirement (60-70 g protein/1000 kcal) *(Freeman, 2002)*.



© Valérie Chetboul

Figure 16 - Cachexic cat with chronic kidney disease and systemic arterial hypertension.
(systolic BP = 170 mmHg)
Cats with cardiac disease have many reasons for not eating. Aside of the weaknesses associated to the disease, drugs prescribed in this condition may induce nausea and the dietary restrictions commonly found in therapeutic diets (e.g. low protein and low sodium) may produce a diet that is not very palatable.

> Taurine supplementation

The essential requirement for taurine to insure normal cardiac as well as other functions in cats has been discussed above.

Studies have shown that dietary taurine supplementation increases the taurine concentration in the myocardium of both healthy cats and cats with heart failure *(Fox & Sturman, 1992)*. Bearing in mind taurine's protective and positive inotrope roles with respect to cardiac function, taurine supplementation may thus be encouraged, whatever the type of cardiopathy. The recommendation is in the range of 625 mg/1000 kcal *(Freeman, 2002)*.

There is a reciprocal relationship between taurine and potassium requirements. Taurine slows the loss of potassium through the cell, while potassium prevents the loss of taurine by the myocardium. Taurine supplementation (> 625 mg/1000 kcal) could therefore be beneficial to cats with potassium deficiency, e.g. those with impaired renal function *(Dow et al, 1992)*.

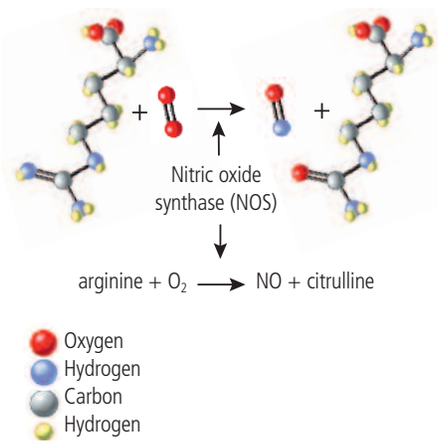
> Dietary arginine

Contrary to other species, cats are unable to synthesize arginine. Arginine must therefore be provided by the diet. Furthermore, the cat's high-protein requirement necessitates high arginine requirements due to its involvement in the urea cycle for ammonia detoxification.

Arginine is a nitric oxide (NO) precursor **(Figure 17)**. NO is produced by the vascular endothelium and acts as a blood vessel myorelaxant. NO thus helps regulate blood pressure. In humans and rodents, arginine supplementation has been shown to increase NO production *(Lerman et al, 1998)*.

NO also has an antithrombotic effect *(Moncada et al, 1991)*. A study reported that cats with HCM and associated thromboembolism presented with lower levels of circulating arginine than healthy cats or cats with an uncomplicated cardiomyopathy *(McMichael et al, 2000)*. Arginine supplementation may therefore have beneficial effects in this condition although this has yet to be proven. The NRC recommends a level of at least 1.93 g/1000 kcal in healthy cats. The optimum range required in patients with heart disease has yet to be determined.

FIGURE 17 - ORIGIN OF NITRIC OXIDE



The reaction is catalyzed by the enzyme, nitric oxide synthase (NOS). There are three forms of NOS:
Endothelial NOS (eNOS): *eNOS is required for maintenance of normal vascular tone*
Neuronal NOS (nNOS): *eNOS and nNOS are constitutive forms and are always produced in low levels*
Inducible NOS (iNOS): *iNOS is inducible by a variety of inflammatory mediators including the cytokines, tumor necrosis factor (TNF), and interleukin-1 (IL-1), and free radicals.*

► Benefits of long-chain omega-3 fatty acids (EPA/DHA)

The composition of dietary fats (especially the ratio of unsaturated omega-6 to omega-3 fatty acids) influences membrane fluidity as well as other hemodynamic factors. In cardiology, many studies have been conducted on the potential role of omega-3 fatty acids. In humans and dogs, much lower plasma concentrations of eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-6) have been shown, regardless of the underlying cardiac disease *(Freeman et al, 1998)*. While few studies have been conducted on cats, the properties of omega-3 fatty acids deserve some attention.

Linseed oil contains high levels of α-linolenic acid but this is only a precursor of EPA and DHA, and the ability of cats to convert α-linolenic acid to EPA/DHA is very limited **(Figure 18)**. Only fish oils are good sources of EPA and DHA. Cod liver oil should not be used due to its high levels in vitamins A and D.

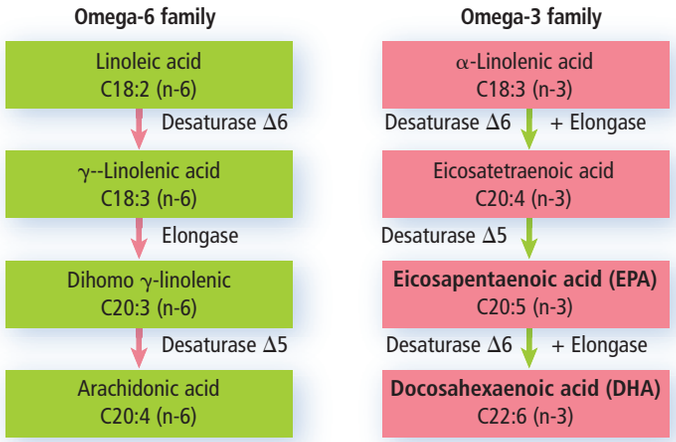
On usual diets, cell membranes contain very low concentrations of long chain omega-3 fatty acids, but these can be increased with a food that is supplemented with fish oil. For example, with a supplementation of 180 mg DHA and 117 mg EPA/cat/day over a 4 week period, the level of EPA in the plasma phospholipids increases by 70% while the DHA levels increased by a factor of 3.4 *(Filburn & Griffin, 2005)*. Dietary enrichment with EPA and DHA can

facilitate membrane peroxidation by free radicals *(Meydani et al, 1991)* but this adverse phenomena can be minimized by adjusting the levels of dietary vitamin E.

> Antithrombotic action

Long chain omega-3 fatty acids are known for their antithrombotic activity. This could be highly beneficial for cats, a species in which platelet activation is easily triggered *(Welles et al, 1994)*. Increasing the omega-3 fatty acids (1.03 g/kg diet vs 0.07 g/kg in the control diet) and decreasing the omega-6 fatty acids (1.20 g/kg vs 1.34 g/kg in the control diet) reduces platelet aggregation and activation in healthy cats by day 112 *(Saker et al, 1998)*. This benefit has yet to be confirmed in cats with HCM.

FIGURE 18 - GENERAL PATHWAY OF LONG CHAIN OMEGA-3 AND OMEGA-6 FATTY ACIDS SYNTHESIS



Cats present an increased risk for PUFAs C_{20} deficiency due to a low activity of the desaturase Δ6 if the diet does not contain enough of these fatty acids.

> Anti-inflammatory effect

In rodents, increasing the level of long chain omega-3 fatty acids in the fat content of food reduces the production of 2 and 4 series eicosanoids from arachidonic acid, which have a pro-inflammatory action *(Broughton & Wade, 2001)*. On the other hand the production of anti-inflammatory 5 series leukotrienes (LT) is stimulated.

In humans with heart failure, long chain omega-3 fatty acids reduce the production of "inflammatory cytokines", TNFα and IL-1 *(Levine et al, 1990)*. These cytokines contribute to cardiac cachexia by increasing energy requirement and muscle catabolism *(Mahoney & Tisdale, 1988)*. Moreover, by regulating the expression of proteosomes, EPA inhibits the loss of lean mass *(Whitehouse et al, 2001)*.

In dogs with cardiac disease, supplementation of EPA (27 mg/kg weight/day) and DHA (18 mg/kg weight/day) improves dietary consumption, reduces the production of inflammatory cytokines and so reduces cachexia *(Freeman et al, 1998)*. To our knowledge, no information with respect to cats with cardiac disease is available at this time.

> Anti-arrhythmogenic effect

Several studies have shown a benefit of EPA and DHA in the management of cardiac arrhythmia in rodents and dogs *(Kang & Leaf, 1996; Charnock, 2000; Smith et al, 2007)*. The mode of action relies on the ability of long chain omega-3 fatty acids to modulate the sodium and calcium flows inside the myocytes *(Gerbi et al, 1997)*.

Arrhythmia is often one of the first signs of feline HCM. Based on observations in other species EPA and DHA supplementation could thus be recommended at early stages of cardiopathy but, to our knowledge, no information on this subject is available at this time.

> Regulating endothelial function

EPA and DHA are involved in the regulation of endothelial function, probably by modulating NO production *(Kristensen et al, 2001)*. In humans, supplementation induces a vasodilatation effect *(Kenny et al, 1992)*. Very high doses (>3 g/day) even led to a fall in BP in hypertensive individuals *(Kris-Etherton et al, 2002)*. Studies in cats with cardiac disease are thus needed.

> Omega-3 fatty acids, ratio versus absolute intake and doses

There is an ongoing debate about whether the dose of omega-3 fatty acids or rather the omega-6 to omega-3 ratio is most important to producing the beneficial effects of omega-3 fatty acids *(NRC, 2006)*. Some results suggest that the total dose of omega-3 is important, although the ratio (n-6/n-3) must also be kept as low as possible to promote the anti-inflammatory effect of omega-3 fatty acids *(Grimm et al, 2002)*. In light of the results obtained in humans, it appears reasonable to recommend tripling the traditional recommended quantity of omega-3 fatty acids in healthy cats to at least 0.06 g/day, corresponding to a concentration in the food of 0.10-0.35 g/1000 kcal *(Freeman, 2002)*.

► Monitor mineral balance

> Sodium and chloride

It is usually recommended to feed cardiac patients a very low sodium diet. There is evidence in dogs, however, that this restriction would not be beneficial especially at early stages of heart disease. Indeed, low Na diets will activate the renin-angiotensin-aldosterone system, while the purpose of medical treatments for heart disease is to inhibit it. Sodium restriction (up to 0.5 g/1000 kcal) is thus only justified when an advanced stage of congestive heart failure is reached.

Studies on the influence of sodium in cardiac patients use salt (NaCl) as the source of dietary sodium. It is therefore impossible to differentiate between the respective influences of those two elements. Some data in rats indicate that chloride can also influence plasma renin activity *(Kotchen et al, 1980)*. Therefore, current knowledge does not go further than recommending observance of a moderate dietary chloride level.

> Potassium

Potassium is an intracellular electrolyte whose plasma concentration must be monitored in cardiac animals undergoing medical treatment (although the plasma level is not a good reflection of body reserves). Hypokalemia can occur when diuretics are prescribed (e.g. furosemide) and in the event of CKD. The symptoms associated with hypokalemia are muscle weakness and bradycardia *(Linder, 1991)*. Hypokalemia will also potentialize digoxin toxicity. As mentioned before, there is a reciprocal relationship between taurine and potassium. Thus, it appears sensible to advise both potassium and taurine supplementation in cats with hypokalemic cardiopathy.

Angiotensin-converting enzyme inhibitors (ACEI) are often used in the management of cardiopathy in both humans and animals. In theory they could promote hyperkalemia by stimulating potassium renal reabsorption *(Lefebvre et al, 2007)*. In practice, hyperkalemia, is minimized by the prescription of furosemide and appears negligible in animals *(Lefebvre et al, 2007)*. Extended administration of ACEI has not been associated with hyperkalemia in dogs *(Pouchelon et al, 2004)*. Dietary potassium levels in cats with cardiac disease should thus be similar to those for adult maintenance (1.5-2 g/1000 kcal) even when treated with ACEI.

> Magnesium

Magnesium is a cofactor in hundreds of enzymatic reactions involving carbohydrate and lipid metabolism. The activity of the heart muscle is dependant on the right balance between magnesium and calcium. Magnesium therefore plays an important role in normal cardiac function and magnesium deficiency is implicated in many cardiopathies across species *(Rush et al, 2000; Gottlieb et al, 1990)*.

Diuretics may promote urinary losses of magnesium, and thus the risks of low magnesium status causing arrhythmias and reduced cardiac output. Plasma magnesium is a poor indicator of body reserves and hypomagnesemia is rare in practice *(Freeman, 2000)*. A study on hospitalized cats found no significant alteration of magnesium status associated with cardiopathies *(Toll et al, 2002)*. Magnesium supplementation in HCM cats did not result in clear clinical benefit *(Freeman et al, 1997)*. There is thus no evidence to date to recommend dietary magnesium levels above those necessary for adult maintenance (0.12-0.25 g/1000 kcal) for cats with cardiac disease.

> Phosphorus-calcium balance

Due to the common association between cardiopathy and renal disease *(McClellan et al, 2004; Nicolle et al, 2007)*, dietary phosphorus levels should be limited to minimize secondary hyperparathyroidism (see chapter 7).

► Reverse any deficiencies

> B group vitamins

Cats naturally have high B vitamin requirements *(Burger, 1993)*. B vitamin deficiencies **(Table 4)** in cardiac patients result from anorexia and increased urinary losses secondary to the use of diuretics *(Rieck et al, 1999)*.

Plasma vitamin B_6 and B_{12} concentrations are significantly lower in cats with HCM than in healthy cats *(McMichael et al, 2000)*. A correlation was found between plasma B_6, B_{12} and folic acid concentrations and the size of the left atrium. The role of these vitamins in the development of HCM (primary or secondary) has yet to be clarified, however.

Based on the evidence, cats with cardiac disease probably have higher B vitamin requirements than healthy cats. Diet for cats with cardiac disease should thus contain two to three times the levels recommended for adult maintenance.

TABLE 4 - B GROUP VITAMINS

Name	Abbreviations
Thiamin	B_1
Riboflavin	B_2
Pantothenic acid	B_5
Pyridoxine	B_6
Biotin	B_8
Folic acid	B_9
Cobalamin	B_{12}
Niacin	PP
Choline	Ch

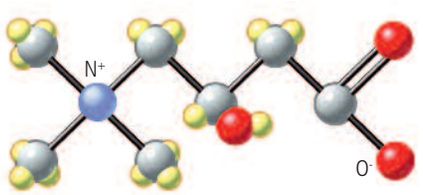
> L-carnitine

L-carnitine is a quaternary amine synthesized in the liver from lysine and methionine **(Figure 19)**. It is present in all striated muscles, but the myocardium contains 95% of the body reserves. Its main role is transporting long-chain fatty acids into the mitochondria, where they are oxidized to produce energy.

DCM associated with carnitine deficiency has been described in humans and some dog breeds such as the Boxer, Doberman and Cocker Spaniel *(Brevetti et al, 1991; Helton et al, 2000; Keen et al, 1991)*.

It has been suggested that HCM could be associated with abnormal fatty acid metabolism. Therefore, L-carnitine could be beneficial in avoiding the intracellular accumulation of fatty acids in the myocardium *(Lango et al, 2001)*. In humans, L-carnitine supplementation (3-4 g/day) in combination with lower long-chain fatty acid intakes improves the clinical status of HCM patients *(Bautista et al, 1990)*. This has yet to be demonstrated in cats.

FIGURE 19 - CARNITINE MOLECULE

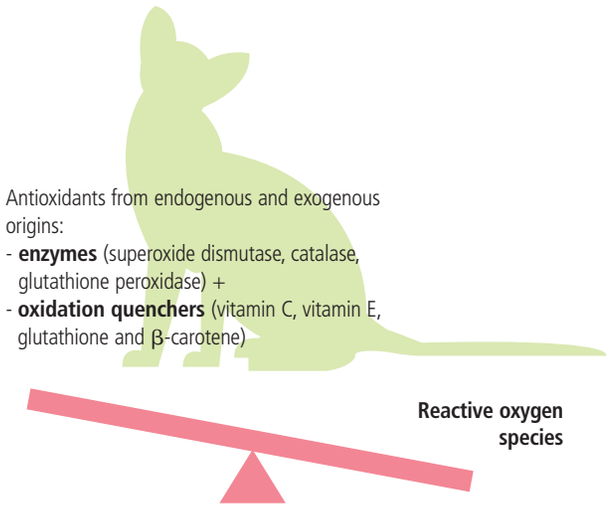


Discovered in 1905, L-carnitine is synthesized from lysine and methionine, if vitamin C and pyridoxine (vitamin B_6) are present. It is a quaternary amine that acts as a water soluble vitamin. Carnitine can be synthesized in D or L forms, but L-carnitine is the only one of relevance for cats with cardiac disease.

► To strengthen the antioxidant defenses

The role of antioxidants in the prevention and treatment of human heart diseases has been extensively studied. Free radicals are the by-products of oxygen metabolism, against which the body defends itself by producing endogenous antioxidants. An imbalance between oxidants and antioxidants (oxidative stress) may increase the risk of cardiopathy **(Figure 20)**. Antioxidants can also be provided in the diet. The main antioxidants are enzymes (superoxide dismutase and its cofactor copper, catalase, as well as glutathione peroxidase and its cofactor selenium) and free radical

Figure 20 - Origin of oxidative stress



Oxidative stress occurs when there is an imbalance between the production of free radicals and antioxidant defenses.

scavengers (vitamin E, vitamin C, glutathione, taurine, carotenoid pigments). Current research is also focused on new classes of antioxidant such as polyphenols.

Some antioxidants will now be reviewed but it is important to remember that synergy can be observed by using a mixture of antioxidants. Different antioxidants will also be located in different areas of the cell (membrane, intracellular organelles and nucleus).

> Vitamin E

The antioxidant effect of vitamin E (α-tocopherol) has been the subject of studies for many years. In the cardiovascular domain many studies show its beneficial role, especially via two particular effects:
- It maintains endothelial tissue relaxation through NO *(Plotnick et al, 1997)*
- It reduces platelet adhesion and aggregation *(Mower & Steiner, 1982; Calzada et al, 1997)*. Its role is especially clear in human atheroma patients.

An imbalance between oxidant and antioxidant production has been shown in DCM dogs with heart failure *(Freeman et al, 1999)*. As the cardiopathy develops, the animals increasingly produce quantities of oxidants (malondialdehyde is used as a marker for lipid peroxidation) and present lower levels of vitamin E *(Freeman et al, 1999)*. Oxidative stress is thus said to play a role in the development of DCM. Similar observations were made within the framework of a recent study of dogs with heart failure secondary to degenerative valve disease or DCM.

In the light of the data obtained on humans and dogs, vitamin E supplementation is not expected to have any negative effects in cats with cardiac disease. In fact, such supplementation is expected to be beneficial, although this is yet to be confirmed as no studies have been conducted in this species. The optimal supplementation level depends on the quantity of unsaturated fatty acids in the food.

> Vitamin C

Vitamin C is water-soluble. In addition to preventing oxidation of LDL lipoprotein, it is known to facilitate the regeneration of vitamin E. Studies on humans show that a single dose of vitamin C (2000 mg) or administration of 500 mg/day for four weeks promotes vasodilatation in coronary disease patients *(Kugiyama et al, 1998)*. However, no specific data are available for cats and unlike humans, cats can synthetize vitamin C.

> Copper

In cats deficient in copper and genetically sensitive to HCM, a high saturated fat content compared with omega-3 fatty acids (2:1) exacerbates the cardiac anomalies induced by copper deficiency *(Jalili et al, 1995)*. This suggests that copper could be involved in HCM, although there is nothing to warrant changing the usual recommendations for copper (1.25-7 mg/1000 kcal in the cat). Furthermore, excess copper can act as a pro-oxidant.

> Coenzyme Q10 (CoQ10)

Coenzyme Q10 (also known as ubiquinone) is an antioxidant that is naturally present in the mitochondria. It is found throughout the electron transport chain that produces energy, improving energy production by shunting defective elements from the respiratory chain *(Rosenfeldt et al, 2002)*. Some studies on humans show its potential benefit in the event of cardiovascular pathology.

> Flavonoids

Flavonoids are substances belonging to the family of plant-extracted polyphenols. Epidemiological studies on humans show an inverse relationship between the consumption of fruits and vegetables, which are rich in flavonoids, and cardiovascular risk *(Steinmetz & Potter, 1996)*.

A very high number of in vivo and in vitro cardiovascular pathology studies show the benefit of consuming diverse sources of flavonoids: black and green tea *(Duffy et al, 2001a,b; Geleijnse et al, 2002)*, grape juice *(Keevil et al, 2000)* and red wine *(Rimm et al, 1996; Rein et al, 2000a)*.

Flavonoids have several modes of action. In addition to their antioxidant action, they have an antithrombotic action *(Rein et al, 2000b)* and, by increasing endothelial production of NO, a vasodilative action *(Karim et al, 2000)*. Their beneficial role in cats with cardiac disease is yet to be determined.

> Selenium

Selenium is an essential trace element that is an integral part of glutathione peroxidase, an antioxidant enzyme. It works in synergy with vitamin E. Selenium intake must be carefully dosed as tolerable minimum and maximum levels are fairly close to each other. An adequate intake of selenium goes hand in hand with the fulfillment of glutamate, cysteine and glycine requirements; these three compounds are necessary for glutathione synthesis.

> Taurine

Besides its major role in cardiac inotropism, taurine also has an antioxidant action that protects the myocardium membrane.

Conclusion

The first dietary goal in the event of cardiac disease in cats is to combat the occurrence of cachexia, which can in turn contribute to the progression of the disease. This can be achieved in several ways: increasing level of dietary protein, increasing levels of omega-3 fatty acids and promoting food intake.

Taurine supplementation is necessary in the event of DCM (especially taurine-deficiency DCM). It is also indicated in the event of hypokalemia.

Low-sodium foods should be restricted to symptomatic animals (with signs of heart failure). When used too early in the stage of the disease, sodium restriction may induce undesired side-effects, such as stimulation of the renin-angiotensin-aldosterone system.

Unfortunately, no data is available concerning the benefits of long chain omega-3 fatty acids in the feline cardiac patient. Their antithrombotic and anti-arrhythmic roles as demonstrated in other species would be very beneficial in cats. The same can be said of antioxidants.

Frequently asked questions about the influence of diet on cardiovascular diseases

Q	A
My cat suffers from compensated hypertrophic cardiomyopathy. Should its diet have a low sodium content?	The traditional recommendation for cats with cardiac disease is a diet that is very low in sodium. The current data, on the other hand, suggest that such a restriction will be beneficial only when the heart disease is decompensated. Too low a sodium content stimulates the renin-angiotensin-aldosterone system (RAAS), which can have harmful effects on the cat's heart and renal functions.
My cat suffers from decompensated hypertrophic cardiomyopathy (history of pulmonary edema). Should its diet have a low sodium content different than for compensated hypertrophic cardiomyopathy?	Sodium restriction (up to 0.5 g/1000 kcal) is justified when the cardiopathy has reached the stage of congestive heart failure. Some results obtained in rats suggest that insufficient intake of energy by the cells may contribute to the development of hypertrophic cardiomyopathy. The administration of short- and medium-chain fatty acids is said to limit the consequences of cardiac hypertrophy. The benefit for cats has yet to be evaluated.
My cat suffers from systemic arterial hypertension. Should its diet have a low sodium content?	Large sodium intake (> 2 g/1000 kcal) must be avoided but clinical studies fail to determine whether a low-sodium diet facilitates medical treatment to control arterial pressure. Major sodium restriction is not recommended in hypertensive cats. Excessive restriction will stimulate the renin-angiotensin-aldosterone system (RAAS), a classic pressure regulator, and promote hypokalemia by increasing potassium loss through the urine.
My cat suffers from systemic arterial hypertension secondary to chronic kidney disease. Is a food specifically formulated for cats with chronic kidney disease indicated or are additional nutritional measures needed?	Diets for cats with chronic kidney disease contain low or moderate levels of sodium (0.5-1 g/1000 kcal) (see chapter 7). In cats with chronic kidney disease showing a clear increase in arterial pressure, restricting the consumption of sodium chloride is not sufficient to prevent arterial hypertension, which must be treated medically. Other nutrients that may help control arterial pressure include: - Arginine: precursor of nitric oxide (NO•), which helps regulate arterial pressure - Omega-3 fatty acids, EPA and DHA: in humans, very high doses (>3 g/day) produce a vasodilator effect and a reduction in arterial pressure. This effect has not been established in cats.
My cat suffers from decompensated hypertrophic cardiomyopathy and chronic kidney disease. What type of food is best recommended?	Food with a sodium content of around 0.5 g/1000 kcal is recommended for cats with chronic kidney disease. Reducing the phosphorus content in this food will slow down the progression of the renal disease. Furthermore, foods formulated for cats with chronic kidney disease are enriched in omega-3 fatty acids, which is also beneficial in the event of cardiopathy.
My cat is obese and suffers from hypertrophic cardiomyopathy. What type of food should be prescribed?	The priority is implementing medical treatment and a diet that best supports cardiac function. Restricting energy intake will then be desirable, as obesity is associated with increased cardiovascular risk. Some studies on rodents show that dietary restriction reduces the level of oxidative stress and protects against some degenerative diseases, especially cardiomyopathies. This has not been studied in cats.

Q	A
When should taurine deficiency be suspected during dilated cardiomyopathy?	Taurine deficiency in cats has been uncommon since the end of the 1980s, because commercial foods are now supplemented with taurine. This deficiency may however be suspected if the cat is fed a home-prepared ration, a vegetarian diet or poor quality foods. Measuring the taurine level in the whole blood (>250 nmol/mL) will help establish a definitive diagnosis. As central retinal degeneration is irreversible, it can be used to determine whether the cat has been fed with a taurine-deficient food for several months during the course of its life, but not whether its current diet is taurine-deficient.
Should cats with cardiac disease be prescribed potassium supplements?	Hypokalemia may appear with the use of diuretics (e.g. furosemide). Hypokalemia also occurs in 20% of cats with chronic kidney disease, and it increases the risk of hypertension (see chapter 7). Hypokalemia potentializes the toxicity of digoxin as well. In cardiopathic cats, the correction of hypokalemia through the supplementation of potassium is therefore strongly recommended. Supplementation, on the other hand, is not necessary in the absence of hypokalemia. In cats treated with an angiotensin converting enzyme inhibitor, which stimulates reabsorption of potassium by the kidneys, the potassium content of the food must not be different from that of a maintenance food (1.5-2 g/1000 kcal).

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Focus on:

Taurine

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In cats, taurine deficiency leads to central retinal degeneration within a few months.

Taurine is a sulfur-containing amino acid ($H_2N - CH_2 - CH_2 - SO_3H$). It is found in most animal tissues but not in plants. Seventy-five percent of the taurine is found as free forms within striated muscle cells *(Dillon, 1991)*.

Physiological essentials

By conjugating with cholic acid, taurine facilitates the hepatic synthesis of biliary salts. This is its best-known role, but taurine also acts as an osmoregulator by influencing the flow of calcium between the inside and outside of the cell *(Schaffer & Kramer, 1980)*. This mechanism explains the role of taurine in:

- platelet aggregation
- neuron excitability
- myocardium function *(Freeman, 1998)*.

KEY ROLES OF TAURINE IN MAMMALS
(from Huxtable, 1987)

Target organs	Key roles
Liver	Synthesis of biliary salts
Eye	Integrity of the retina
Heart	- Inotropic effect - Antiarrhythmic role - Integrity of heart muscle cells
Nervous system	- Development and integrity of the nervous tissue - Anticonvulsive effect
Reproduction system	- Spermatozoid mobility factor - *In utero* development
Muscles	Myocyte membrane stabilization factor
Other	- Coagulation mechanisms - Immune reactions - Regulation of cholesterolemia - Regulation of glycosuria - Regulation of glycogenesis - Antioxidant activity

The key roles of taurine are summarized in the table.

Consequences of taurine deficiency in cats

Numerous studies have confirmed the essentiality of taurine in cats since 1975. In cats, taurine deficiency is associated with many disorders including:

- blindness and retinal degeneration *(Hayes et al, 1975)*
- reproductive problems and stunted growth *(Sturman et al, 1986)*
- dilated cardiomyopathy (DCM) *(Pion et al, 1987)*
- nervous problems *(Sturman et al, 1985)*
- skeletal deformations *(Sturman et al, 1985)*
- platelet hyperaggregation *(Hayes et al, 1989)*
- immune system disruptions *(Schuller-Lewis et al, 1988)*

Several factors explain the essentiality of taurine in cats.

- Cats synthesize little taurine due to the very low enzyme activity of the decarboxylase needed to convert cysteine into taurine (cysteine sulfinic acid decarboxylase). Its activity is around a hundred times inferior to the one observed in dogs.
- A lot of taurine is lost through the enteral cycle of bile acids.

At least 0.10% of dry matter (DM) in a dry food or 0.17% DM in a canned food helps prevent taurine deficiency *(NRC, 2006)*. The difference is explained by the higher catabolism of taurine by the digestive flora when canned foods are consumed.

Consequences of taurine deficiency on the cat's eyesight

In cats, normal retinal function depends on a sufficient intake of taurine *(Hayes et al, 1975)*. An absolute deficiency of taurine for 25 weeks reduced taurine concentration to 16-25% of normal retinal concentration in the retina *(Pasantes-Morales et al, 1986)*. This decrease induces alterations in the integrity of cellular photoreceptors and the underlying structure of the *tapetum lucidum*. Without rapid correction of the taurine status the photoreceptors will atrophy, leading to gradual but irreversible blindness. This is independent of the level of retinal stimulation by incoming light.

Consequences of taurine deficiency for the cat's reproductive function and kitten growth

Several studies have attempted to measure the impact of dietary taurine on reproductive function. The performances of queens fed with a taurine-deficient diet for six months prior to breeding are clearly inferior to those of the control group. The kittens from taurine-deficient mothers have motility problems of neurological origin *(Sturman et al, 1986)*.

Taurine deficiency affects reproductive function and may lead to developmental abnormalities in kittens.

Kittens with mothers that receive a "normal" level of taurine grow best (0.2%) *(Sturman et al, 1992)*.

A high level of taurine (1%) has no apparent secondary effect on reproduction or the health of kittens born during the trial *(Sturman et al, 1992)*.

Effect of taurine supplementation in cats with taurine deficiency cardiomyopathy

DCM caused by taurine deficiency is associated with faulty myocardial contractility (see above). Clinical signs of the disease may be reversed by adequate taurine supplementation, provided treatment is started soon and the disease is not already too advanced. The recommended dose is 250 mg of taurine per cat, twice daily (per os). This supplementation will achieve remission within 2-4 months in 65% of cats *(Pion et al, 1987)*.

The results of 37 cases supplemented by taurine have been reviewed by *Pion et al* (1992):

- Early death (within the first 30 days of supplementation) was recorded in 14 cats (38%).
- Clear improvement of the clinical and ultrasound signs was observed in 22 cats (59%). Survival was longer than 240 days. The clinical state of these cats remained stable in spite of cessation of all medical treatments (except taurine supplementation).

Conclusion

DCM caused by taurine deficiency illustrates the link that may exist between nutritional balance and heart function. DCM has become rare in cats, as the overwhelming majority of prepared foods for cats does now contain an adequate level of taurine.

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Nutrition and oral health in cats

ABBREVIATIONS USED IN THIS CHAPTER

C: canine
DR: dental resorption (type 1 or 2)
FORL: feline odontoclastic resorptive lesion
I: incisor
M: molar
PM: premolar
PRN: plaque reduction nutrient
TMJ: temporo-mandibular joint

Nutrition and oral health in cats

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The teeth have an essential influence on the cat's general health. They have a role to play in many different functions, such as hunting, grasping and breaking food, self-defense and competition. There are few precise epidemiological studies describing the oral health of cats. Data on cats are mostly extrapolated from dogs, although the oral-dental pathology of cats in all their diversity has special particularities that veterinarians need to know.

Periodontal diseases are common in cats but are often underrated by veterinarians and treated superficially. Recent advancements in feline veterinarian dentistry have provided new tools for their evaluation and diagnosis, as well as more effective prevention tools. All this information must be at the center of the care agreement between the clinic and the owner and aimed at minimizing pain and associated infections.

1 - Dietary behavior in cats

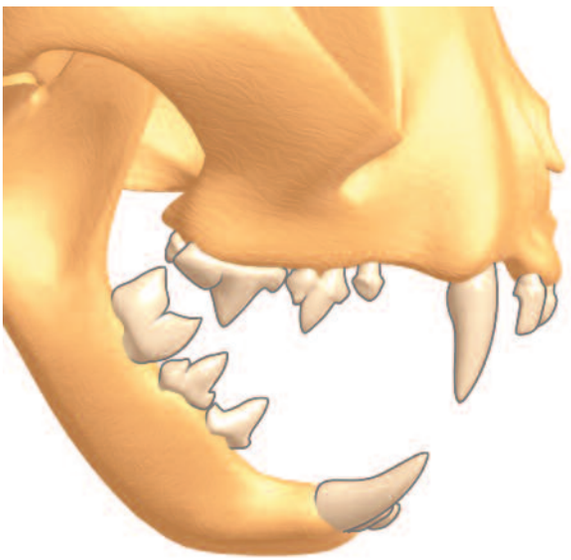
► Anatomical and pathological specificities

Cats are genuine carnivores and their dentition is the same as the major Felidae **(Figure 1)**. They have four types of teeth [incisors (I), canines (C), premolars (PM) and molars (M)] but unlike dogs and other carnivores, cats do not have any chewing teeth – upper molars **(Figures 1 and 2)**.

In the various sequences of dietary behavior, the role of teeth is to capture and dismember small prey, using groups of differentiated teeth.

- The shape of the incisors enables them to cut, hollow out and hack.
- The canines are profiled to pierce and grasp prey.
- The premolars serve to transport the food and to break it into small pieces.

Figure 1 - Profile view of the dentition of an adult cat



The four largest cutting teeth at the back of the upper and lower jaws are called carnassials (PM4 upper and M1 lower).

Dental formula of an adult cat (per quadrant):
I 3/3; C 1/1; PM 3/2; M 1/1
Collectively, there are 30 teeth in the oral cavity of the adult cat.

The oral cavity of cats can be opened wide to enable the canines to grasp the prey, while facilitating the powerful action of the carnassials. Once the prey has been broken up into pieces, it is swallowed *(Wiggs & Lobprise, 1997)*.

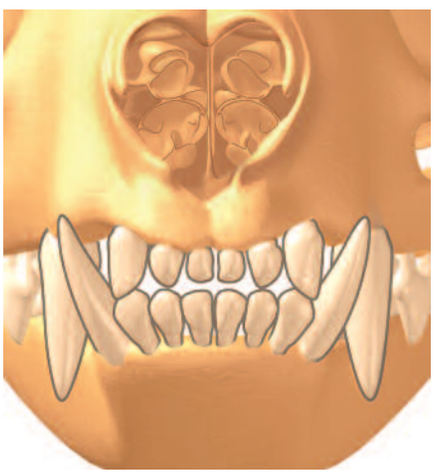
The movements of the jaws are limited sagittally (no transversal masticatory movement). This extreme specialization of the jaws and the temporomandibular joints in cats guarantees great efficiency with respect to the forces exercised when prey is grasped and broken down *(Orsini & Hennet, 1992)*. In domesticated cats, the canines apply around 23 kg of pressure, the carnassials around 28 kg *(Buckland, 1975)*. Joint integrity is maintained by powerful lateral ligaments covered by an effective jaw musculature. Typically, while the carnassials break the food up, the temporomandibular joints twist and rotate it, doubling the effect. The fibrous symphysis connecting the two branches of the mandible enables the distinct movements of the right and left jaw according to the needs and the side used by the cat *(Harvey & Emily, 1993)*.

► Varied oral prehension techniques

In nature, the diet of a wild cat comprises mostly of small rodents, rabbits, birds and some lizards. After catching its prey, step-by-step the cat cuts and swallows it in small pieces.

While domestication has changed their behavior to a degree, domesticated cats still have the ability to return to their wild life, as they retain the hunting instinct, separate from the feeding function. Only 13% of tracked prey is actually caught *(Kays & DeWan, 2004)*. A study shows that, even properly fed housecats with outdoor access will continue to hunt and eat prey, although the proportion of such prey in the total ration is clearly lower than in that of cats that permanently live outdoors (66 g/day vs. 294 g/day) *(Liberg, 1984)*.

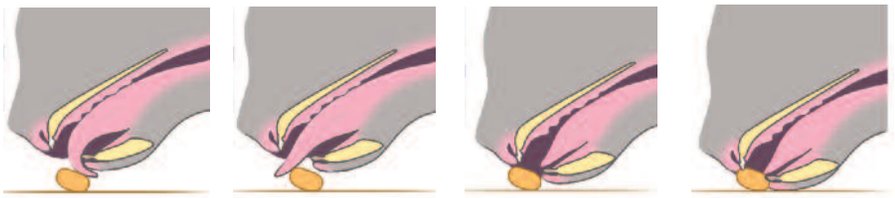
Figure 2 - Front view of dental occlusion in the cat



When the oral cavity is closed, the incisors of the lower jaw rest directly behind the incisors of the upper jaw, and the lower canine is between the upper canine and the third upper incisor.

Figure 3 - Video analysis of the oral prehension method of Persian cats.
Analysis conducted in association with Royal Canin, École Nationale des Arts et Métiers d'Angers (ENSAM) and Ecole des Mines d'Alès (EMA).

FIGURE 4 - DIFFERENT ORAL PREHENSION METHODS OBSERVED IN CATS



Supra-lingual mode
First point of contact with the kibble is the upper side of the tongue.

Sub-lingual mode
First point of contact with the kibble is the lower side of the tongue.

Labial mode
First point of contact with the kibble is the lips.

"Shovel" mode
First point of contact with the kibble is the incisors.

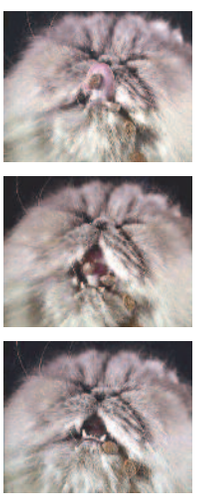
The palatability of commercial food has been studied in detail to continually improve product quality. Dry kibbles in various shapes, sizes, textures and densities are given to cats to evaluate their reaction. Analyzing videos of the feeding behavior of different breeds of domesticated cats **(Figure 3)** has enabled the characterization of how cats grasp their food in general, while also identifying several kibble prehension methods **(Figure 4)**:
- *supra-lingual mode*: using the upper side of the tongue
- *labial mode*: using the lips and jaws
- *"shovel" mode:* using the incisors
- *sub-lingual mode*: using the lower side of the tongue

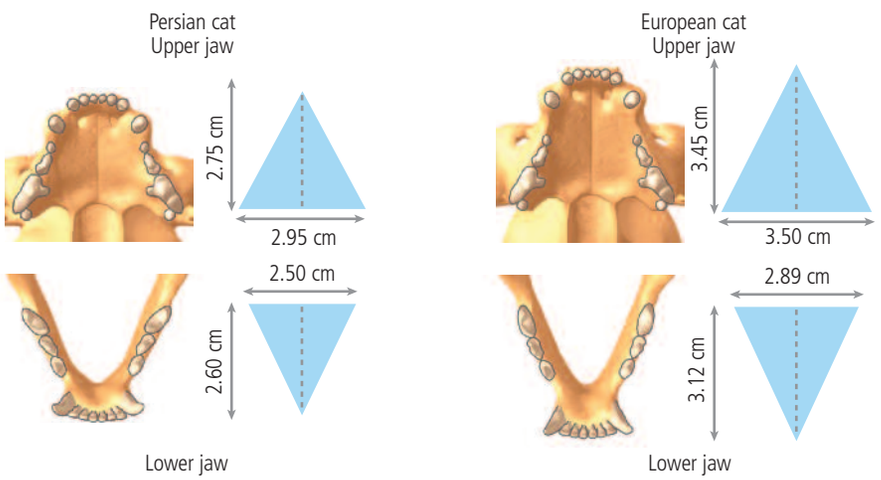
The kibble prehension method varies with the breed. A certain degree of adaptability in terms of prehension and mastication behavior is observed depending on the kibble shape and size *(unpublished internal Royal Canin studies, 2002)*.

Observing brachycephalic breeds (e.g. Persians), it is clear that they have difficulty grasping standard-sized, round kibbles, particularly with the incisors. Persians use the tongue to trap a standard kibble in 80% of cases (60% lower tongue **(Figure 5)** and 20% upper tongue). They use their lips just 20% of time, while the "shovel" method is not observed.

FIGURE 5 - COMPARATIVE JAW CONFORMATION BETWEEN A BRACHYCEPHALIC CAT (PERSIAN) AND A MESOCEPHALIC CAT

Source: Royal Canin Research Center, 2002





Impressions show the teeth of a Persian are implanted closer together in the jaw. A particular prehension method is observed in this breed (sub-lingual mode).

- Dolichocephalic cats (e.g. Siamese) like to use their incisors **(Figure 6)**. The "shovel" method is observed in 30% of cases, which is more efficient when the kibble bowl is full. Prehension tends to progress towards the upper tongue method as the bowl empties (to ensure the tongue grasps the kibble). Siamese cats use the upper tongue method in 70% of cases.

- Mesocephalic cats (e.g. Maine Coon) make almost equal use of upper tongue and lips at the start of the meal (in 57% and 42% of cases respectively) **(Figure 7)**. The upper tongue method may become more prevalent during the course of the meal or if the kibbles are smaller (83% tongue vs. 17% lips).

The influence of anatomical particularities related to breed also affects others aspects of feeding behavior. After grasping a standard kibble, Persians chew in only around 10% of cases, whereas the chewing percentage is 90% among Maine Coons and Siamese cats *(unpublished internal Royal Canin studies, 2002)*.

Hence, prehension methods differ significantly from one breed to the other, and especially from one maxillofacial biometric to another.

► Feeding rhythm in domesticated cats

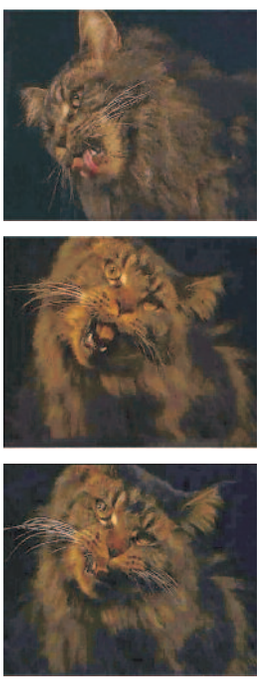
Domesticated cats habitually divide up much of their daily food. When different types of dry food are offered, the frequency and average duration of meals varies according to the breed and the food *(internal Royal Canin studies, 2006)*.

On average, a cat fed ad libitum will feed a dozen or so times a day. Each session lasts about two minutes, with the cat consuming around 6 g of food. In one 24-hour period, the cat therefore devotes an average of 20 minutes to eating and digesting 50-60 g of kibbles **(Table 1)**. Nocturnal consumption accounts for 30% of all food ingested. At night, meals are generally larger and take longer. A strong correlation between breed and feeding rhythm **(Figure 8)** and the quantities ingested at each meal has been shown.

The influence of maxillofacial biometric variations on the feeding method of the domesticated cat is accordingly self-evident. The significant differences observed between facial morphologies provide more proof of different prehension methods, feeding rhythms and quantities of food ingested. The low adaptability of jaw movements (see above) requires them to adapt the natural sequences of prehension and ingestion to suit the food.

Source: Centre de Recherche Royal Canin, 2002

Figure 6 - Traditional food prehension method used by the Siamese cat.
The sequential analysis of 4800 prehension sessions shows that the Siamese uses its incisors in 30% of cases. The jaws open at a very wide angle.



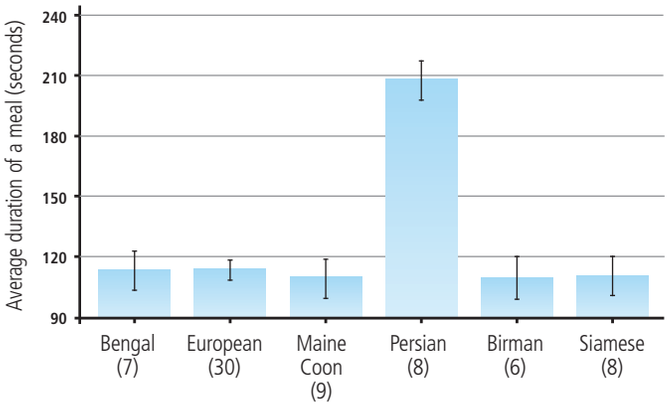
Source: Centre de Recherche Royal Canin, 2002

Figure 7 - Traditional food prehension method used by the Maine Coon cat
The sequential analysis of 7200 prehension sessions shows that the Maine Coon uses the lower tongue and labial method almost equally.

TABLE 1 – FOOD CONSUMPTION INDEXES IN CATS FED DRY FOOD AD LIBITUM
(Data from 16 cats fed ad libitum one of four foods consecutively – internal Royal Canin studies, 2006)

	Food 1	Food 2	Food 3	Food 4	Average
Number of meals/24 h	9.5	8.4	10.0	10.1	**9.5**
Size of meal (g)	6.7	6.7	5.6	5.3	**6.1**
Total consumption/24 h (g)	57.1	53.1	53.7	52.8	**54.2**
Average duration of meal (min' sec")	1'48"	2'16"	2'16"	2'09"	**2'07"**
Total consumption time/24 h (min' sec")	16'39"	18'35"	22'28"	21'46"	**19'53"**
Speed of consumption (g/min)	4.1	3.3	2.9	2.7	**3.2**

FIGURE 8 - INFLUENCE OF BREED ON THE AVERAGE DURATION OF MEALS IN CATS FED WITH A DRY FOOD



When cats are fed a standard dry food they feed around a dozen times in a 24-hour period. The average duration of each meal is 2 minutes (’), all breeds included. This average is however twice as long among Persians: 3’27”, compared with 1’49” among all other breeds (unpublished Royal Canin data, 2005).

Domesticated cats have however retained the principle features of their wild feeding behavior. This feeding behavior continues to be studied frequently to evaluate the impact of commercial food on the oral health of cats as precisely as possible.

2 - Common oral diseases

► Prevalence of feline oral diseases in wild and domesticated populations

Whether wild or domesticated, a cat’s diet is dictated by its environment. In this respect, commercial food preparation is often considered to be an aggravating factor in the event of oral diseases. The analysis of the oral diseases of a population of wild cats provides an opportunity to study the potential link between a well-defined diet and the various diseases identified.

Four cats were introduced on Marion Island in the Indian Ocean in 1949 and the cat population grew rapidly. The diet of these cats is mostly seabirds (96%) associated with the ingestion of some pebbles. The postmortem analysis of a collection of 300 skulls from this cat population enabled the study of oral health. Despite the average age of the group being estimated at 2-3 years, the prevalence of periodontal disease in a moderate to severe form, was 48%. Taking account of missing teeth (probably due to periodontal disease), periodontal disease was prevalent in 61.8% of cats and 14.8% of the teeth observed. The prevalence of dental trauma and feline odontoclastic resorptive lesions (FORLs) was also high, statistically associated with the prevalence of periodontal disease. On the other hand, only 9% of cats in this study presented calculus, and then typically on the upper carnassials.

The highly specific diet of this wild cat population undoubtedly explains the high frequency of periodontal lesions and the low prevalence of dental calculus observed in such a young colony. When the cat tears apart the carcasses of seabirds, the sharp bone sections are probably responsible for gum trauma, which is assumed to favor the development of more severe periodontal inflammation *(Verstraete et al, 1996)*.

In an Australian study, the analysis of oral diseases based on clinical and radiographic criteria in 29 wild cats and 20 domesticated cats *(Clarke & Cameron, 1998)* established that the prevalence of periodontal disease was not significantly different in cats fed with commercial foods and cats whose diet was mainly made up of small prey. A hunting-based diet does not provide natural protection from oral diseases for wild cats.

Veterinarian examination of 15,226 domesticated cats *(Lund et al, 1998)* showed that oral diseases are the most common of all diseases observed. Calculus is present in 24% of cats and 13% of them suffer from some form of gingivitis.

A more detailed analysis conducted by veterinarians specialized in dentistry confirms a strong prevalence of oral diseases. 73% of a population of 753 cats studied presented gingivitis; 67% pre-

sented dental calculus; 28% of them had missing teeth; 25% FORLs; 19% severe periodontitis; 12% stomatitis and 11% tooth fractures *(Verhaerte & Van Wetter, 2004)*.

Periodontal disease is found in 32% of individuals presented to veterinarians specialized in dentistry. Out of a population of 152 cats, gingivitis and missing teeth were observed in 59% of cases, FORLs in 57% of cases, teeth fractures in 23% of cases and stomatitis in 2.6% of cases. The prevalence of dental calculus was estimated at 90% *(Crossley, 1991)*.

The postmortem analysis of 81 cats whose death was unrelated to an established oral disease, based on pathological and clinical examination, reported a high prevalence of periodontal disease. 52% of cats older than 4 years of age presented a form of periodontal inflammation. More than 40% of animals aged over 9 years presented a severe form of the disease. Less than 3% of animals aged over 15 years presented any form of lesion due to periodontal disease *(Gengler et al, 1995)*.

To summarize the studies above, the high prevalence of periodontal disease in cats cannot be ignored. There are no major differences between wild and domesticated populations and no apparent influence of commercial food. The presence of oral diseases is therefore not something that characterizes domesticated cats alone and is not necessarily associated with the feeding of commercial foods.

This information is unfortunately always underestimated. It does however shed light on the fact that the high prevalence of oral inflammation in cats is the most common cause of infectious disease in the species. The clinical impact turns out to be much greater than it appeared at first sight. It is especially clear in groups of wildcats whose health is generally related to interspecies competition and conditions the very survival of individuals. In the case of domesticated cats, the pain caused by oral disease is typically underestimated. Once they have been treated, these cats do show major behavioral modifications. Some owners describe this return to health as a “rebirth”.

In wild cat populations, oral inflammation could threaten the health and even the survival of individuals.

► Periodontal disease

Periodontal disease is the most common disease in cats. It is an inflammatory oral disease associated with the development of dental plaque. Periodontal disease is not a disease as such as much as a collection of periodontal inflammations with varied clinical characteristics chronic or aggressive, local or generalized. All stages are possible: from early-stage periodontal disease to moderate or severe forms. The way periodontal disease develops depends on the mechanical constraints that oppose the development of dental plaque, but also the local immune response of each individual.

The incidence of periodontal disease on the general health of cats is widely underestimated. It is the source of chronic pain that owners are often unaware of and chronic bacterial diseases whose effects on the kidneys, lungs and heart are just starting to be better understood. Periodontal disease is the most common disease reported in cats, with a prevalence estimated at 30-70% of individuals according to studies and the evaluation criteria.

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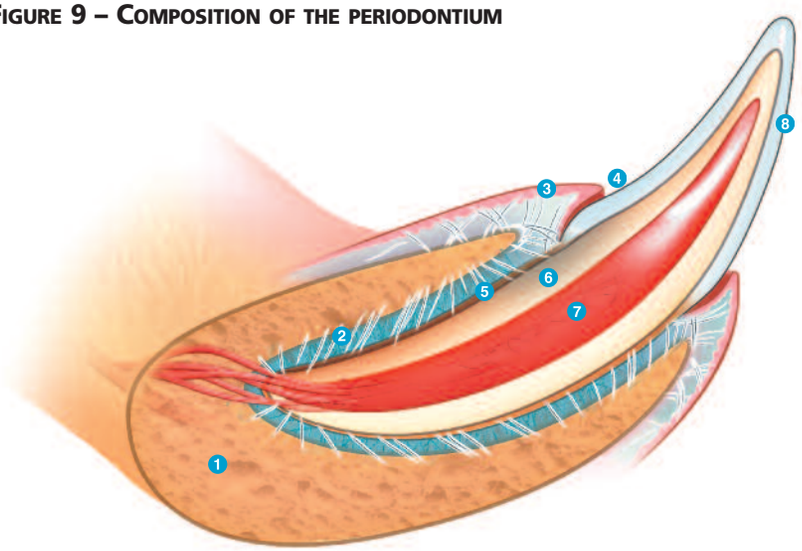
Figure 9 – Composition of the periodontium

1. Jaw bone
2. Periodontal ligament
3. Gum
4. Sulcus
5. Cement (covers the root)
6. Dentine
7. Pulp
8. Enamel (covers the crown)

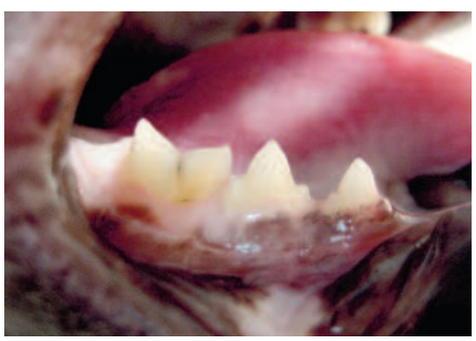


> Description and function of the periodontium

The periodontium is the tissue that supports the teeth in the oral cavity. It connects the teeth, the bone structure of the jaws and the oral mucosa. Its development is associated with the eruption of the tooth and it disappears with its exfoliation. The periodontal tissue guarantees the integrity of dental structures and effectively protects the underlying anatomical structures from aggressions in the oral environment.

The periodontium is composed of the gum, the periodontal ligament, cement and the alveolar bone **(Figure 9)**.

The alveolar bone is a differentiated part of the jawbone. It is responsible for positioning the roots of the teeth in depressions known as dental alveoli.
The periodontal ligament is composed of collagen fibers, which connects the surface of the tooth root (cement) to the alveolar bone. Like a hydraulic shock absorber the periodontal ligament absorbs the pressures placed on the alveolar bone during prehension and the tearing of food. These specialized fibers improve the resistance to pressure of underlying bone tissue and generate a pain signal when the limit of its mechanical resistance is reached.
The cement covers the root of the tooth. It has a similar structure to bone, but without lacunas and channels.
The gum covers the underlying alveolar bone and tightly hugs the base of the crown of the tooth. The gum is composed of a squamous, keratinized epithelium, which is different from the loose, vascularized and non-keratinized alveolar mucosa. It is made up of two parts.



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Healthy gum.

- *The free gum* is located at the level of the crown. It defines a space against the crown known as the gingival crevice, whose physiological depth is less than 0.5 mm in cats. The weak point of the tooth/gum junction is always the gingival crevice. The delimited space is fairly closed and is predisposed to accumulating dental plaque and various food debris. As its histological nature makes it more sensitive to the inflammatory process, the gingival crevice forms a gateway for periodontal disease. As a consequence, all attention must be focused on periodontal disease treatment and prevention programs.

- *The gum attached* to the tooth and the alveolar bone is an essential barrier against bacterial aggression. The seam of the gum is stuck against the bulge of the base of the crown and enhances this protective action.

Some 100 billion bacteria are discharged in the saliva every day. The oral cavity is therefore never sterile. There is always a minimal residual inflammation of the mucosa and the oral epithelium. A "healthy" periodontium is therefore defined clinically. The criteria for evaluating a healthy periodontium in cats are the absence of visual evidence of inflammation and the depth of the gingival crevice less than 0.5 mm.

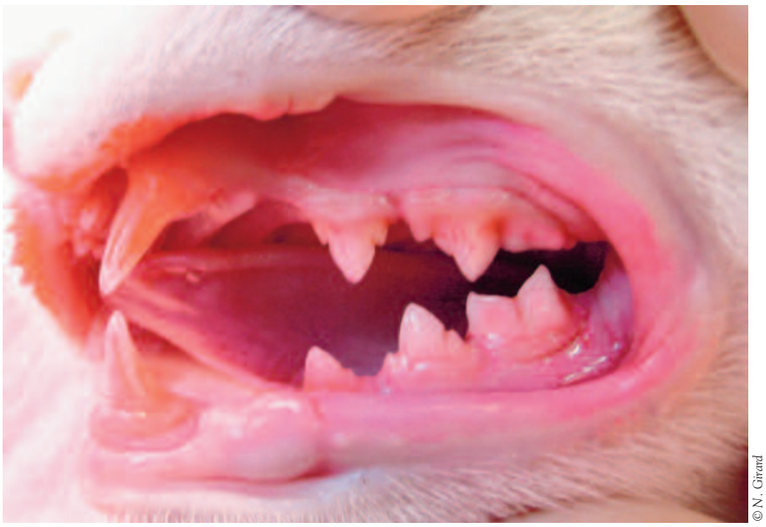
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Figure 10 - Supragingival dental plaque on healthy teeth and gums. *The phenomena of bacterial coaggregation and coadhesion facilitate the installation of 90% of the biomass of the dental plaque within 24 hours (the dental plaque is revealed using eosin-type vital staining).*

> Pathogenesis of periodontal disease

The development of dental plaque in contact with all the surfaces of the tooth is a natural process resulting from the interaction between tooth and saliva. The anatomical sites predisposed to the deposition of dental plaque are the limit of the crown and the seams of the gum as well as the contacts between the teeth.

The adhesion and proliferation of bacteria on the surface of the enamel is not possible as such. The gradual colonization of the tooth surfaces by the bacteria is a succession of steps that steadily facilitate the adhesion and multiplication of bacteria:
- physical adhesion of an organic film to the surface of the teeth.
- secondary colonization by specific or pioneer bacteria.
- bacterial proliferation from the colonized organic film.

The adhesion of pioneer bacteria to the tooth surface is possible only after the development of an organic film (acquired pellicle) essentially formed from salivary components (glycoprotein, polypeptides, carbohydrate). Within a few hours of its development, specific bacteria *(Streptococcus sanguis, Actynomyces viscosus)* arrive to colonize the acquired pellicle, gradually saturating the entire surface (>6 million/sq. mm) and forming a biofilm, **dental plaque (Figure 10)**. New bacterial appositions, which stimulate the phenomena of coaggregation and coadhesion, establish 90% of the dental plaque's biomass within 24 hours.

Initially, dental plaque is essentially composed of aerobic Gram+ bacteria but this population develops rapidly. With the increase in the bacterial population comes the fall in oxygen in the air, from 12-14% in the mouth to 1-2% at the base of the gingival crevice. These new environmental conditions, which are associated with various sources of nutrients (diet, bacterial degradation, epithelial degradation), lead to the development of an anaerobic bacterial flora.

As the inflammatory process advances, so the proportion of Gram– bacteria (*Porphyromonas sp, Prevotella sp, Peptostreptococcus sp*), *Fusobacterium* and spirillians increases. The pathogenic role of these aggressive bacteria is much more pronounced and is exercised through various enzymes, toxins and degradation products *(Haake et al, 2002)*.

To summarize, the dental plaque is a biofilm that forms on the tooth surface. It is composed of a community of bacterial species embedded inside an extracellular matrix of polymers produced by the hosts and the bacteria themselves *(Marsh, 2004)*. Modification of its composition is closely associated with the development of periodontal inflammation. Its interrelation with the cat's immune defense mechanisms conditions to some extent the scale of the periodontal inflammation.

Calculus is only a mineralized, fossilized form of dental plaque, consequential to the catalytic activity of some bacteria. It is deposited both above and under the gum **(Figure 11)**. While calculus does not contain any pathogenic bacteria, its porous character favors the new accumulation of dental plaque. So while it does not cause the inflammation of the periodontium it is an aggravating factor.


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Figure 11 - Deposit of dental calculus in the cat. *Accumulation of calculus on 100% of the upper PM4 associated with gum recession and exposure of the furcation.*

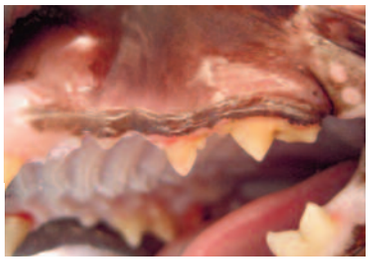


Figure 12 - Generalized gingivitis. *Pronounced gum edema from the canine to the carnassial; spontaneous bleeding around PM3.*

The accumulation of dental plaque in the gingival crevice leads to inflammation of the gum seams **(Figure 12)**. At this point, professional care together with the removal of the dental plaque will ensure full remission of the lesions. Without treatment, the dental plaque continues to accumulate and inflammation advances. The environmental conditions in the oral cavity become more favorable to an anaerobic bacterial population containing more and more Gram negative bacteria. **Gingivitis**, the reversible inflammatory stage, may stabilize or develop into periodontitis.

The advancement of the inflammatory process inexorably leads to the collapse of the connecting tissues on the surface of the tooth. Dental plaque then colonizes the tooth root further down. The epithelium of the junction, which constitutes the lower limit of the gingival crevice, migrates to an apical region to heal in the "non-inflammatory" zone, creating a periodontal pocket. **Periodontitis (Figure 13)** is the irreversible stage of periodontal disease. The lesions are final and the main objective of treatment is to halt their advancement. The main cause of the development of periodontal disease is the disruption of the balance between the pathogenic bacterial flora of the dental plaque and the host's immune response.

> Description of periodontal disease in cats

First and foremost, it should be noted that few publications deal with periodontal disease in cats, contrary to a large quantity of publications on the disease in dogs. We would also observe that the expression of periodontal disease in cats is generally described on the model of the dog or human, without taking account of any feline particularities.

- A clinical radiographic and histological study has helped outline the development of periodontal disease in 15 cats *(Reichart et al, 1984)*. A loss of attachment appeared in 25% of premolars and molars, essentially localized to the buccal surface. A pronounced to severe gingivitis was shown in 56% of premolars and molars (buccal surface) and 25% of canines and incisors (buccal surface). After radiographic analysis, alveolar bone loss appeared to be significant in 77% of premolars and molars. Bone loss was also observed on the buccal surface of 82% and on the oral surface of 75% of incisors and canines. The general distribution of observed lesions in cats (gingivitis, alveolar bone loss, inflammatory FORL) was more pronounced in the premolars and molars.

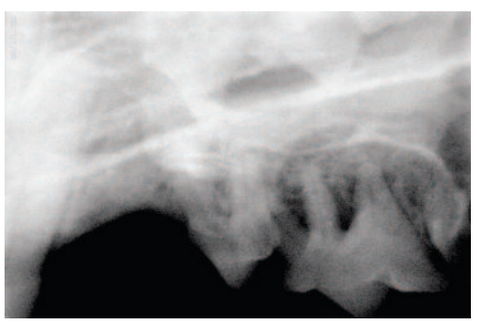
Bearing in mind the high percentage of bone loss shown in the canines and incisors, however, together with the high percentage of missing incisors, it would appear that these teeth are highly susceptible to periodontal disease *(Reichart et al, 1984)*.

A form of periodontitis was shown using dental radiography in 69% of cats presented to the specialist veterinary dentistry department of the University of California, Davis. The results of this

FIGURE 13 - SEVERE LOCAL PERIODONTITIS OF THE UPPER LEFT PM4

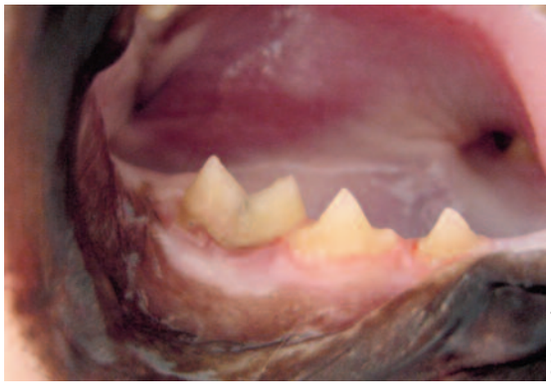
13A - Severe gingivitis on the mesial and vestibular surface.

13B - Severe gum recession on the mesial and palatine surface.

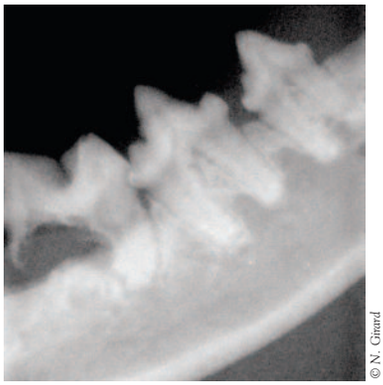


13C - Severe horizontal alveolysis.

FIGURE 14 - GENERALIZED HORIZONTAL BONE LOSS DURING PERIODONTAL DISEASE IN THE CAT WITH RESPECT TO THE RIGHT LOWER CARNASSIAL



Severe periodontitis.



Generalized severe horizontal bone loss.

study confirm that generalized horizontal bone loss **(Figure 14)** is the most common form of bone loss in cats (38%). In total, the height of the alveolar bone was normal in just 28% of cases *(Lommer & Verstraete, 2001)*.

A clinical and radiographic study based on the oral examination of 109 healthy cats fed with dry food confirms these results. The presence of moderate to severe gingivitis associated with the presence of bleeding during periodontal probing was 13%. The average loss of periodontal attachment observed was 0.49 mm (c=1.28) with higher average values in the canines: 1.2 mm in the upper canine and 0.8 mm in the lower canine. Loss of attachment greater or equal to 2 mm was observed in 3.4% of examinations of the vestibular surface, 3% of the distal surface, 2.3% of the mesial surface and 2.2% of the lingual part. Gum recession **(Figure 15)** was observed in 10% of teeth. Absent teeth were most often upper premolars and incisors (21.1% and 11.4% respectively). Furcation **(Figure 16)** was observed in 18% of multi-root teeth and on average in two teeth of every cat examined. The radiographical analysis revealed a high prevalence of bone loss with respect to the dental arches: 21% of upper teeth and 42% of lower teeth. Horizontal and/or vertical bone loss was revealed in 52% and 14% of lower teeth respectively. The simplified analysis of premolars and molars underlines the importance of the inflammatory process: bone loss was observed in 66.5% of teeth *(Girard et al, 2008)*.

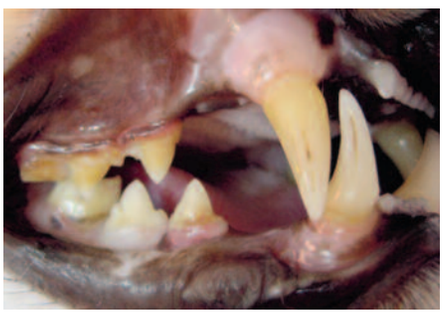
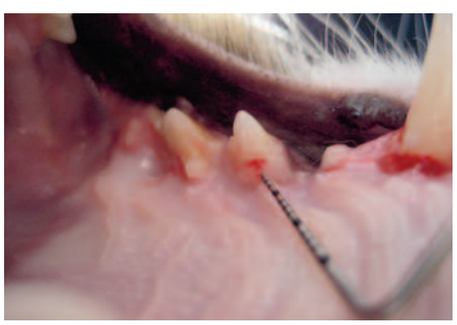


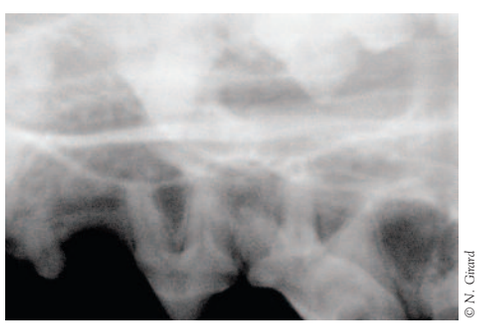
Figure 15 - Severe gum recession around a canine tooth in the cat.
Pronounced gum recession and alveolar bone loss around the upper and lower canines.

Periodontal disease in cats is characterized by a low proportion of periodontal pockets **(Figure 17)**, the strong prevalence of osteolysis in its horizontal form, a high proportion of gum recession and the early appearance of furcation.

FIGURE 16 - FURCATION AROUND THE UPPER PM3 IN THE CAT

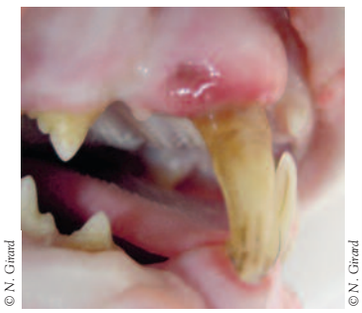


Profuse bleeding following periodontal probing of the furcation.

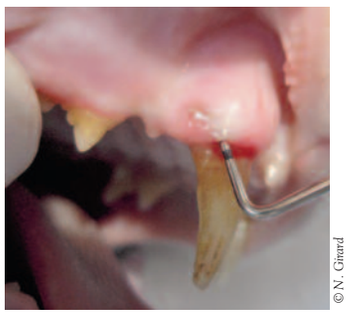


Vertical bone loss.

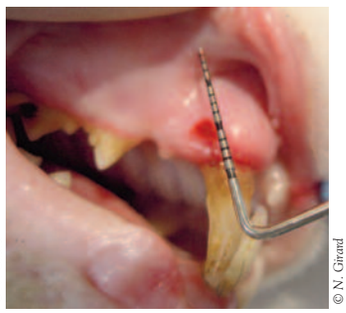
Figure 17 - Periodontal pocket in the cat



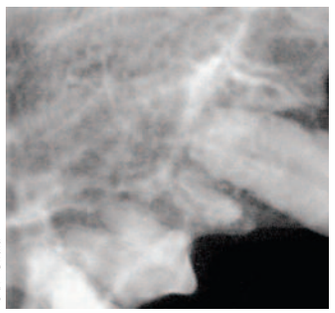
Pronounced recession and severe gingivitis.



Insertion of the periodontal probe.



Evaluation of the depth of the periodontal pocket: 13 mm.



Severe horizontal alveolar bone loss.

> Predisposing factors

Many factors have an influence on the development of periodontal disease:
- excessive accumulation of dental plaque in the junction between the tooth and gum (absence of oral hygiene, low fiber diet)
- inflammation promoted by a probable insufficiency of the local immune system or in the presence of systemic diseases such as diabetes mellitus, thyroid, liver or kidney insufficiency
- a familial and/or genetic effect is often evoked but never proven
- facial conformation, malocclusion, occlusion trauma.

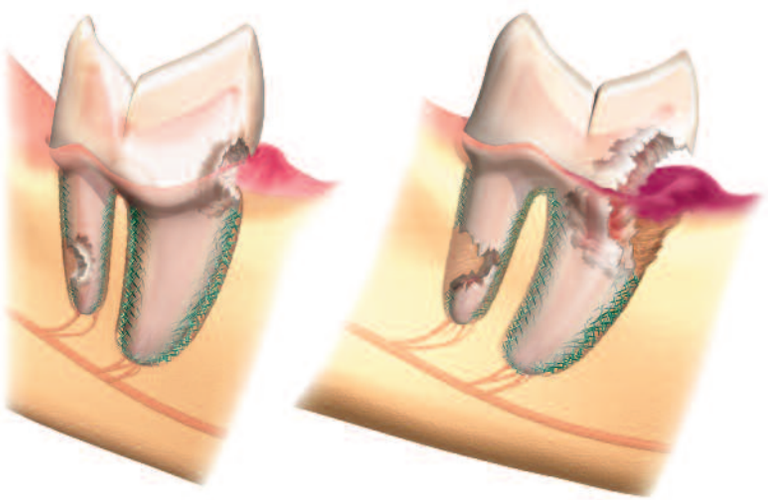
► Tooth resorptions

> Definition

Tooth resorptions are lesions by which the gradual loss of tooth substance is observed **(Figure 18)**. In cats, they are commonly known as feline odontoclastic resorptive lesions (FORLs), as the process of tooth resorption is controlled by multinuclear odontoclastic cells (odontoclasts) *(Gautier et al, 2001)*. These lesions affect the interior and/or exterior of the tooth and their clinical diagnosis is often delicate. Tooth resorptions are also observed in humans and dogs. They are generally due to periodontal inflammation or mechanical constraints with respect to the periodontal ligament (orthodontic treatment, tooth trauma).

Figure 18 - Feline odontoclastic resorptive lesion

Feline odontoclastic resorptive lesions are initiated in the radicular cement and then develop through the dentine and/or the crown. The alveolar bone and the adjacent periodontal ligament are also included locally in the tooth resorption process. The tooth canal is only affected at the end of the process, signaling an internal tooth resorptive lesion.



> Prevalence

A high prevalence of FORL has been shown in various cat populations and especially in domestic cats. According to the populations studied and/or the methodology used, the results were between 28% and 67% *(Coles, 1990; Van Messum et al, 1992)*. Such a variation is connected with the choice of population studied (specialist dental department, general dental department, healthy population) or the diagnostic methods used (clinical examination +/- radiological examination). Two studies of healthy cat populations reporting both a clinical and radiological examination revealed an average prevalence of 30% *(Ingham et al, 2002a; Girard et al, 2008)*.

> Pathogenesis

FORLs in cats are mostly external tooth lesions. The resorbed tooth tissue is gradually replaced by newly formed cement or bone tissue. FORLs are initiated in the radicular cement and then develop through the dentine and/or the crown. The alveolar bone and the adjacent periodontal ligament are also included locally in the tooth resorption process.

The tooth canal is only affected at the end of the process, signaling an internal tooth resorptive lesion. Inflammation of the tooth pulp is rare except at the end, when a degenerative state is described. The enamel of the crown may resorb itself in time, but more commonly it fractures due to the absence of underlying support, leading to the clinical appearance of a tooth cavity *(Okuda & Harvey, 1992)*.

FORLs mainly appear in the buccal part of the crown. Sixty-nine percent of the FORLs revealed are associated with an inflammatory phenomenon and 30% display signs of repair *(Reichart et al, 1984)*.

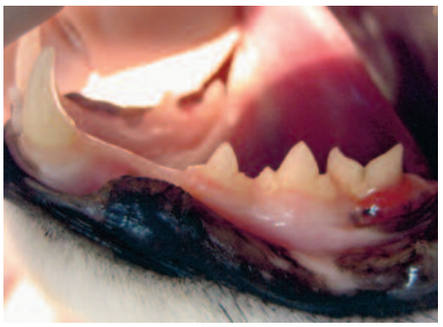
> Etiologies of FORLs

External FORLs may have one or more origins. In human dentistry, the disease may be associated with:
- a chronic inflammatory process adjacent to a cyst, benign or malignant tumor,
or
- be the consequence of dental trauma (mechanical/occlusal) or orthodontic tooth displacement.
Lesions are qualified differently depending on whether an inflammatory process is present. Surface FORLs, dentoalveolar ankylosis and replacement lesions are considered to be the consequence of tooth traumas and qualified as non-inflammatory. On the other hand, apical FORLs and periradicular periodontitis are the consequence of lesions of the tooth pulp and are qualified as inflammatory lesions (radicular inflammatory tooth resorptions).

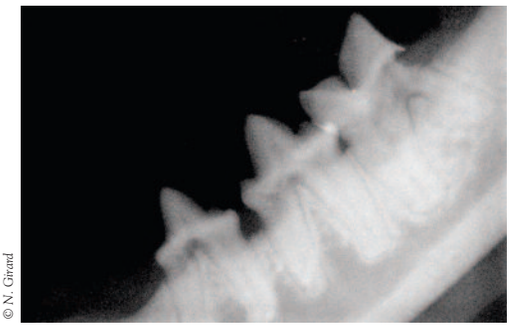
FORLs of the neck of the tooth are often confused with radicular inflammatory tooth resorptions. They are considered to be inflammatory because they are associated with inflammatory damage to the epithelial attachment (in the event of periodontal disease for example) *(Andreasen, 1985; Trope et al, 2002)*.

The precise etiology of FORLs remains unknown and is still the subject of discussion and research. The suspected role of masticatory mechanical constraints and chronic inflammation due to periodontal disease is underlined in various histological *(Gorrel & Larsson, 2002; Roux et al, 2002)* and radiographic *(DuPont & DeBowes, 2002)* studies as well as one clinical study *(Girard et al, 2008)*. Excessive vitamin D intake through the diet *(Reiter et al, 2005)* is proposed as a cofactor, although this continues to be debated. The precise role of specific histological dental structures in cats (vasodentine, osteodentine) has not been fully explained. Any interactions in the calcium regulation process associated with resorptions have been proposed *(Okuda & Harvey, 1992)*.

FIGURE 19 - TYPE 1 FORL OF THE LOWER M1



Severe gingivitis in the distal part.



Inter-oral radiography: type 1 FORL.

Current veterinary recommendations propose the differentiation of FORLs based on the results of the radiographic evaluation:

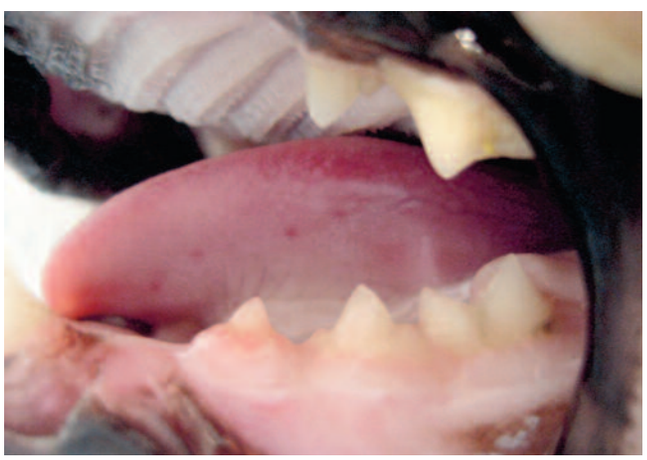
- **type 1 FORL:** observation of a physiological periodontal ligament space (*lamina dura*) and radio density of the affected root similar to that of healthy adjacent roots **(Figure 19)**

- **type 2 FORL:** disappearance of the lamina dura in the radiographic examination and radio density of the affected root similar to that of the adjacent alveolar bone (bone remodeling) **(Figure 20)**.

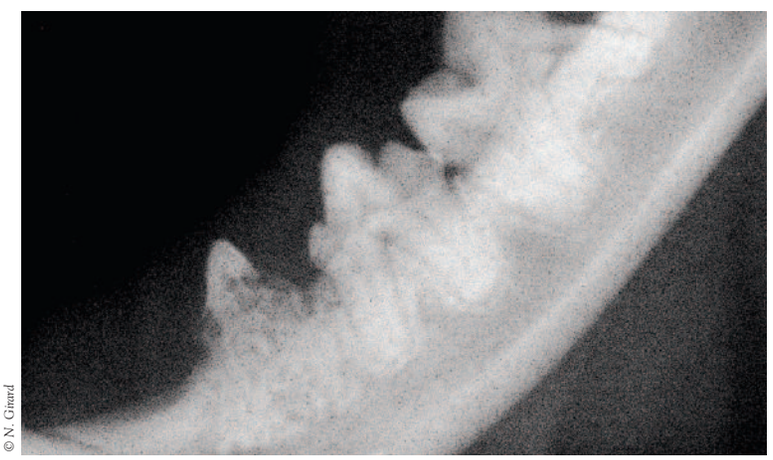
The combined study of the location of FORLs depending on their radiographic type shows significant differences *(Girard et al, 2008)*. Among house cats, the greater prevalence of type 1 lesions is observed in the lower carnassial and type 2 lesions in PM3. Among purebred cats a significant difference is observed for incisors (Type 2 FORL) and the lower carnassial (Type 1 FORL). The distribution of FORLs in the mouth is not uniform according to the type of lesion observed radiographically. This information corroborates the hypothesis that different etiologies cause feline resorptive lesions.

The analysis of FORLs in a population of cats treated at the dentistry department of the University of California, Davis, reveal a significant association between FORL and the presence of severe localized vertical alveolar bone loss *(Lommer & Verstraete, 2001)*.

FIGURE 20 - TYPE 2 FORL OF THE LOWER LEFT PM3



Early gingivitis.



Type 2 FORL.

The high prevalence of FORLs in the wild cat population on Marion Island (see above) fed almost exclusively with seabirds reduces the role some authors feel commercial food plays in the appearance of these tooth lesions. The author rather sees a consequence of feline oral inflammatory pathologies like periodontal disease and feline stomatitis *(Verstraete et al, 1996)*.

An in-depth statistical analysis of the distribution of FORLs and 14 clinical and radiographic criteria associated with periodontal disease underlines a strong association *(Girard et al, 2008)*. The global prevalence of FORLs may be significantly correlated to 6 of these periodontal parameters as well as age. Type 1 and 2 resorptions appear as two different phenomena without any association criteria. Type 1 FORL is significantly associated with 8 of the periodontal variables and so is strongly associated with periodontal disease. Type 2 FORL is correlated with just 2 periodontal parameters so the correlation to periodontal disease is low.

Age appears to be a factor strongly associated with the presence of type 2 FORL and weakly associated with type 1 FORL. All of these observations suggest that type 1 FORL is less sensitive to age with regard to its supposed link to the development of periodontal disease.

► Stomatitis

The term feline stomatitis covers all the oral diseases characterized by a pronounced inflammation of the oral mucosa **(Figure 21)**. Their prevalence appears to be low, although few statistical studies have been published on the subject (2.6% according to *Crossley, 1991*; 12% according to *Verhaert & Van Wetter, 2004*). Studies of large human populations show a prevalence of 5-15% of aggressive forms of periodontal inflammation, supposedly associated with ethnic predisposition *(Wolf et al, 2005)*.

The analysis of tooth diseases in a population of 109 cats reveals 5.5% cases of stomatitis (3.7% buccal stomatitis, 1.8% caudal stomatitis) and 12.8% aggressive periodontitis *(Girard et al, 2008)*. All these aggressive inflammatory diseases affected purebred cats, none of them housecats. The real impact of breed is still undergoing evaluation with respect to the probable familial effect.

The different types of stomatitis are known and dreaded, because they are generally a real therapeutic challenge. They are so painful that they disrupt the appetite and even the very survival of affected animals. The veterinarians' feeling of helplessness is amplified by the many uncertainties related to the etiology of these diseases.

The clinical management of feline stomatitis demands great diagnostic and therapeutic rigor. Recent studies confirm the role of the Calicivirus in the development of caudal stomatitis *(Addie et al, 2003)*. The most descriptive clinical examination is needed to advance the etiological analysis of feline stomatitis. Few published studies use an appropriate terminology to correctly evaluate a given type of medication, complementary examination or viral etiology. More precise information on the therapeutic benefits of selected substances, the role of selected viruses (FCV, HV1, FIV, FeLV) and the best histopathological (especially immunohistological) knowledge in this disease is expected to be found in the years to come.

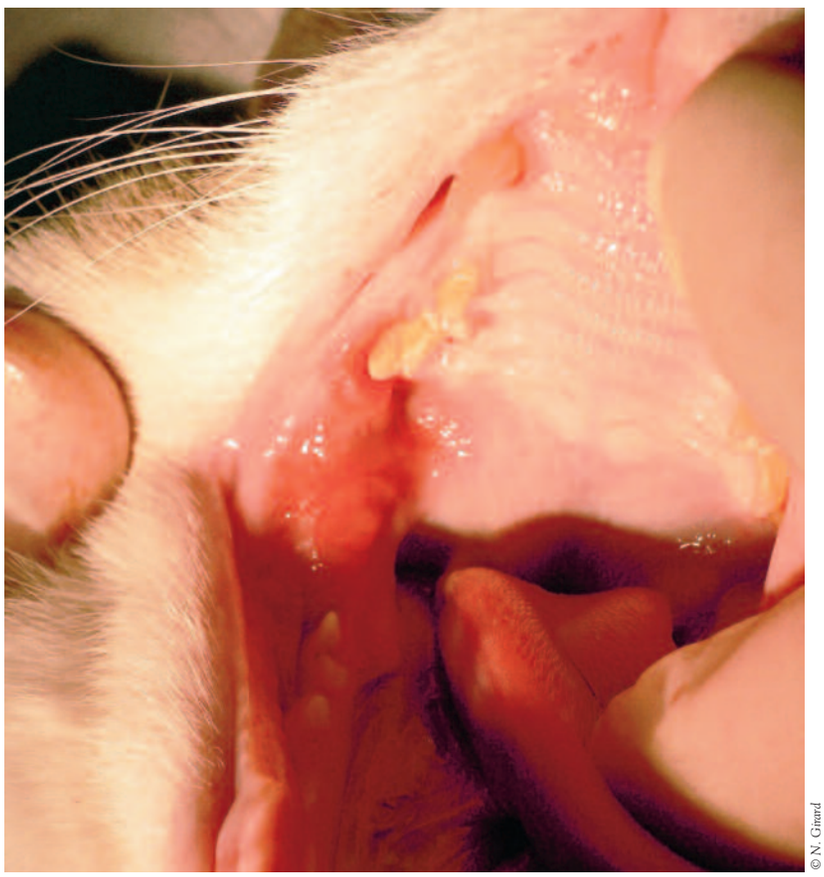
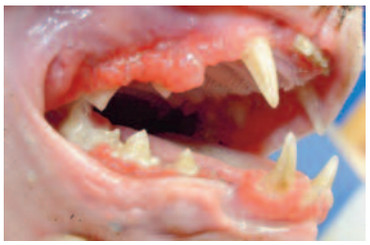


Figure 21 - Stomatitis lesions in a cat. *Jugal buccal stomatitis*.

Figure 22 - Illustration of the efficacy of tooth brushing in a cat.



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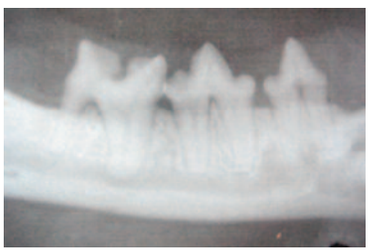

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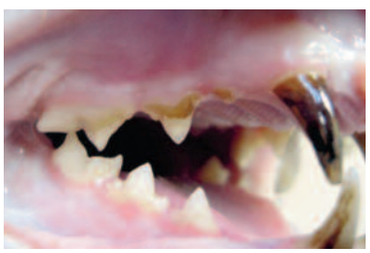
A case of aggressive ulceroproliferative periodontitis in an eight-month-old Sphinx cat (photograph and radiograph).



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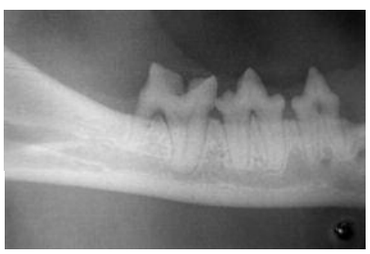

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Post-surgery re-examination after 18 months during which time professional care was administered under general anesthetic three times a year and tooth brushing twice a day.

► Conclusion

Feline oral diseases are varied and in the majority of cases they include an inflammatory component. While the prevalence of periodontal disease is not really different from its occurrence in other species, the cat does suffer from relatively aggressive forms: inflammatory extension with respect to the oral mucosa (stomatitis) and FORLs that may render the clinical diagnosis more delicate when associated with chronic periodontitis. The local immune system is often perceived as one of the key factors of aggressive oral inflammation.

3 - Prevention of oral diseases

The conventional treatment of inflammation of the periodontium has three stages:
- initial therapy: explain the appropriate hygiene measures
- control the risk factors: diabetes mellitus, thyroid disease, FeLV, FIV.
- eliminate plaque and calculus by scaling and surfacing the roots and/or subgingival debridement under the gum

The success of treatment is then based on the maintenance phase. It is necessary to help the owner maintain optimal oral hygiene in the cat and to check the results every 6 months *(Houle & Grenier, 2003)*.

► General consequences of oral diseases

Responding to periodontal inflammation appears to be one of the main goals in terms of the cat's long-term general health. Pain and infection are always connected with the development of inflammatory diseases of the oral cavity in cats. In dogs, prospective studies on the systemic consequences of periodontal disease have revealed a significant connection between the development of the disease and the scale of inflammatory histological lesions in the kidneys, liver and the mitral and tricuspid heart *(DeBowes et al, 1996; Pavlica & Petelin, 2003)*. These studies suggest blood dissemination of inflammatory substances produced as a result of periodontal disease (cytokines, IL-1, IL-6, IL-8, TNFα) *(Pavlica, 2002)*. The remote action of pathogenic periodontal bacteria through a chronic bacteremia is strongly suggested but as yet unproven *(Tou et al, 2005; Boutoille & Gauthier, 2006)*.

In cats, there is a lack of results to specify the general impact of periodontal disease, although the pathogenesis is "relatively" similar in dogs and cats. The low life expectancy of wild cats on Marion Island (4-5 years) does however suggest the negative effect of the development of this disease. It may prevent the individual from being competitive in its group and so reduce its chances of survival *(Verstraete et al, 1996)*.

► Controlling dental plaque

The main challenge in combating periodontal inflammation is disorganizing the biofilm that makes up the dental plaque *(Barbieri, 2000)*. Dental plaque forms within hours and matures after 48 hours *(Perry & Schmidt, 2004)*. Efficient daily action is therefore essential.

Pathogenic bacteria develop in a bacterial community and are embedded in a glycoprotein mesh organized around the channels and lacunas, which limits the host's defense capacities and the efficiency of many drugs. On the other hand, a properly targeted mechanical action can disrupt the physical balance of dental plaque. In dogs, the absence of mechanical control on the development of dental plaque is closely associated with the appearance of gingivitis in 7-21 days *(Tromp et al, 1986a)*. Daily checks will however resolve the gingivitis, confirming its reversible character *(Tromp et al, 1986b)*.

Dental plaque only has negative effects. By some it is considered to protect against desiccation and forms a defensive shield against colonization by much more pathogenic exogenic bacteria. The current aim is to control dental plaque as best as possible, without expecting to eliminate it completely *(Marsh, 2004)*.

► Brushing

Tooth brushing appears to be key to preventing and treating gingivitis and periodontal diseases *(Brandtzaeg, 1964)* **(Figure 22)**. A one-week study on cats showed a 95% reduction in calculus accumulation on teeth brushed once a day or twice a week *(Richardson, 1965)*.

A two-year study *(Ingham et al, 2002b)* on the other hand highlighted the low efficacy of brushing in cats, probably closely linked to the great technical difficulty of doing this on a daily basis. In the study, brushing reduced gingivitis on the buccal surface of teeth but did not show any significant difference.

More recently, a six-month field study involving 88 cat owners compared the efficacy of tooth brushing together with a specialized diet. At the end of the study, the observance of tooth brushing was just 40% *(Theyse, 2003)*.

► Mechanical role of food

Producers of cat kibbles have studied the dietary behavior of domesticated cats extensively. The size, shape and texture of kibbles are regularly tested with the aim of adapting them to the different facial conformations of different breeds of cat and encourage them to use their teeth in a physiological way. Commercial food producers have especially studied the texture of kibbles to improve the control of dental plaque **(Figure 23)**.

> Influence of the texture of the food

Texture, especially fibrous character, appears to be the most important physical aspect with respect to reducing the development of dental plaque. Numerous studies describe the negative impact of a wet food on the development of periodontal disease in dogs *(Egelberg, 1965; Harvey et al, 1996)*.
While there have been fewer studies on cats, all available results confirm the essential impact of food texture on dental plaque.

- In kittens, wet foods are implicated in promoting the appearance of calculus, gingivitis, tooth recession and bad breath *(Studer & Stapley, 1973)*.
- A significant reduction in dental plaque is observed after two weeks of study between two groups of cats fed with a dry food rather than a wet one *(Boyce, 1992)*.
- In tigers, a fiber supplement in the diet twice a week has been shown to help reduce the development of dental plaque and associated periodontal inflammation *(Haberstroh, 1984)*.
- The daily distribution of a chewing stick to 15 cats, supplementary to a dry food, helps obtain a significant reduction in dental plaque (-20%) and calculus (-39%) on premolars, molars and canines. Associated gingivitis was not as pronounced with the stick, although these data provide no statistical value *(Gorrel et al, 1998)*.
- In a similar study, 24 cats were fed with a dry food plus a chewing treat once a day for four weeks. The reduction in calculus was significant (-64%) compared with the group of cats fed exclusively with dry food. A significant difference was also observed with respect to the reduction in dental plaque (-15%) and the average gingival index (-11%) *(Ingham et al, 2002a)*.

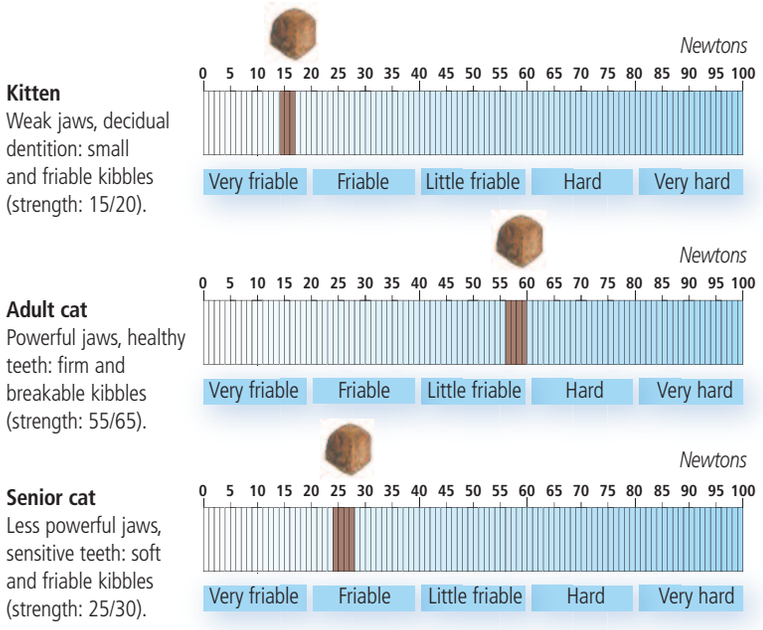
> Influence of size and shape of the food

The impact of the shape and texture of a kibble distributed ad libitum in cats have been studied together. A significant reduction of 41% in the accumulation of plaque was observed in cats fed with bigger, rectangular kibbles of a texture with a higher penetration index (+ 25%) compared

Figure 23 - Measure of a kibble's resistance to pressure
The texturometer is a good way to measure the resistance of the kibble to the forces exerted on it by the cat's jaws and teeth. Interchangeable modules mimic the shape and dimensions of cat teeth based on age and breed.

FIGURE 24 – INFLUENCE OF ERGONOMICS AND KIBBLE TEXTURE ON MECHANICAL TOOTH BRUSHING

Indicative value (Newton) measured at the Royal Canin Research Center (2002)



Due to its particular texture, the kibble encourages deeper penetration by the tooth, improving the efficacy of mechanical brushing.

with small triangular kibbles **(Figure 24)**. This reduction in dental plaque is explained by the more complete mechanical action of large kibbles. When brushing is encouraged and the kibble texture enables the tooth to penetrate deeper before it fractures, the dental friction time is longer and the efficacy of brushing is improved *(Servet et al, 2003)*.

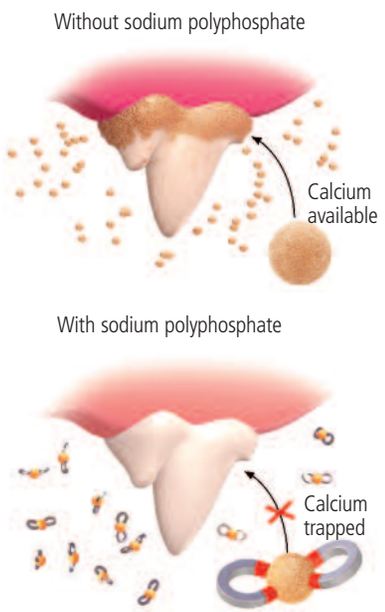
► Role of the composition of the food

The food may also contain certain ingredients that act against dental plaque and calculus, and so help prevent periodontal disease, when they are released in the oral cavity during mastication.

> Benefit of polyphosphate salts

The efficacy of some polyphosphate salts **(Figure 25)** in curbing the development of calculus is well known and clinically validated. The Ca^{2+} cations in the saliva are responsible for calcifying the dental plaque and transforming it into calculus. If polyphosphates with the capacity to chelate the versatile cations (e.g. Ca^{2+}, Mg^{2+}) are released in the oral cavity they naturally trap the calcium in the saliva in an ionic form, limiting its integration in the dental calculus matrix. The calcium is then released normally in the digestive tract so that it can be absorbed in accordance with the individual's needs. A significant reduction in the accumulation of calculus (-32%) has been observed in cats fed with a food coated with a calcium chelator, compared with a control group fed with the same kibbles without polyphosphate salts *(Servet et al, 2003; 2006)* **(Figure 26)**.

FIGURE 25 - ACTION OF SODIUM POLYPHOSPHATE SALTS WITH CALCIUM IN SALIVA



The chelated calcium ions are unavailable for the formation of calculus.

> Benefit of essential oils

The use of essential oils (thymol, eucalyptol, menthol, methyl salicylate) has also undergone long-term clinical evaluation in human dentistry. A reduction of dental plaque (-20-35%) as well as a significant reduction in associated gingivitis (-25-35%) has been obtained by using mouth-rinse solutions containing essential oils *(Perry & Schmidt, 2002)*. The benefit of this type of substance has gradually led to its incorporation in commercial foods. However, no study has yet been published on its specific efficacy.

> Other agents active against dental plaque

Current oral health research focuses on the development of new active components to combat the development of dental plaque.

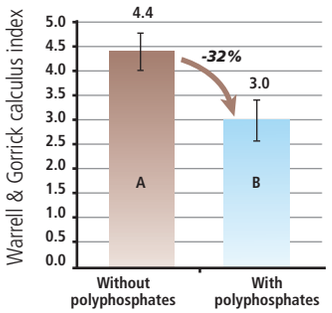
In cats, an ingredient identified in research for human cosmetics (plaque reduction nutrient or PRN) has been shown to inhibit the development of dental plaque in a standardized comparative study. Its inclusion in a dry reference food (already possess-

ing beneficial mechanical properties due to its special texture) led to a significant reduction in the accumulation of dental plaque *(Servet et al, 2006)*. After one month, a 12% reduction in dental plaque **(Figure 27)** was observed on all teeth tested (upper C, P3 and P4; upper P3, P4 and M1). A more detailed analysis of the gum line showed a reduction in plaque of 22% on all teeth tested **(Figure 28)** and 36% when the following teeth were excluded: upper premolars P3-P4 and lower M1. This validates the chemical effect on all the cat's dentition. This study also highlights the greater efficacy with respect to the food's target teeth: upper P4, P3 and lower M1.

New plaque reduction nutrients will probably be developed with the discovery of substances that act not only on bacteria cell integrity but also on the physical interface between dental plaque and the tooth, to facilitate its detachment.

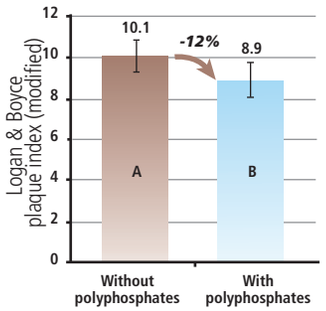
Combining the impact of size/texture and the composition of daily food, it is now possible to promise a significant reduction in the deposition of dental plaque in cats in the region of 30% and of calculus in the region of 50%. Given the cat's very particular chewing mechanism, the action due to the food's physical properties is more pronounced on the carnassials. The addition of PRNs also produces this effect in the rostral part of the oral cavity (canines and incisors).

FIGURE 26 - REDUCTION IN CALCULUS ACCUMULATION
(Royal Canin, 2005)



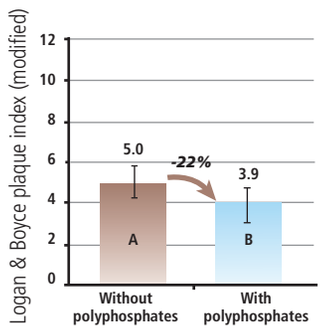
Global calculus deposit index before and after two months of a dry food enriched with polyphosphates.

FIGURE 27 - REDUCTION IN PLAQUE ACCUMULATION
(Royal Canin, 2005)



Global dental plaque accumulation index before and after one month of a dry food enriched with PRN.

FIGURE 28 - REDUCTION IN PLAQUE ACCUMULATION
(Royal Canin, 2005)



Dental plaque gingival index before and after one month of a dry food enriched with PRN.

Conclusion

The prevalence of oral inflammation in cats is widely underestimated. The clinical impact proves to be more important than it appears. In fact it is the number one cause of infectious disease in the species. Contrary to what many people think, periodontal disease is not the same in cats and dogs. It is expressed differently. The most recent studies to evaluate the secondary systemic effects of periodontal inflammations cast new light on the benefit with respect to oral diseases. The aim is not simply to combat bad breath, it is much more ambitious. It is to improve the cat's medical health and life expectancy.

Appropriate treatment reduces the chronic pain and infections associated with oral diseases. Owners are often amazed by the positive effects on their cat when the appropriate care is given. Toothache often produces major behavioral change. After treatment, the cats are generally more active, they eat better and their general condition by and large improves.

Full attention needs to be focused on preventing the development of dental plaque. The potential role of the food as an effective support for oral hygiene is now accepted. It is especially beneficial in cats, bearing in mind the difficulty of daily tooth brushing and their low interest in objects for chewing. The efficacy of this approach will no doubt be improved by working on the physical presentation of the food and searching for new PRNs.

Fallacies regarding oral diseases in cats

F	A
"Cats rarely suffer from oral lesions."	Pain is difficult to evaluate in cats by simply observing their day-to-day behavior. Dental care often leads to an improvement in the animal's health a posteriori. Any oral lesion (periodontitis, tooth resorption, stomatitis) must therefore always be considered potentially painful.
"Dental caries is common in cats."	Caries is NEVER observed in cats. The absence of caries is thought to be due to several factors: the conical shape of the teeth, the peculiarities of the diet and the composition of the dental plaque.
"Regular scaling prevents the emergence of periodontal disease in cats."	Calculus as such does not cause inflammation of the periodontium, but rather the daily accumulation of dental plaque and the bacterial populations it is composed of. There are therefore few benefits of removing calculus. Scaling helps suppress the dental plaque in a specialized dental procedure, but it does not unfortunately address the problem of permanent plaque development on the surface of the teeth. To prevent chronic periodontitis, regular scaling must always be combined with other oral hygiene techniques.
"The regular distribution of antibiotics eliminates dental plaque."	Unfortunately not. The bacteria in dental plaque are trapped in a protective complex that strengthens their cooperation. At best, antibiotics will be effective on a very superficial part of the bacterial population. Furthermore, their regular use contributes to the emergence of new strains in the plaque that have developed resistance to antibiotics.
"You have to start looking after a cat's teeth when it gets older."	The prevention of oral disease is always more effective when lesions are diagnosed early. Most cats less than 3 years of age already have tooth lesions that justify specific care. An inspection of the cat's mouth should accordingly be part of every vaccination visit.
"It's not possible to brush a cat's teeth."	While it is clearly difficult to get owners to brush their cat's teeth, the procedure is not impossible. Patience and motivation are often keys to surprising prophylactic results.
"Feeding a cat kibbles helps prevent the development of chronic periodontitis."	Simply giving your cat dry food kibbles will not be enough to reduce dental plaque. Kibble shape, size and texture need to be studied extensively to produce mechanical friction on the tooth surface enough to slow down plaque deposits and calculus formation. It now appears to be very important to combine this mechanical effect with the organic effect produced by nutritional factors that can act by diffusion on the composition of the oral flora.

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Focus on:

Nutrients acting on oral health in cats

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Introduction

It has been shown that diets consisting of dry, hard foods result in less accumulation of plaque and tartar compared to canned or other soft foods. This is due to the abrasive nature of the dry food which can scrape or brush the accumulated materials off the tooth surface. In addition, the shape of the kibble has an important role in efficacy of brushing the tooth (when the owner cannot perform tooth brushing of the cat on a regular basis). A previous study *(Servet et al, 2003)* has reported that in cats, a rectangular kibble is more effective in preventing plaque than a triangular kibble.

The purpose of this study was to determine if chelated polyphosphates (sodium polyphosphate- SPP), a unique plaque reducing nutrient (PRN) and a larger kibble size would result in a significant reduction in calculus and plaque formation. SPP is a cation sequestrant that forms soluble complexes with calcium within dental plaque, thereby preventing the accumulation of calculus. A larger kibble of a rectangular shape should require additional prehension, biting and chewing to impact calculus and plaque formation.

Materials and methods

Animals

A total of 30 healthy mixed breed cats were used in the study. To be included in this study, cats had to have normal dentition, scissor-configuration occlusion, dental plaque accumulation and no or mild gingivitis. Cats were housed in groups of 10 and provided their respective diet *ad libitum*. Fresh water was also provided *ad libitum*.

Diets

Cats were exclusively fed dry extruded diets throughout the study. No snacks, calculus or plaque control treats, chews or chew toys were allowed. Three different dietary regimens were compared:

- Diet A: A dry-expanded diet with triangular kibble shape and no oral care purpose, as a negative control diet
- Diet B: A dry-expanded diet with rectangular kibble shape formulated for oral care purpose, including SPP and PRN
- Diet C: A dry-expanded diet with triangular kibble shape and oral care provided by SPP.

All diets were formulated to meet the nutritional levels established by the AAFCO Cat Food Nutrient Profiles for adult maintenance.

Study design

All 30 cats were fed Diet A for 14 days in a pre-study phase **(Table 1)**. At the end of the pre-study phase, all cats were anesthetized and a dental prophylaxis performed to remove all supra and subgingival calculus and plaque. Each cat was deemed to begin the study with a "clean tooth model". All cats remained on Diet A and after a further seven days, plaque indexes were evaluated according to the Logan & Boyce procedure *(Logan & Boyce, 1994)*. Cats were then randomly assigned by gender and plaque forming ability to one of 3 diets. Plaque indexes were evaluated at 7 days. At 28 days, plaque and calculus indexes were evaluated by the *Logan & Boyce* (plaque) and *Warrick & Gorrel* (calculus) procedures *(Warrick & Gorrel, 1995)*. Calculus formation was evaluated a second time at day 56 **(Table 2)**. One scorer was used to score all cats in a blinded procedure to the different feeding regimens and the scoring order of the cats.

The scored teeth were the canines (C), pre-molar 3 and 4 (PM3 and PM 4) for the upper jaw (maxilla) and C, PM3, PM 4, and molar 1 (M1) for the lower jaw (mandible).

Gingivitis was evaluated according to the method of *Loe & Silness*. Teeth scored were incisor 3 (I3), C, PM3, PM4, M1 for the maxilla and C, PM2, PM3, PM4, M1 for the mandible.

TABLE 1 - STUDY DESIGN

Day -28	
Pre-study period	
Day -7	Dental scaling Plaque evaluation Allocation to group
Dietary transition	
Day 0	Dental scaling Plaque evaluation
Day 7	Plaque evaluation
Day 28	Plaque and calculus evaluation
Day 56	Calculus evaluation

Table 2 – Criteria for calculus determination	
Coverage	0 - no observable calculus 1 - scattered calculus covering less than 24% of the buccal tooth surface 2 - calculus covering between 25-49% of the buccal tooth surface 3 - calculus covering between 50-74% of the buccal tooth surface 4 - calculus covering more than 75% of the buccal tooth surface
Thickness	L = light = 1 (for calculations) M = moderate = 2 (for calculations) H = heavy = 3 (for calculations)

Data Analysis

Dental plaque and calculus scores were expressed as a whole mouth score for each cat and were calculated from the mean value of the scores for each target tooth. Data were expressed as mean ± standard error of the mean (sem). Repeated-measures ANOVA tests were used to derive F-tests for significant differences between treatments. F-values with p-values less than 0.05 were considered significant. Analyses were performed using the General Linear Model procedures in Statgraphics V5 statistical software.

Results

Plaque score at day 7 **(Figure 1)** was significantly lower for Diet B compared to Diet A and Diet B compared with Diet C (28.3% and 28.1%, respectively). In addition, gingival plaque score at Day 7 **(Figure 2)** was significantly lower for Diet B compared with Diet A and Diet C (27.3% and 30.5%, respectively). Diet B was associated with a 30.3% lower plaque score at day 28 compared to Diet A, and 30.1% lower plaque score at day 28 compared to Diet C **(Figure 3)**. Likewise, Diet B was associated with a significant reduction in gingival plaque scores at day 28 **(Figure 4)** compared to both Diet A and Diet C (31.7% and 29.2%, respectively).

Calculus score at day 28 **(Figure 5)** was significantly lower for Diet B compared to Diet A and Diet B compared with Diet C (47.4% and 23.8%, respectively). In addition, there was a significant reduction (30.9%) in calculus score for Diet C compared with Diet A. The calculus score **(Figure 6)** for Diet B was significantly lower than Diet A or Diet C at 56 days (44.6% and 18.9%, respectively). The calculus score for Diet C was significantly lower (31.7%) than Diet A at 56 days.

Figure 1 - Plaque Score Day 7

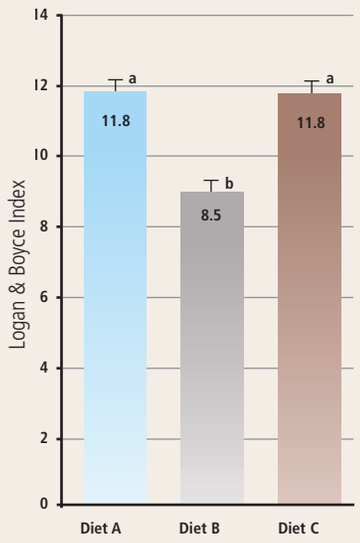


Figure 2 - Gingival Plaque Score Day 7

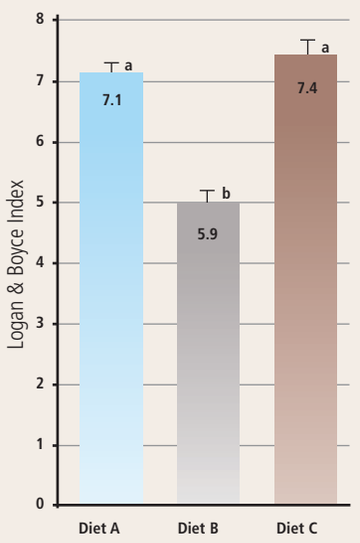
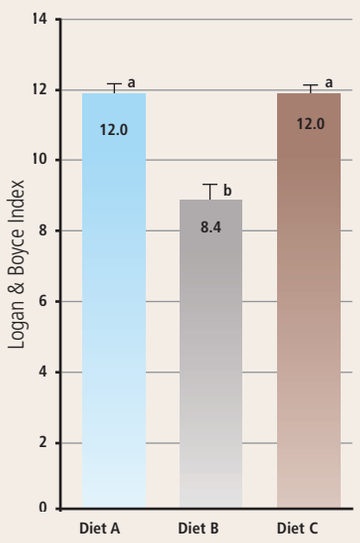


Figure 3 - Plaque Score Day 28



Discussion

The results of this study demonstrated that plaque and calculus accumulation can be significantly reduced in cats when they are fed a diet that has been specifically formulated with a larger rectangular kibble coated with sodium polyphosphate and a specific plaque reducing nutrient. Plaque was reduced by approximately 30% and calculus was reduced by approximately 45%.

Coating the kibble with sodium polyphosphate alone (Diet C) resulted in significantly less calculus build up compared to the control diet (Diet A), but no significant reduction in plaque was observed. These results confirm that sodium polyphosphate has a significant impact only on calculus, and the results are in agreement with other available feline calculus data *(Stookey, 1995; Johnson & Cox, 2002)*.

Sodium polyphosphate, coated on the external surface of the kibble is released into the oral cavity where it chelates salivary calcium so that it is unavailable for plaque calcification into calculus. When swallowed, the calcium polyphosphate complexes are not stable in the acid environment of the stomach and are rapidly converted to orthophosphates and used as a dietary phosphate source.

The larger, rectangular kibble coated with sodium polyphosphate resulted in significantly less calculus accumulation compared to the smaller triangular kibble coated with sodium polyphosphate (Diet C). Previous studies have shown that diet texture, kibble shape, size and design all impact calculus formation in cats (Servet et al, 2003). Indeed, it has been shown that dry kibble in a rectangular shape as opposed to a triangular shape aids in scraping away plaque when the cat bites and chews the kibble (Servet et al, 2003). This lower plaque deposition rate is attributed to the specially designed kibbles that convey an enhanced mechanical action, attributed to increased friction, induced both a higher crunching rate and by optimized crushing with greater teeth penetration into the kibbles. This process mimics tooth brushing. The significant impact on plaque deposition was attributed to the addition of the unique plaque reducing nutrient, coupled with the size, shape and texture of the kibble, which enhanced the mechanical action and simulated a brushing effect.

Conclusion

A 30% reduction in plaque and 45% reduction in calculus accumulation can be achieved when cats are fed a diet that has been specifically formulated with a larger rectangular kibble coated with sodium polyphosphate and a specific plaque reducing nutrient.

Figure 4 - Gingival Plaque Score Day 28

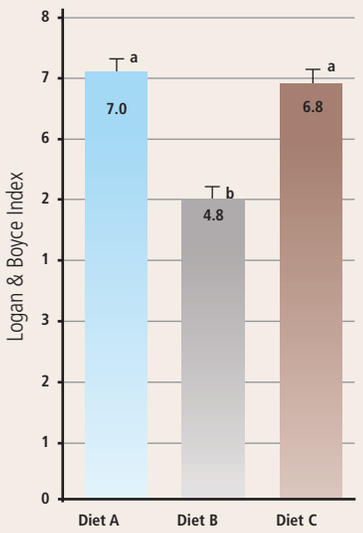


Figure 5 - Calculus Score Day 28

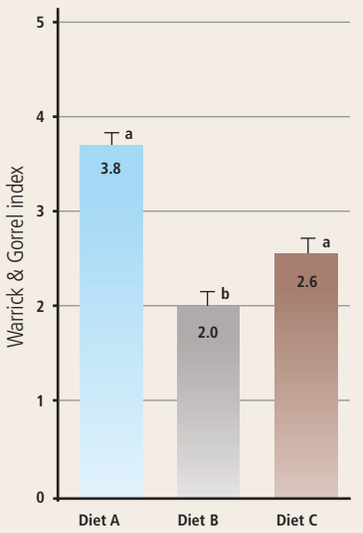
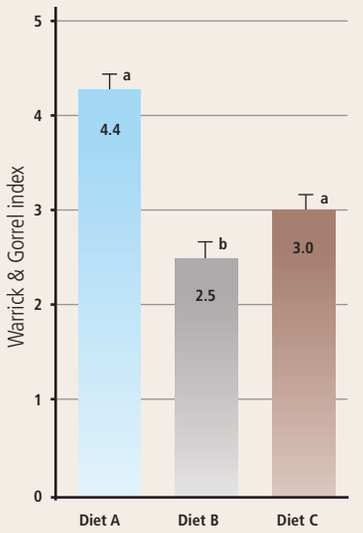


Figure 6 - Calculus Score Day 56



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70% of cats aged over 3 years old present oral lesions (Harvey, 2004).

Key points
to remember:

Periodontal disease in cats

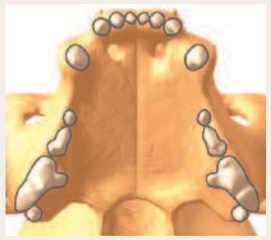
Dental health can have repercussions for the cat's general health. It is important that the teeth and oral cavity are regularly examined during a veterinary check-up.

Periodontal disease is the most common disease, affecting 70% of cats aged 20-27 months to various degrees *(Ingham et al, 2002)*. It develops in three phases:

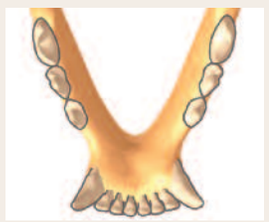
- **phase 1:** deposition of dental plaque, constituting an organic film of salivary polysaccharides and glycoproteins, colonized by aerobic bacteria;
- **phase 2:** development of gingivitis and mineralization of the dental plaque into calculus. The aerobic bacteria are replaced by anaerobic bacteria and bad breath is caused by the formation of volatile sulfur compounds;
- **phase 3:** destruction of the periodontal ligament (periodontitis). The bacteria reach the base of the root and attack the bone in which the tooth is embedded. Gum recession and osteolysis facilitate the tooth's loosening.

DENTAL FOLLOW UP

Upper jaw

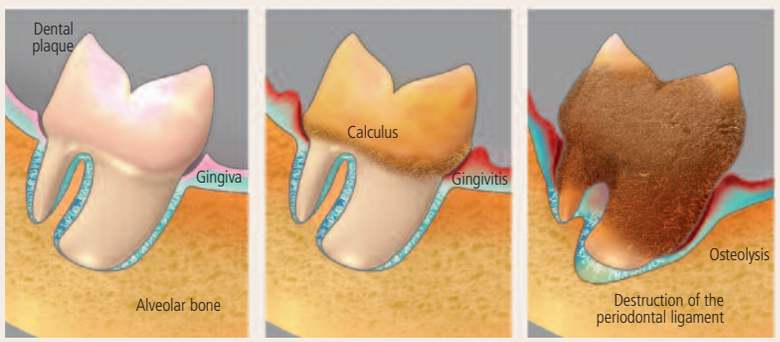


Lower jaw



Date	Age	Comments

O: absent tooth
X: extracted tooth
B: broken tooth
GR: unembedded tooth
FORL: feline odontoclastic resorption lesion
M: loose tooth



Nutritional responses

Tooth brushing is the best means of preventing the development of periodontal disease. When it is not possible because the owner is not available or the cat is uncooperative, the food can play a beneficial preventive role based on its mechanical and/or chemical effects. The expected benefits are observed only when the cat eats nothing else on a daily basis.

Mechanical effect

Dry foods can have a light abrasive effect on the teeth when they are chewed correctly before swallowing. This permits the destruction of the bacterial mesh that constitutes dental plaque. It is important not to crush or mash the kibbles, as this will negate these benefits.

The mechanical effect is based on matching the appropriate kibble size, shape and texture to the age and size of the individual animal. The aim is maximum penetration of the kibble by the tooth before the kibble crumbles, so as to obtain relative "brushing".

The fact that the cat chews also stimulates the production of saliva, which has a beneficial antibacterial role.

Effect on bacterial flora

Some nutrients can inhibit the deposition of dental plaque by curbing the adhesion of bacteria and/or acting as a bactericide *(Servet et al, 2006)*. The aim is to reduce the proliferation of the anaerobic bacterial population and the production of volatile sulfur compounds responsible for halitosis.

While no specific studies have been published on cats, several studies have demonstrated the efficacy of some nutrients in limiting bad breath. Of the nutrients studied, organic zinc salts (e.g. zinc citrate) and inorganic zinc salts (e.g. zinc sulfate: $ZnSO_4^{2-}$) present beneficial bacteriostatic properties *(Weesner, 2003; Waller, 1997)*.

There are also bacteriostatic and bactericidal oils. Eucalyptus oil for example helps actively reduce the production of sulfur fatty acids *(Pan et al, 2000)*. Lastly, some bacteria are highly sensitive to the action of tea polyphenols *(Isogai et al, 1995)*, the antioxidant properties of which are well known.

Chemical effect

Sodium polyphosphates have a chelator effect on the calcium in saliva and so help limit the calcification of dental plaque.

Conclusion

Adding up the impact of size/texture and composition of daily food, it is now also possible to promise a significant reduction in the deposition of dental plaque in cats.

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Cancer

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Nutritional status of cats with cancer: nutritional evaluation and recommendations

ABBREVIATIONS USED IN THIS CHAPTER

BCS: body condition scoring
CNS: central nervous system
FeLV: feline leukemia virus
MER: maintenance energy requirement
NSAIDs: non-steroidal anti-inflammatory drugs
RER: resting energy requirement
SGA: subjective global assessment

Nutritional status of cats with cancer: nutritional evaluation and recommendations

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Kathryn Michel graduated from the school of Veterinary Medicine at Tufts University with a doctorate in Veterinary Medicine in 1983. She completed a residency in small animal clinical nutrition and a master's degree at the University of Pennsylvania, followed by a postdoctoral fellowship with the Nutrition Support Service at the School of Medicine. She is a diplomate of the American College of Veterinary Nutrition and currently an associate professor of nutrition and chief of the Section of Medicine at The University of Pennsylvania. Her research interests include nutritional assessment, nutritional requirements of hospitalized companion animals, and nutrient modulation of gastrointestinal and endocrine diseases.

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The impact of diet on neoplastic disease is multi-faceted. Both dietary habits and nutritional status have been found to be risk factors for the development of certain types of cancer. Nutrition, including special diets and specific nutrients, has also been investigated for its therapeutic role in cancer patients. In addition, the response to chemotherapy and tolerance of treatment has been found to be associated with nutritional status.

With the current lack of nutritional investigation specific to feline cancer patients, the focus of this chapter will be on what we know about the clinical presentation of this population, the process of assessing nutritional status in cats, the significance of poor nutritional status in cats affected with neoplasia, and what strategies we currently have at our disposal to intervene in cancer patients who are experiencing anorexia, weight loss, and a decline in body condition.

The interactions of diet and neoplasia have been much more extensively investigated in human patients, and what preliminary studies exist in veterinary medicine almost all focus on canine cancer patients. Cats, however, do make up a substantial portion of the oncological caseload and one might be tempted to apply findings in other species to the feline patient. This, however, should be done with caution given the many unique aspects of feline physiology, metabolism, and disease. For example, one report found that the minority of canine cancer patients (5%) had an underweight body condition *(Michel et al, 2004)*. Conversely, the clinical impression has been that feline cancer patients are often in poor body condition. A recent investigation at the University of Pennsylvania found this to be the case with 44% of patients assessed as having an underweight body condition and > 90% as having evidence of muscle wasting *(Baez et al, 2007)* **(Figure 1)**.

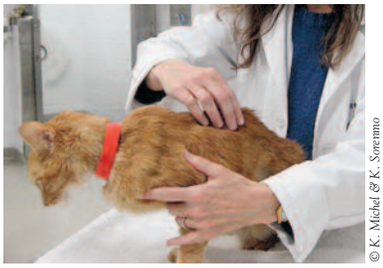
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Figure 1 *- Over 90% of feline cancer patients examined in an investigation at the University of Pennsylvania were found to have experienced muscle wasting (Baez et al, 2007).*

1 - Characteristics of the feline cancer population

Cats comprise approximately 26% of all cancer patients seen by the oncology service of the University of Pennsylvania and the fraction of cats versus dogs has remained constant over the past decade. Despite the fact that cats represent a significant portion of patients that undergo treatment through the oncology section, there is limited information regarding the feline cancer population on how nutritional factors might influence treatment and outcome. In order to characterize the feline cancer population better in terms of age, breed, sex, body weight, and what types of malignancies they were treated for, information on all cats with malignancies that were seen by all sections of the Veterinary Hospital of the University of Pennsylvania over the past three years was collected. This population may be representative of the feline cancer population in many other larger urban referral centers.

► Epidemiologic data

A total of 712 cats with a diagnosis of various types of cancer were evaluated. Eighty percent were domestic short hair cats, with a slight over-representation of males versus females (52.7 versus 47.3%) of which all but one cat was neutered. The majority of cats were middle-aged to older, with a mean age of 11 years and a mean body weight of 4.58 kg. Sixty percent of the cats had different types of solid tumors and 40% had lymphoma or leukemia. When comparing cats with solid tumors to cats with lymphoma or leukemia, we found that these two groups differed significantly in age and body weight; cats with solid tumors were significantly older and heavier than cats with lymphoma/leukemia with a mean age of 12.0 years versus 10.5 years ($p< 0.0001$) and a mean body weight of 4.7 kg versus 4.4 kg ($p= 0.049$). This difference is not surprising since most cats with lymphoma present with signs of systemic disease and multi-organ involvement at the time of diagnosis.

► Feline lymphoma

Cats with lymphoma represent a significant portion (40%) of the total hospital feline cancer population and an even higher proportion of the oncology section's cat population, since many of these are treated with systemic chemotherapy. The original World Health Organization Classification system listed the various anatomic forms as generalized, alimentary, thymic, skin, leukemia (true, i.e. only blood and bone marrow involved) and others *(Owen, 1980)*. A more simplified and practical classification system includes only 4 groups and feline lymphoma is typically classified according to anatomic site: the thoracic form, the alimentary form, the multicentric form, and an unclassified form (skin, leukemia, CNS, nasal etc) *(Moore et al, 2001)*.

Alimentary lymphoma is the most common anatomic form of lymphoma currently seen in our hospital. This is probably also representative of the situation in most other oncology practices since most cats with lymphoma that are diagnosed today are FeLV negative with primary alimentary involvement. Cranial mediastinal lymphoma typically found in FeLV positive younger outdoor cats is not as common anymore *(Gabor et al, 1998; Vail et al, 1998; Richter, 2003;*

Unlike many dogs, cats with lymphoma are typically diagnosed when they have clinical signs from their lymphoma. Systemic signs secondary to lymphoma will constitute a sub-stage B category, which according to many studies is associated with a worse prognosis. In fact, sub-stage B is a more consistent negative prognostic factor in the canine lymphoma literature than stage of disease *(Valerius et al, 1997; Baskin et al, 2000; Garrett et al, 2002; Simon et al 2006).*

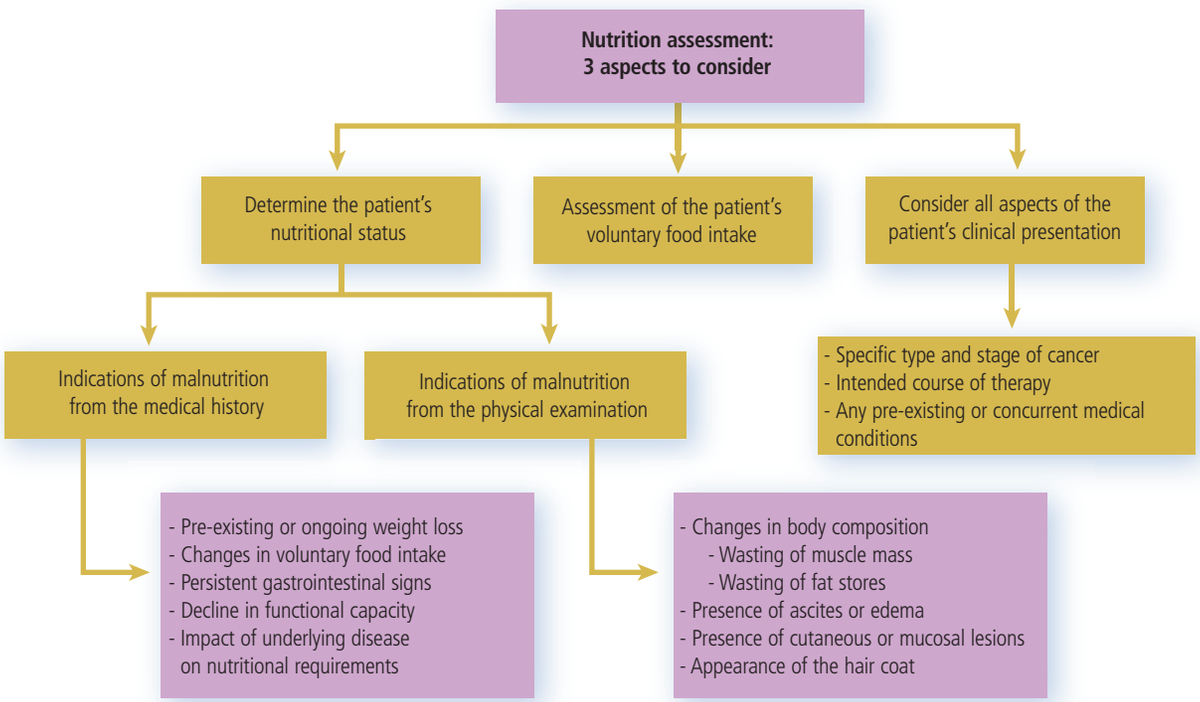
Louwerens et al, 2005; Milner et al, 2005). The alimentary forms of lymphoma often pose a challenge to the clinician both from a therapeutic and a nutritional point of view.

The list of which signs qualify as B-signs has not been completely defined, and leave some room for subjectivity, but in general include any signs of systemic disease at diagnosis, regardless whether these signs are directly associated with the lymphoma, are paraneoplastic, or are from other concurrent illness. Many of these B-signs are typical presenting complaints when cats with lymphoma present for initial evaluation and diagnostics. The typical clinical signs associated with alimentary lymphoma include: decreased appetite, anorexia, vomiting, diarrhea, weight loss and fatigue *(Richter, 2003)*. The clinical signs might have lasted for weeks to months, and many of these cats present in poor nutritional condition. Successful management of these patients requires effective treatment of the underlying malignancy, i.e. chemotherapy, while at the same time controlling nausea, vomiting, diarrhea, anorexia and instituting adequate nutritional support.

2 - Clinical nutritional assessment of cancer patients

The process of nutritional assessment involves evaluation of not only the patient's nutritional status but also the diet it is receiving and how that diet is being fed. Furthermore, this process should not be an initial one time exercise but an on-going practice throughout the patient's course of treatment so that adjustments can be made in diet and feeding recommendations based on the patient's response to therapy. The actual task of nutritional assessment involves several steps **(Figure 2)**. First determine the patient's nutritional status which is a subjective evaluation based on the medical history and physical examination. Next the patient's voluntary food intake should be assessed. Once the patient's nutritional status and food intake have been evaluated, other aspects of the patient's clinical presentation should be considered, including the specific type and stage of cancer, the intended course of

FIGURE 2 - A STEP-BY-STEP APPROACH FOR THE NUTRITIONAL ASSESSMENT OF FELINE CANCER PATIENTS



therapy, and whether or not there are any pre-existing or concurrent medical conditions. Formulating a suitable nutritional plan for each patient needs to encompass all of this information.

The nutritional assessment will help determine whether the patient is experiencing malnutrition or at risk of becoming malnourished, whether the diet and the intake of that diet are adequate to the patient's nutritional needs, whether any specific dietary management, including assisted feeding, is indicated and, in the case of assisted feeding, which route of feeding will be the safest, most effective and best tolerated by the patient. The process of nutritional assessment can also identify potential problems that might arise as a consequence of the dietary management, and allow for planning to prevent them or anticipate them through appropriate monitoring.

► Determining nutritional status

A technique referred to as subjective global assessment (SGA) was developed for the nutritional assessment of human patients approximately 20 years ago *(Detskey et al, 1987)*. The technique was designed to utilize readily available historical and physical parameters in order to identify malnourished patients who are at increased risk for complications and who will presumably benefit from nutritional intervention. The assessment involves determining:
- whether nutrient assimilation has been restricted because of decreased food intake, maldigestion or malabsorption;
- whether any effects of malnutrition on organ function and body composition are evident;
- and whether the patient's disease process influences its nutrient requirements.

To adapt the SGA to cancer patients, the medical history should be assessed in five areas:
- pre-existing or ongoing weight loss
- extent of voluntary dietary intake
- the presence of persistent gastrointestinal signs either from the primary disease or treatment the patient is receiving
- the patient's functional capacity (e.g., weakness, presence of exercise intolerance)
- and the impact of the patient's underlying disease state.

When dealing with cancer patients one must consider the ways in which the tumor could directly or indirectly affect food intake, the impact that cancer therapy may have on food intake and metabolism, and the recognition that the tumor itself may exert effects on metabolism that negatively influence nutritional status.

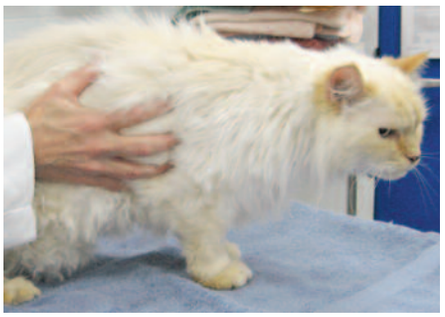
It is often difficult to document a history of weight lost since most animals are only weighed when they come in to a veterinary clinic and not always then. It is critical that cats being treated for cancer are weighed consistently on the same scale and that the scale is sensitive and accurate for animals in the feline weight range. It is also important to know the time course over which the weight loss has occurred. Rapid weight loss is generally of greater concern because it is more likely to involve a greater percentage of lean tissue catabolism than a more gradual weight loss. Having said that, cancer cachexia syndrome, as documented in human cancer patients is characterized by loss of both lean body mass and adipose tissue and can take a chronic course.

The physical examination focuses on changes in body composition, specifically wasting of fat stores and muscle mass, the presence of edema or ascites, the presence of mucosal or cutaneous lesions, and the appearance of the patient's hair coat. Several excellent body condition scoring systems (BCS) have been developed for cats *(Laflamme, 1997; German et al, 2006)*. However, these systems do not apply well to cats with cancer because they depict patients that deviate from optimal based on under- or overconsumption of protein and calories. It has been reported in a study from the University of Pennsylvania that over 90% of cats diagnosed with cancer have evidence of muscle wasting even in cases where the patient had adequate or even excessive fat stores *(Baez et al, 2007)*. Without careful examination, which involves palpation of skeletal muscle mass over bony prominences (such as the scapulae or vertebral column), some of these patients might be misclassified as overweight

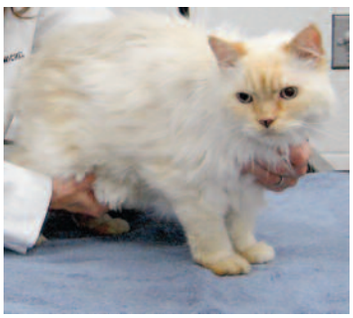
Regardless of the reason a cat is presented at the clinic, the body weight must be recorded.

Figure 3 - Evaluation of the cat's body composition.

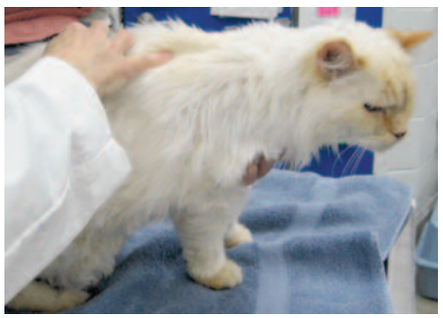
Feline cancer patients can present with a relatively normal body silhouette and weight.



Hence, body condition scoring requires manual palpation to assess both fat and lean body mass.



Assessment of body fat in cats should always involve palpation of the abdominal fat pad, in addition to palpation over the rib cage.



In addition to the standard techniques used for body condition scoring, feline cancer patients should always be assessed for evidence of muscle wasting by palpation for muscle mass over boney prominences such as the vertebral spinous processes.

TABLE 1 - MUSCLE MASS SCORING SYSTEM

Score	Muscle Mass
0	Severe muscle wasting as evidenced by pronounced decreased muscle mass palpable over the scapulae, skull, or wings of the ilia.
1	Moderate muscle wasting as evidenced by clearly discernable decreased muscle mass palpable over the scapulae, skull, or wings of the ilia.
2	Mild muscle wasting as evidenced by slight but discernible decreased muscle mass palpable over the scapulae, skull, or wings of the ilia.
3	Normal muscle mass palpable over the scapulae, skull, or wings of the ilia.

or even obese **(Figure 3)**. Thus we recommend subjectively evaluating muscle mass **(Table 1)** in addition to using one of the standard body condition scoring systems available.

The findings of the historical and physical assessment are used to categorize the patient as:
A: well nourished
B: borderline or at risk of becoming malnourished
C: significantly malnourished.

Coupling this assessment with the patient's cancer diagnosis, stage, treatment protocol, and prognosis will aid in making decisions about nutritional therapy.

► Assessment of voluntary food intake

In order to be able to assess whether that patient's food intake is adequate, you must have a caloric goal, select an appropriate food, and formulate a feeding recommendation for the patient. By doing so, you will have an accurate account of how much food is offered to the patient, and will be able to evaluate the patient's intake based on how much of the food is consumed.

> Hospitalized patients

For hospitalized patients, we recommend using an estimate of resting energy requirement (RER) as your initial caloric goal **(Table 2)** as most hospitalized patients are not expending much more energy than RER while they are caged. Under such conditions most patients eating at least RER will

lose little if any weight. Clearly if a patient is willing to consume calories in excess of RER it should be permitted to do so. However, starting out with this amount of food will provide a goal to aim for with patients who have a decreased appetite. It is critical to monitor both the patient's food intake and body weight to establish whether the patient is in energy balance or not and to permit timely adjustment of the dietary plan if the patient is not responding as anticipated **(see chapter 13)**

> Out-patients

The majority of cancer patients are treated as out-patients and therefore will require additional caloric intake to compensate for energy expended on voluntary physical activity. Under these circumstances, the daily maintenance energy requirement (MER) should be estimated **(Table 3)** and used to calculate the initial caloric goal.

This information should be converted into clear feeding directions for the cat's caregiver using specific portions of whichever foods are being offered to the patient in a manner analogous to how a drug dosage would be calculated and prescribed. There should be a plan for reporting back to the clinician about daily food intake and for accurately monitoring body weight on a regular basis to assess the patient's response and allow for modification of the feeding plan as appropriate.

TABLE 2 - ESTIMATION OF RESTING ENERGY REQUIREMENT (RER)

RER = 70 BW(kg)$^{0.73}$
or RER = 30 BW(kg) + 70*

BW (kg)	RER = 70 BW(kg)$^{0.73}$
1	70
1.5	94
2	116
2.5	137
3	156
3.5	175
4	193
4.5	210
5	227
5.5	243
6	259
6.5	274
7	290
7.5	305
8	319

**patients weighing >2 kg*
[For patients with excessive adipose tissue use a conservative estimate of the individual's lean body weight for the calculation.]
BW: body weight

TABLE 3 - ESTIMATION OF DAILY MAINTENANCE ENERGY REQUIREMENT (MER)

MER = 1.1 to 1.2 x RER

BW (kg)	1.1 x RER (kcal)	1.2 x RER (kcal)
1	77	84
1.5	103	113
2	128	139
2.5	151	164
3	172	187
3.5	193	210
4	212	232
4.5	231	252
5	250	272
5.5	267	292
6	285	311
6.5	301	329
7	319	348
7.5	336	366
8	351	383

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Figure 4 - Assessment of weight loss. *Many feline cancer patients have already experienced weight loss at the time of diagnosis and are at risk of further deterioration in body condition during the induction phase of chemotherapy.*

► Determining the need for assisted feeding

Patients who are unable to eat or whose voluntary food intake is insufficient to maintain energy balance will require some form of intervention whether it is as simple as coax feeding or a more aggressive approach using some form of assisted feeding **(see chapter 13)**. Clearly the feeding management of those patients who are already significantly malnourished at the time of presentation should receive immediate attention.

It is often the case that reduced food intake as a consequence of cancer therapy can be anticipated. Therefore a plan should be in place for nutritional intervention should the need arise, particularly in the case of patients whose nutritional status is considered borderline at the commencement of therapy.

3 - Cancer cachexia syndrome

► Distinction between weight loss due to starvation and cachexia

It is well recognized that weight loss is a common finding in human cancer patients and one which has been shown to have associations with clinical outcome *(Tisdale, 1997)*. As already stated, weight loss in association with neoplasia can occur for a number of reasons including the effects of the tumor and the cancer therapy. However, the weight loss seen in many human cancer patients does not appear to be attributable to decreased food intake alone. In simple starvation, individuals lose principally adipose tissue, whereas patients with neoplasia can experience loss of both lean and adipose tissues *(Moley et al, 1987)*. Furthermore, the magnitude of the weight lost often does not correspond to the amount of food consumed, and this weight loss cannot be reversed by a concomitant increase in caloric intake *(Costa et al, 1980)*.

This paraneoplastic syndrome of cancer cachexia is hypothesized to result from metabolic alterations that exist as a consequence of the underlying tumor. Derangements in carbohydrate, lipid, and protein metabolism have been found in both human and canine cancer patients that may contribute to weight loss *(Shapot & Blinov, 1974; Nixon et al, 1980; Nolop et al, 1987; Shaw & Wolfe, 1987; Vail et al, 1990; Tayek, 1992; McMillan et al, 1994; Ogilvie et al, 1994;1997; Vail et al, 1994; Dworzak et al 1998)*. There is also evidence that cytokines, including TNFα, IL-1, and IL-6, could play a role in these metabolic alterations *(Gelin et al, 1991; Moldawer and Copeland, 1997)*.

What remains unknown is to what extent the weight loss seen in feline cancer patients is attributable to decreased appetite or the direct effects of the tumor or therapy on nutrient assimilation or metabolism and to what extent cancer cachexia syndrome **(Figure 4)** may be responsible. This is important because in the former situation careful attention to feeding management should be able to avert or ameliorate loss of weight and body condition, whereas in the latter situation, effective means of counteracting the progression of cachexia remain elusive.

► Body condition as a prognostic factor

Cancer cachexia syndrome has been implicated as a negative prognostic factor for survival, surgical risk, response to chemotherapy, and tolerance of treatment in human cancer medicine *(Daly et al, 1979; DeWys et al, 1980; McCaw, 1989)*. There have been some preliminary studies in companion animal cancer patients looking at body condition and weight loss. When body condition was evaluated in dogs seen at the oncology service at the University of Pennsylvania only 5% of the dogs were considered significantly underweight with a BCS <2.5/5 (1= cachectic, 3=optimal; 5=obese) while 29% were classified as significantly overweight (>4/5) *(Michel et al, 2004)*.

Conversely, an investigation of feline cancer patients at the same institution documented that up to 44% of cats with cancer treated through the oncology service had a BCS <3/5 *(Baez et al, 2007)*.

This study also found that both a low BCS as well as a low body weight had a negative impact on prognosis. Both cats with solid tumors and cats with lymphoma have significantly shorter survival times if their BCS or their body weight were low. Furthermore, a positive correlation between remission status and BCS was found.

Cats in remission are more likely to weigh more and have a higher body condition score.

The presence of weight loss or cachexia was not found to be an independent negative prognostic indicator as it has been in similar studies in human oncology *(Vigano et al, 2000)*. Nevertheless, the results suggest that weight loss and deterioration of body condition are significant problems in feline cancer medicine and may have consequences for response to treatment, remission duration and quality of life.

4 - Nutritional consequences of anti-cancer therapy

Debilitated cats with advanced alimentary lymphoma represent some of the most challenging cases in medical oncology. The poor nutritional status in these patients is typically a result of a combination of factors resulting in prolonged inadequate nutrition. These signs may be direct effects of gastrointestinal involvement, stage of disease or may also, in part, be due to a deranged metabolic state secondary to cancer cachexia syndrome.

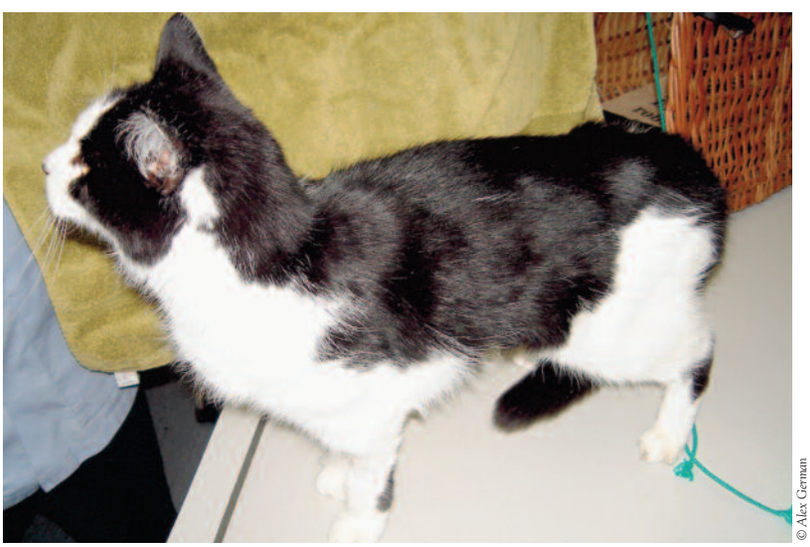
► Secondary effects of chemotherapeutic protocols

Regardless of the pathogenesis, in order to reverse these signs, treatment of the underlying malignancy is necessary. This requires the use of chemotherapy. The choice of chemotherapeutic protocol is influenced by cell type or lymphoma grade. Most oncologists use a combination of chemotherapeutic drugs including, prednisone, asparaginase, vincristine, cyclophosphamide, methotrexate, and doxorubicin to treat cats with intermediate to high grade lymphoma (intermediate to large cell type) *(Moore et al, 1996; Valerius et al, 1997; Vail et al, 1998; Zwahlen et al, 1998; Krystal et al, 2001; Teske et al, 2002; Richter, 2003; Milner et al, 2005)*. Many of these drugs are associated with gastrointestinal signs such as nausea, vomiting, anorexia, diarrhea, and fatigue; clinical signs which many of these cats already exhibit. Debilitated patients may be more likely to experience adverse reactions to treatment, require dose reductions, have a decreased response to treatment and have a worse outcome. The induction phase can be particularly difficult and requires careful monitoring of tumor response, addressing toxicity from treatment as needed and constant assessment of the general status of the cat.

A cat with alimentary lymphoma and severe weight loss.

► Variability of individual responses

Lymphoma is a chemotherapy-responsive malignancy and some cats with high grade lymphoma may go into remission quickly, tolerate the chemotherapy and improve without specific nutritional intervention. However, others may take longer to respond and/or become increasingly intolerant to chemotherapy and suffer progressive weight loss through the induction phase. Some of these cats may never attain remission and fail early, and others may be taken off chemotherapy prematurely due to unacceptable toxicity and poor quality of life. These cats require intervention.



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Dietary aversion

If a food is associated with distress, an unpleasant experience (hospitalization) or digestive problem (poisoning), the food is likely to be avoided in the future. This phenomenon is known as aversion. Aversion is a form of negative conditioning used by animals to avoid foods that are unsuitable for them.

In cats, aversion sets in very quickly. A single meal associated with unpleasantness leads to a refusal to eat. Such aversion can persist for at least 40 days *(Bradshaw et al, 1996)*. The smell alone of a food associated with digestive disorders is enough to elicit aversion. Cats even go so far as to show aversion for their usual food if it is served in the presence of an air current bearing the odor of a food to which they have developed an aversion.

Table 4 - Signs of learned food aversion

The patient initially shows interest in food when it is offered but backs away after smelling or tasting the food.
The patient salivates, swallows repeatedly or turns its head away when food is offered.
A caged patient positions itself as far away as possible from the feeding bowl.

A prospective study on the incidence of toxicity and overall quality of life in dogs and cats treated with chemotherapy at the University of Pennsylvania confirmed that weight loss, vomiting, and anorexia were more common in cats than dogs *(Bachman et al, 2000)*. Sixty percent of the cats lost weight in the induction phase, this is in sharp contrast to the situation in dogs, where close to 70% gained weight (p = 0.0077). Doxorubicin was the drug most often associated with weight loss and vomiting in both cats and dogs. These results reflect the complexity of the situation. Chemotherapy is necessary to treat the underlying malignancy, yet it may also exacerbate the clinical signs and contribute to further weight loss, vomiting, diarrhea and reduced quality of life. The overall median survival of cats with lymphoma is less than one year; poor nutritional status and low body weight are associated with worse outcome in cats *(Baez et al, 2007)*. It is unknown whether early intervention to reverse the loss of weight and body condition improve outcome in these cats, but these results clearly show that more attention should be paid to ensuring adequate nutritional support, both to improve quality of life as well as to potentially prolong survival.

5 - Dietary intervention

► Coax feeding

When a cat exhibits a decreased appetite it is natural to try to tempt it to eat by offering a variety of palatable foods. Very often the caregiver will further attempt to coax the patient to eat by putting the food close to the cat's face or actually placing food in its mouth. Sometimes these techniques can be successful and lead to adequate food intake by the patient. However, such efforts are labor intensive and time consuming. A feeding plan with specific caloric goals should be formulated in advance so the caregiver can assess the adequacy of the patient's food intake. Furthermore, it is very important to recognize that cats sometimes associate nausea, general indisposition, or pain with the act of eating or even the sight or scent of food. This is called learned food aversion and can further complicate achieving adequate food intake in a patient.

Therefore, whenever attempting to coax feed a cat, one must remain alert to the signs of food aversion **(Table 4)** and recognize that there will be circumstances when it will be necessary to resort to assisted feeding for a time because of the risk of causing or exacerbating this condition. **Table 5** lists some general guidelines on how to approach these patients. However, every patient will be different and it is necessary to observe each individual's behavior in order to decide how best to proceed.

► Assisted feeding

Much of the information gleaned in your nutritional assessment will aid in making the choice of the best route for assisted feeding access. Other information to evaluate in the decision making process should include:

- assessment of gastrointestinal tract function
- assessment of other organ systems that may have an impact on the patient's ability to tolerate specific nutrients
- assessment of the patient's ability to tolerate a feeding tube and tube placement
- assessment of the patient's risk for pulmonary aspiration.

If parenteral nutrition is contemplated, it is also necessary to include assessment of the ability to obtain vascular access and the patient's fluid tolerance.

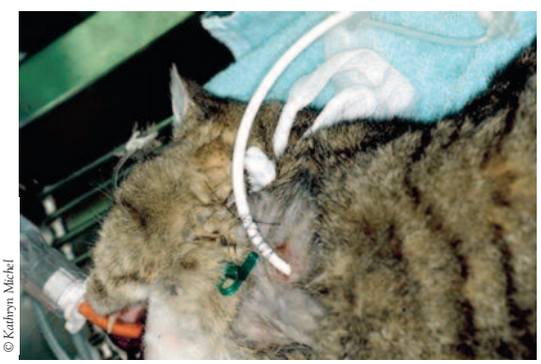

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Figure 5 - Assisted feeding by esophagostomy tube. *Esophagostomy tubes are relatively non-invasive and simple to place and provide well-tolerated access for assisted feeding in feline patients.*

There are some additional considerations to take into account when assessing cancer patients for assisted feeding. Certain chemotherapeutic agents can impair wound healing with the consequence of a greater risk of septic complications with tubes that are placed into the peritoneal cavity (e.g. gastrostomy and enterostomy tubes). This risk can be magnified if the patient is receiving immunosuppressive drugs. Radiation therapy can have similar consequences if the tube placement is within the field of treatment. The esophagostomy tube has many of the advantages of a gastrostomy tube but carries a lower risk of serious

septic complications **(Figure 5)**. These tubes are simple and inexpensive to place and usually well-tolerated by feline patients.
One final consideration is the fact that assisted feeding is a form of life-support. Used properly it could have the benefit of both prolonging life and ensuring a better quality of life for the patient. However, there may be circumstances, in terminal patients, where humane euthanasia is in the better interest of the patient then prolonging life. It is often more difficult for involved pet owners to terminate life supporting therapies than to initiate them and therefore the decision to use assisted feeding in a patient should bear in mind these ethical issues.

Figure 6 is a decision tree that illustrates how these various factors should be taken into account to choose the safest and most effective route of assisted feeding. Assisted feeding in feline patients is covered in more detail in chapter 13.

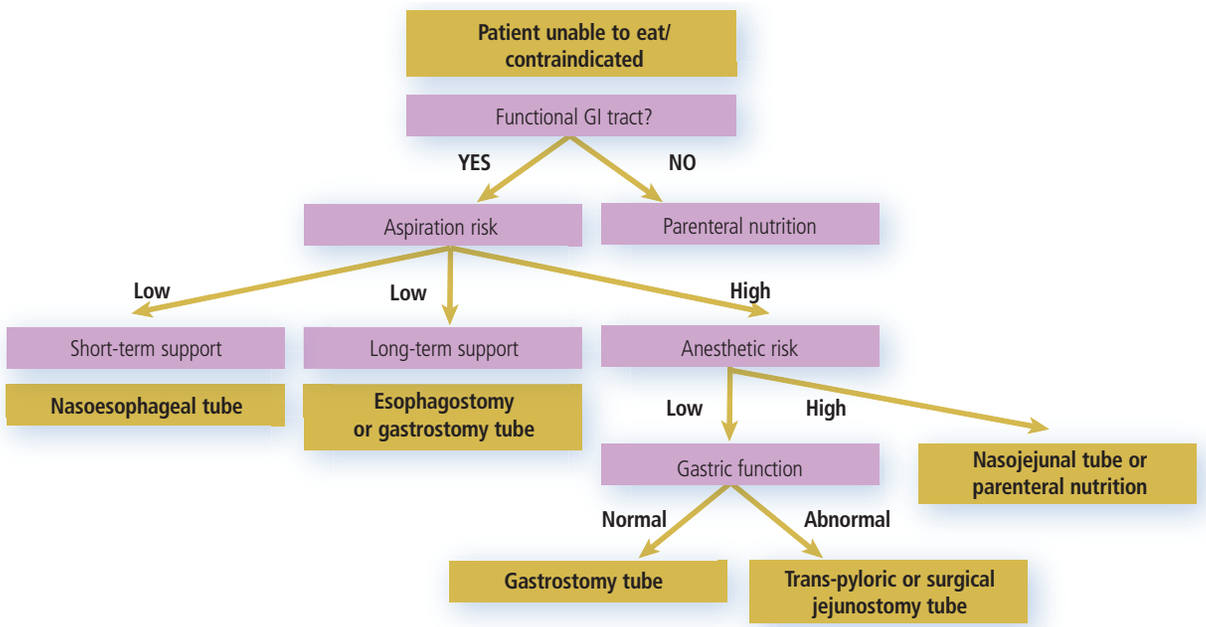
► Diet selection

In general, diet selection is based on which of patient's problems can and should be addressed with nutrition and the nutritional requirements of the patient. While there have been many investigations of ways in

TABLE 5 - GUIDELINES FOR COAX FEEDING

Resist the temptation to coax a cat to eat when it is showing overt signs of nausea and discomfort. Cats that gulp or salivate at the sight or scent of food, who turn their heads away from the food or spit it out when it is placed in their mouths should not have food forced on them.
Consider the possibility of using anti-emetic drugs if vomiting and nausea are a problem.
Consider the use of assisted feeding as an alternative.
Consider appetite stimulant drugs; however, these should only be used in patients that either have no signs of food aversion or who have begun to feel better and may now be able to overcome a food aversion.
For cats that are showing some interest in food: - try novel food items. Remember that table foods will not provide all of the nutrients that a cat requires and if a cat eats an exclusively home cooked diet for more than a few days, that diet should be evaluated by a veterinary nutritionist for nutritional adequacy; - make mealtimes as comfortable and unstressful as possible. Try not to schedule them at the same time as other treatments such as the administration of medications; - divide the day's food into as many small meals as possible. Offering small meals of fresh food is more likely to meet with success than a few large meals no matter how tempting the food is; - the food ingredients that increase palatability for most cats include moisture, fat, and protein. Switching from a dry pet food to a canned food or the other way around may improve food acceptance; - remember that "mouth feel" (the texture and consistency of food) is an important aspect of palatability for cats (so switching to canned foods will not always meet with success).
Trying foods with increased fat or protein content should be done with consideration of the patient's tolerance for these nutrients.
The standard advice for getting anorexic cats to eat has been to warm the food to just below body temperature. This is believed to increase the aroma of the food, which in turn will enhance the taste. However, this might be counterproductive in patients that are showing food aversion.

FIGURE 6 - DECISION TREE TO DETERMINE THE ROUTE OF ASSISTED FEEDING



which diet and specific nutrients may be used to slow or antagonize tumor growth, modulate immune function, or counteract the cancer cachexia syndrome, most of this research has been done in rodent models or human patients. There have been preliminary clinical investigations involving canine cancer patients, but none to date that have involved cats. A canned low carbohydrate diet that was fortified with fish oil and arginine was found to increase survival time and disease free interval in dogs with stage III lymphoma *(Ogilvie et al, 2000)*. With the exception of the additional fish oil, many conventional canned cat foods have a similar formulation to the diet that was used in this investigation.

The major consideration for diet selection for cats with cancer should be acceptance by the patient. The diet should meet feline nutritional requirements and if it does not, it should be supplemented to address any deficiencies. Ideally, the diet should be of high caloric density, as this will aid in ensuring sufficient energy intake by the patient, especially in cases when appetite is decreased. In addition, if the patient has clinical signs or disease secondary to or in addition to cancer that would benefit from dietary management, efforts should be made to select and feed a diet formulated to address those conditions.

Lastly, in patients with alimentary neoplasia, in particular lymphoma, nutrient malabsorption can occur. While this can lead to generalized protein-calorie malnutrition, it can also lead to specific micronutrient deficiencies. One nutrient deficiency which has been reported in cats with gastrointestinal disease, including lymphoma, is cobalamin deficiency *(Simpson et al, 2001)*. Cats with inflammatory bowel disease complicated by cobalamin deficiency have shown improved weight gain and response to therapy with parenteral supplementation of this vitamin (cobalamin, 250 µg SC once weekly, for 4 weeks) *(Ruaux et al, 2005)*. It is our clinical impression that cats with alimentary lymphoma also can benefit from parenteral cobalamin supplementation.

6 - Pharmacological intervention

In addition to treating the underlying malignancy with surgery, radiation therapy, chemotherapy or a combination of these modalities, additional medications may be indicated and necessary to reverse weight loss and improve quality of life. In order to choose the most effective drugs and provide the optimal care for the individual patient it is important to determine the cause for the inadequate food intake and weight loss.

► Causes of dysorexia and anorexia

Anorexia is the failure of the usual appetite signals and can be a direct or indirect effect of the cancer itself or the cancer treatment, specifically chemotherapy. Decreased or loss of appetite may be a direct result of abdominal pain or discomfort, and early satiety due to restricted gastric accommodation or delayed emptying secondary to tumor infiltrate. Primary intestinal tumors may lead to complete or incomplete obstruction, ileus, malabsorption, diarrhea or constipation which again can lead to discomfort, bloating, anorexia or nausea *(Uomo et al, 2006)*.

Chemotherapy may contribute to further decreasing appetite by its effects on the vomiting center as well as the effect on the gastrointestinal tract. Certain chemotherapeutic drugs such as vincristine can cause ileus and constipation, which again may feed into the cycle of anorexia and depression *(Ogilvie et al, 2001)*. The direct cytotoxic effects on the intestinal epithelial lining may lead to sloughing and make possible bacterial translocation and secondary intestinal bacterial overgrowth.

Chemotherapy induced gastroenteritis can induce nausea, vomiting and diarrhea. The risk for sepsis is especially important if the patient experiences concurrent myelosuppression. If there is a potential for sepsis, broad-spectrum antibiotics with good gram positive and gram negative coverage are indicated in these patients.

► Analgesia

Pain and discomfort may contribute to anorexia and weight loss. It is often difficult to determine whether veterinary patients are in pain, especially visceral pain. Visceral pain is commonly reported in human cancer patients with abdominal organ cancer, especially pancreatic cancer. Cancer cachexia is more common in pancreatic cancer than in any other cancer type and up to 80% of the patients are reported to be cachetic *(Splinter, 1992; Ryan et al, 1998)*. Pain medications are routinely provided to palliate these patients *(Li et al, 2004)*.

It is feasible that cats with alimentary lymphoma experience some degree of discomfort or pain, however, the effectiveness of pain medications in improving appetite and reversing the cycle of weight loss in these patients has not been evaluated, and pain medications may not be routinely prescribed. Pain is easier to recognize and therefore more likely to be treated in cats with visible non-resectable solid tumors that invade or destroy bone or that compress nerves. Palliative care with the focus of treating the cancer pain with oral or parenteral pain medication and/or palliative radiation therapy is routinely offered to cats with oral squamous cell carcinoma or osteosarcomas. It is the authors' subjective impression that some of these cats improve and increase their voluntary food intake with such measures. However, there are no studies to confirm these observations.

► Anti-inflammatory drugs

The systemic effects of cancer and metabolic changes associated with cancer cachexia syndrome are mediated by a complex network of pro-inflammatory cytokines *(Jatoi et al, 2001; Walker, 2001)*. Anti-inflammatory drugs may therefore have a role in reversing some of these effects. Non-steroidal anti-inflammatory drugs (NSAIDs) include several different drugs with anti-cycloxogenase activity. These drugs have both analgesic and well as anti-inflammatory effects, and may therefore provide dual benefits to patients suffering from a painful non-resectable tumor and/or the systemic inflammatory effects of the tumor and cancer cachexia syndrome. In addition, the effects against cycloxogenase-2 may have direct anti-cancer effects, especially in tumors over-expressing this enzyme. The direct anti-cancer affects of NSAIDs have been reported only in dogs at this point *(Schmidt et al, 2001; Knapp et al, 2002; Mustaers et al, 2003; Mohammed et al, 2004; Mustaers et al, 2005)*. NSAIDs have been reported to improve some of the symptoms associated with cancer cachexia syndrome and improve quality of life in human pancreatic and other gastrointestinal cancer patients *(Wigmore et al, 1995; McMillian et al, 1997; McMillian et al, 1999)*.

► Appetite stimulating drugs

The use of appetite stimulating drugs and anti-depressants may also be indicated in some patients. It can be very difficult and often impossible to distinguish between anorexia resulting from nausea and anorexia as part of the cancer cachexia syndrome. Therefore anti-emetics should always be considered first or in conjunction with drugs to stimulate appetite. Administering appetite stimulating drugs without providing effective anti-emetics may worsen nausea and cause more vomiting with the potential of creating a learned food aversion. It is also important to rule out and treat any physical causes of nausea, vomiting and subsequent anorexia such as gastrointestinal tumors, intestinal obstruction or chemotherapy-induced gastroenteritis prior to prescribing appetite stimulating drugs.

Megestrol acetate is effective in feline cancer patients and used to improve appetite and promote weight gain.

© Yves Lanceau/RCF/Norwegian Forest Cat

Megestrol acetate is the most effective and commonly prescribed drug to combat weight loss and cachexia in human oncology. A large meta-analysis found that cancer patients receiving megestrol acetate were significantly more likely to gain or maintain weight than those who did not receive the drug *(Berenstein et al, 2005)*. The exact mechanism of action of megestrol acetate is complex and thought to involve stimulation of appetite by both direct and indirect pathways as well as antagonism of the metabolic effects on the principal catabolic cytokines *(Uomo et al, 2006)*. Megestrol acetate is also effective in feline cancer patients and used to improve appetite and promote weight gain.

However, **corticosteroids** are used more commonly in the USA, especially in feline lymphoma. Corticosteroids are part of the chemotherapy protocol for lymphoma and used for their cytotoxic effects, however, corticosteroids have additional benefits including appetite stimulation and anti-inflammatory effects which might be beneficial in combating the cancer cachexia syndrome.

Cyproheptadine, an anti-serotonergic, is another appetite stimulant used relatively frequently in cats and still favored by many veterinarians despite the fact that prospective trials in human cancer patients found no improvement in nutritional status in patients receiving cyproheptadine versus placebo *(Kardinal et al, 1990)*.

Appetite stimulating drugs are often used in conjunction with other palliative measures in cats. Some seem to benefit from these measures, but it may be impossible to determine which of the palliative drugs is indeed effective in patients where many different strategies to improve appetite are instituted simultaneously; the improvement may in fact be a result of synergistic or complimentary additive effects of a combination of drugs. A combination of drugs or a multimodality approach may indeed be necessary to maintain weight or reverse weight loss.

Nevertheless, it is important to assess all of the above potential contributing factors, i.e. tumor stage and direct gastrointestinal involvement, presence of nausea, pain or discomfort, chemotherapy induced gastroenteritis, or the presence of the cancer cachexia syndrome, so that the most appropriate drugs or drug combinations are administered. There may be a practical limitation to how many different oral medications a cat will tolerate, and forceful administration of excessive unnecessary medications may make the situation worse. **Tables 6** and **7** include drugs with recommended dosages used to decrease nausea, stimulate appetite, improve nutritional status and combat weight loss in cats with cancer.

TABLE 6 - ANTI-EMETIC DRUGS

Drug	Dosage	Comments
Metoclopramide	0.2-0.4 mg/kg [0.1-0.2 mg/lb], SC or PO q6-8 1-2 mg/kg/day [0.5-1 mg/lb], IV CRI	Promotes gastric emptying and acts centrally on the chemoreceptor trigger zone (central effects are less potent in the cat than in other species)
Prochlorperazine	0.1-0.5 mg/kg [0.05-0.2 mg/lb], SC or IM q6-8	Sedative and hypotensive effects (adrenergic antagonist) acts centrally on the vomiting center and chemoreceptor trigger zone
Dolasetron Mesylate Ondansetron	0.5-1.0 mg/kg [0.2-0.5 mg/lb], IV or PO q24 0.3-1.0 mg/kg [0.1-0.5 mg/lb], PO q 24 hr	Acts centrally on the chemoreceptor trigger zone
Dexamethazone	1-3 mg/cat (given as a single dose in conjunction with other anti-emetics)	Unknown mechanism of action; potentates the effect of other anti-emetics

The licensing arrangements for therapeutic agents varies worldwide. Some of these agents may not be licensed or approved for use in cats.

Table 7 - Appetite stimulant drugs		
Drug	Dosage	Comments
Benzodiazepine Derivatives* Diazepam Oxazepam	0.2 mg/kg [0.1 mg/lb], IV 0.5 mg/kg [0.2 mg/lb], PO q12-24	Causes sedation Contraindicated in cats with hepatic failure Effects wane with time when used in sick animals
Cyproheptadine*	0.2-0.5 mg/kg [0.1-0.2 mg/lb], PO q12	Anti-serotonergic Can cause excitability, aggression and vomiting
Megestrol Acetate	0.25-0.5 mg/kg [0.1-0.2 mg/lb], q 24 hr for 3-5 days, then q 48-72 hr	Stimulates appetite by direct and indirect pathways Antagonistic effects on the principal catabolic cytokines Diabetogenic
Prednisone	0.5-1.0 mg/kg [0.2-0.5 mg/lb], q 24	Direct central effects Inhibition of tumor and host-induced substances Direct cytotoxic effects in lymphoma

* *Both the benzodiazepine derivatives and cyproheptadine cause only a momentary increase in appetite and are unreliable for ensuring adequate caloric intake.*

The licensing arrangements for therapeutic agents varies worldwide. Some of these agents may not be licensed or approved for use in cats.

Conclusion

The primary goals of cancer therapy are to prolong life and maintain a good quality of life. Ensuring adequate nutrition is a requirement for both goals to be fulfilled. Human cancer studies have found that cachectic patients have a worse outcome, more complications and a lower response to therapy. The situation is likely similar in cats, as illustrated by one recently published investigation, where:

- remission was positively correlated with a higher BCS
- cats with solid tumors and lymphoma that had an underweight body condition had significantly shorter survival times than cats with a higher BCS *(Baez et al, 2007)*.

Weight loss and the associated reduced quality of life may not only have a negative impact on treatment, but may also have direct consequences for survival, because it may lead to a decision to euthanize. The ability, interest, and willingness to eat voluntarily are major components of having a good quality of life. Most owners and veterinarians will likely agree that a cat that does not eat voluntarily or adequately over long periods of time may not feel well and may be suffering.

Therefore, providing effective nutritional support and offering the appropriate palliative medications to decrease nausea, improve appetite and facilitate voluntary food intake become crucial for prolonging survival. On our service we have found that the majority of cats with lymphoma lose weight in the induction phase of chemotherapy *(Bachman et al, 2000)*. A significant proportion of cats with lymphoma die or are euthanized within the first months of starting chemotherapy. These facts suggest that more focus should be directed towards ensuring adequate nutrition and preventing weight loss in these patients. Early nutritional intervention may not only improve quality of life in cats with cancer but may also have positive impact on survival.

Frequently asked questions

Q	A
How do we know whether it is the treatment or the cancer itself that makes the cat appear nauseated and have a reduced appetite?	This is probably one of the most frequently asked questions by both veterinarians and owners. In order to answer this it is necessary to re-assess the remission status of the cat and to perform a thorough review of the previous treatment history in order to determine whether there is a pattern to the weight loss or whether the nausea might be associated with certain chemotherapeutic drugs. This may require performing an abdominal ultrasound in cats with gastro-intestinal lymphoma and comparing the findings to the pre-treatment staging ultrasound. If the results suggest improvement or even clinical remission, the suspicion is that it is the chemotherapy that is the culprit. If this is the case, giving the cat a short break from treatment may result in a resolution of the problem. Continued chemotherapy should be initiated carefully with prophylactic anti-emetics and dose-reductions should also be considered. If the ultrasound shows persistent lymphoma or even worsening status, other chemotherapeutic drugs with concomitant anti-emetics may be needed.
Is my cat suffering because it is not eating?	It is reasonable to assume that a cat that does not eat does not feel well. There is a gradual scale from not "feeling well" to suffering. A temporary decrease in appetite or even anorexia may be acceptable in most owners' and veterinarians' opinion as long as it is assumed that it does not significantly impact on or interfere with other aspects of the cat's life. However, severe prolonged anorexia and weight loss secondary to any terminal disease for which there is no treatment or palliation is a clear sign of an unacceptable quality of life.
What can I do to improve my cat's food intake?	Appetite is affected by many internal and external signals. Many cancer patients may experience a reduction in appetite due to direct or indirect effects of the tumor and the treatment they are undergoing. Every effort should be made to optimize the patient's wellbeing including addressing conditions such as dehydration, fever, pain, and nausea. Make feeding times as unstressful as possible. Try offering small amounts of a variety of tempting foods but be alert for signs of learned food aversion. Offering many small meals through out the day may meet with more success than fewer larger meals. Sometimes warming the food to body temperature will increase its appeal.
My cat's appetite is very poor and he is losing weight despite a good response to chemotherapy. I have been told a feeding tube could help him through this period but I am concerned about the impact this would have on his quality of life.	Tube feeding is well-tolerated by many feline patients. Esophagostomy tubes, in particular, seem to cause little discomfort to the patient and provide access that permits the feeding of canned cat foods. Tube feeding is not possible in patients that have uncontrolled vomiting. However, when these conditions are not present or are properly managed, tube feeding will improve the patient's nutritional status, energy level, and overall sense of well-being. Since the cat is in remission but still losing weight, the weight loss may be due to chemotherapy induced nausea and fatigue, minor dose reductions and effective anti-emetics should also be considered in addition to feeding tube placement.

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Critical care

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Nutrition and critical care in cats

ABBREVIATIONS USED IN THIS CHAPTER

ATP: adenosine triphosphate
BCAA: branch-chain amino acid
BER: basal energy requirement
CK: creatine kinase
CPN: central parenteral nutrition
DPG: diphosphoglycerate
DHA: docosahexaenoic acid
EFA: essential fatty acid
EPA: eicosapentaenoic acid
FFA: free fatty acid
FHL: feline hepatic lipidosis
GI: gastrointestinal
GLN: glutamine
IGF1: insulin growth factor 1
IV: intravenous
MER: maintenance energy requirement
PEG: percutaneous endoscopic gastrostomy
PN: parenteral nutrition
PPN: partial parenteral nutrition
PUFA: polyunsaturated fatty acid
RER: resting energy requirement
SGA: subjective global assessment
TNF-α: tumor necrosis factor

Nutrition and critical care in cats

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The cat is not a small dog especially with respect to critical care medicine. The physiologic response to shock, the procedures required for resuscitation, and the parameters that require careful monitoring present specific challenges that are unique for the critically ill cat. Although some feline disorders cause an increased appetite (diabetes mellitus or hyperthyroidism), the majority of feline illnesses result in partial or total anorexia.

Introduction

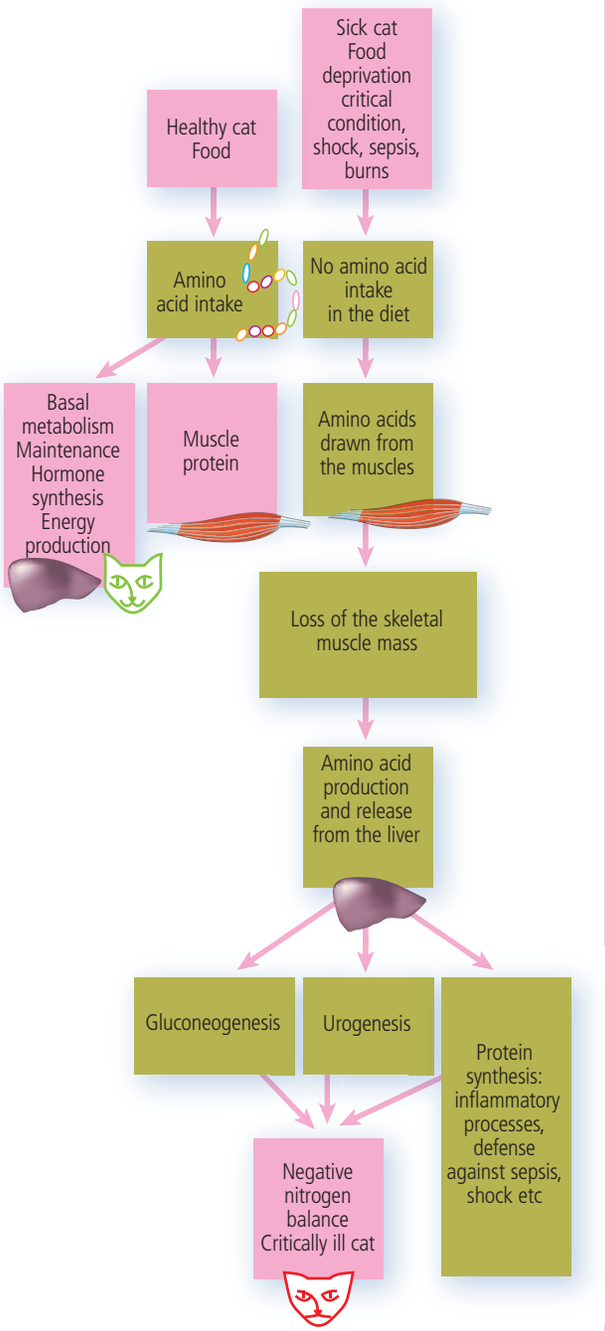
With the emphasis in first diagnosing the underlying disease process, nutrition is often relegated as a late therapeutic process, typically considered when the patient has already been hospitalized for 4-5 days and has received little to no nutritional support. Moreover, a common practice is to wait just one more day, whereby there is some unreasonable expectation that anorexia that persisted for days will simply reverse itself because intravenous (IV) fluids have been administered. In reality, loss of appetite is one of the most powerful and long lasting features of severe disease. Therefore, the correct assumption should be that appetite will not resolve with supportive care and timely nutritional intervention should be implemented.

As more and more research uncovers the benefits of enteral nutrition and the complications that are derived from gut atrophy, critical care human specialists now feed patients much earlier than before in the disease process. This practice has resulted in improved outcomes and fewer complications. In veterinary medicine a similar transition has begun over the last few years, and is gaining momementum.

The two approaches to feeding critically ill cats are:
- enteral feeding, in which some portion of the gastrointestinal tract is utilized
- and parenteral feeding, in which nutrients are administered in a manner other than using the gastrointestinal tract, most commonly via central or peripheral venous access.

In the past several years, transitioning from ineffective strategies such as force- or syringe-feeding, warming foods, and adding flavor enhancers, to more recent recommendations for early tube feeding, novel methods of administrating nutrition to critically ill cats have resulted in increased survival rates.

FIGURE 1 - NITROGEN BALANCE IN A CRITICALLY ILL CAT AND IN A HEALTHY CAT



1 - Nutritional requirements and starvation in healthy cats

► Specific requirements

> Cats are carnivores

Carnivorous by nature, cats require few carbohydrates but need high levels of protein. Adult cats require two to three times more dietary protein than omnivorous species, and have a high requirement for essential amino acids as energy sources *(Zoran, 2002)*. Unable to adapt their urea cycle enzymes or aminotransferases to reduced protein intake, cats possess limited ability to adjust protein metabolic pathways for conserving nitrogen. Feline metabolism mandates cats to use protein for maintenance of blood glucose concentrations even when sources of protein in the diet are limited. These peculiarities help to explain the rapid onset of protein malnutrition in anorectic cats *(Zoran, 2002; Center 2005)* **(Figure 1)**.

Hastened use coupled with an inability to conserve or synthesize certain amino acids, necessitates a higher dietary amino acid intake for cats compared with most other species *(Kerl & Johnson, 2004; Kirby, 2004; Center, 2005)*.

- **Taurine** deficiency has been proven to cause dilated cardiomyopathy, reproductive disorders and retinal degeneration.
- **Arginine** has important roles in nitrogen elimination and the urea cycle in addition to stimulating endocrine secretagogue activity, improving nitrogen retention, reducing nitrogen loss in post-operative patients, enhancing collagen deposition in wounds, enhancing T-cell function, and growth of lymphocytes *(Morris & Rogers, 1978; Barbul & Hurson, 1994; Zoran, 2002; Center, 2005; Saker, 2006)*. Arginine is also a precursor of nitric oxide (NO) *(Barbul & Hurson 1994)*.
- **Methionine and cysteine** are key methyl group donors important for the production of many metabolites such as glutathione, which is an important antioxidant and scavenger of free radicals *(Zoran, 2002; Center, 2005)*.
- **The amino acid glutamine** (GLN) has been described as a "conditionally essential amino acid". Increased demand coupled with poor supply in critical patients may result in compromise of the gut mucosal barrier, with subsequent bacterial translocation and systemic infection. Impairment of reticuloendothelial function, in conjunction with a reduction in antibody production increases the risk of sepsis and multiple organ failure *(Elliott & Biourge, 2006)*. Glutamine also has an important role in acid-base balance. Plasma glutamine levels have been reported to decrease by 58% after critical illness or injury, to remain decreased for up to 3 weeks and was associated with increased mortality in critically ill patients *(Wischmeyer, 2003)*.

> Cats need minimal amounts of carbohydrates

Cats have several physiologic adaptations that reflect their low carbohydrate intake. Cats lack salivary amylase, the enzyme responsible for initiating starch digestion. Cats also have low activities of intestinal and pancreatic amylase and reduced activities of intestinal disaccharidases that digest carbohydrates in the small intestine. These species specific differences however, do not mean that cats cannot use starch. In fact, cats are extremely efficient in their use of digestible carbohydrates. Cats also have minimal activity of hepatic glucokinase and glycogen synthetase probably as a result of a metabolism designed to use gluconeogenic amino acids and fat, rather than starch. As a result, cats have limited ability to rapidly minimize hyperglycemia from a large dietary glucose load *(Zoran, 2002)*.

High levels of dietary carbohydrates may also decrease protein digestibility in cats. This is due to a combination of factors, including increased passage rate. Increased amounts of carbohydrates in diets also results in increased microbial fermentation in the colon and increased production of organic acids *(Kienzle, 1994)*.

> Cats have a specific requirement for polyunsaturated fatty acids

Fat typically provides most of the fuel for energy. Essential fatty acids (EFAs) for cats include linoleic, linolenic, arachidonic, eicosapentaenoic and docosahexaenoic acid. Most species can convert linoleic acid to arachidonic acid, the primary precursor for the 2-series prostaglandins, leukotrienes and thromboxanes. Arachidonic acid is required for maintenance of cell wall and tissue integrity and can be found in diets containing animal sources of fats. Cats however, do not have the enzymatic machinery (lack adequate hepatic Δ-6-desaturase activity and other hepatic desaturases) to synthesize derivatives of arachidonic acid (Zoran, 2002). Therefore arachidonic acid is an essential nutrient needed in the feline diet *(Kirby, 2004)*.

> Vitamin needs of cats are unique

Cats require higher amounts of several water soluble B-vitamins including niacin, thiamine and pyridoxine compared with other species, and are predisposed to depletion during prolonged starvation. In addition, in some disease states, cats also require additional supplementation with cobalamin (B_{12}) *(Zoran, 2002; Kirby, 2004)*.

Cats do not have the ability to convert beta-carotene to active vitamin A (retinol). Cats lack dioxygenase enzymes in the intestinal mucosa that split the beta-carotene molecule to vitamin A aldehyde (retinal). Therefore, preformed vitamin A must be supplied in the diet. Vitamins E and K are also important and may become deficient in cats that have prolonged anorexia *(Zoran, 2002)*.

TABLE 1 - HORMONAL CONTROL AND EFFECTS ON NUTRITION
Adapted from Atkinson & Worthley, 2003

Hormone	Secretion stimulated by	Stimulates	Inhibits
Insulin	Hyperglycemia Amino acids (e.g., arginine, leucine)	Glycogenesis Lipogenesis Protein synthesis	Gluconeogenesis Ketogenesis Proteolysis Lipolysis
Glucagon	Hypoglycemia Sympathetic stimulation Alanine	Gluconeogenesis Ketogenesis Glycogenolysis	Glycogenesis Lipogenesis
Catecholamines	Sympathetic stimulation Hypoglycemia	Gluconeogenesis Glucagon release Lipolysis	Insulin release Insulin effect

► Effect of fasting and starvation in healthy cats

The normal nutrient-metabolism cycle in healthy animals involves an alternating system of feeding and fasting. In the fed state, the hormonal response to the nutrients glucose and amino acids, is stimulation of insulin secretion coupled with a reduction of glucagon secretion (substrate control) **(Table 1).** This results in stimulation of glycogenesis and repletion of the glycogen reserves, an increase in protein synthesis and the storage of fats. During the fasted state, plasma levels of glucose and amino acids fall, insulin secretion is reduced and glucagon secretion is increased which stimulates gluconeogenesis and glycogenolysis.

Periods of fasting longer than three to five days induces a state of starvation. In this situation, there is a further reduction in insulin levels and an increase in glucagon secretion. In addition, mild sympathic activation stimulates hormone-sensitive lipoprotein lipase which increases the release of free fatty acids (FFAs) from adipose tissue. Excess FFAs are converted by the liver to ketone bodies, which substitute for glucose as energy substrates in the brain and other organs. Ketones help to decrease skeletal muscle breakdown and amino acid release by reducing the obligatory demand for glucose, and gluconeogenesis. With chronic starvation, glucagon levels return to their post absorptive levels and catecholamine levels decrease. The basal metabolic rate decreases due to a reduction in the peripheral conversion of thyroxine (T4) to triiodothyronine (T3) *(Atkinson & Worthley, 2003)*.

In carnivores such as cats, glycogen stores are quickly depleted and this leads to the initial mobilization of amino acids from muscle stores. Within days, a metabolic shift occurs toward the preferential use of fat deposits, which spares the catabolic effects on lean muscle tissue *(Chan, 2006; Chan & Freeman, 2006)* **(Figure 1)**.

2 - Consequences of starvation in critically ill cats

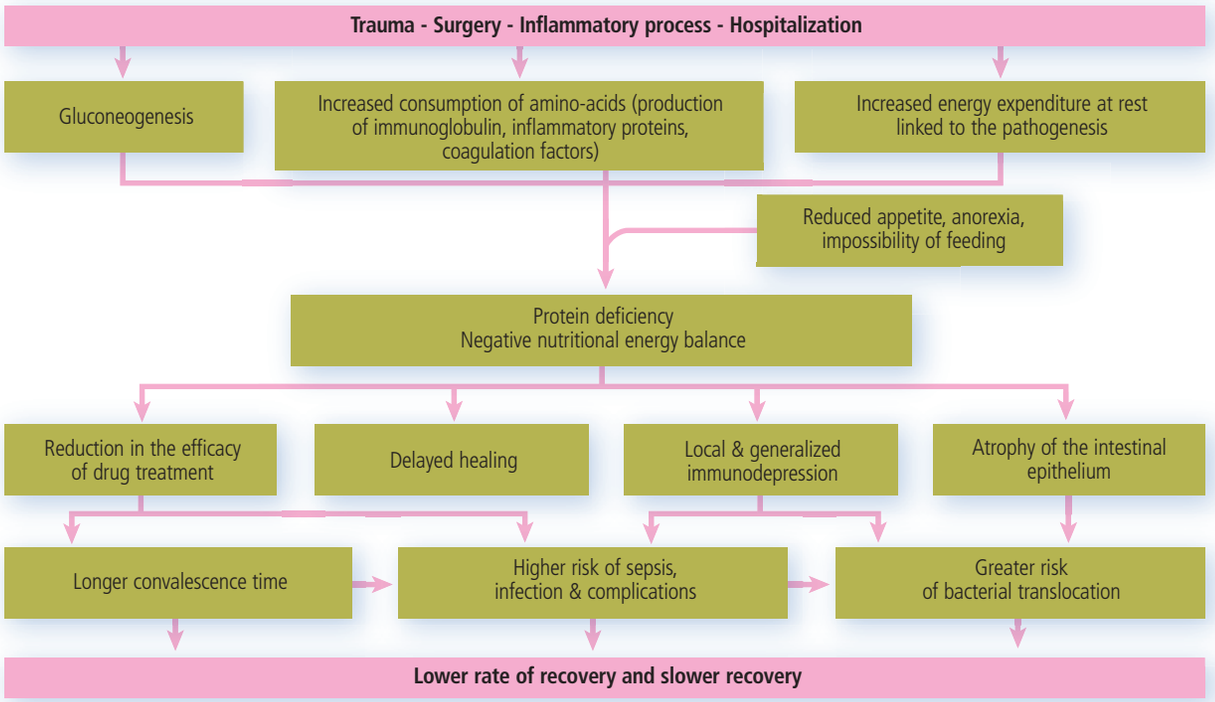
► General consequences of "stressed starvation"

Critical illness induces unique metabolic changes in cats that predispose them to malnutrition and its deleterious effects. An important distinction in the body's response to inadequate nutritional intake occurs in disease or stressed starvation compared with healthy starvation *(Michel, 2004; 2006; Chan & Freeman 2006)* **(Table 2)**.

TABLE 2 - UNSTRESSED STARVATION VERSUS STRESSED STARVATION
Adapted from Michel (2004; 2006)

Unstressed starvation	Stressed starvation
- Mediators secreted in response to the lack of food - Conservation of endogenous proteins - Resolves with feeding	- Mediators secreted in response to tissue injury or inflammation - Catabolism of endogenous proteins - Resolves with healing or treatment of the underlying disease

Figure 2 - General consequences of starvation in critically ill cats



Nutrition directly influences the evolution of the disease and the success of the treatment.

During a critical pathological process, the nutritional hormones are no longer substrate controlled. To maintain hemodynamic homeostasis during acute injury, an increase in sympathetic tone and catecholamine (e.g., epinephrine and norepinephrine) secretion occurs. The catecholamines stimulate glycogenolysis and sensitive hormone protein lipase to increase the plasma levels of FFAs, glucose and insulin. Insulin inhibits ketogenesis. The increase in sympathetic tone increases the resistance of the peripheral tissues to insulin. In septic patients the stress response is exacerbated by the release of polypeptide mediators including tumor necrosis factor (TNF-α) and interleukin-1 that cause functional hepatic abnormalities, increase glucose intolerance and increase skeletal muscle protein catabolism (via the ubiquitin-conjugation proteasome pathway) *(Atkinson & Worthley, 2003)*. The inflammatory response also triggers alterations in cytokines and hormone concentrations and shifts metabolism toward a catabolic state with accelerated proteolysis that typically results in significant negative nitrogen balance **(Figure 1)**. Paradoxically, these patients may preserve fat deposits in the face of lean muscle tissue loss *(Chan & Freeman, 2006)*. The consequences of lean body mass loss include delayed wound healing, immunosuppression, reduced muscle strength (both skeletal and respiratory), and ultimately increased morbidity and mortality *(Marik & Zaloga, 2001; Atkinson & Worthley, 2003)* **(Figure 2)**.

► Specific topics in critically ill cats

> Alterations in carbohydrate metabolism in critically ill cats

Similar to critically ill humans, alterations in carbohydrate metabolism are present in critically ill cats and likely contribute to the hyperglycemia commonly observed in this population. Alterations in carbohydrate metabolism in critical illness include increased glucose production (gluconeogenesis), depressed glycogenesis, glucose intolerance, and peripheral insulin resistance. Concentrations of counter-regulatory hormones, such as glucagon, cortisol, and epinephrine are increased and these hormones play a role in up-regulating gluconeogenesis. In addition, hepatic gluconeogenesis appears to become resistant to the regulatory effects of insulin and blood glucose, further contributing to hyperglycemia.

Activation of inflammatory cytokines and neuroendocrine pathways are believed to play a key role in lipid, protein and carbohydrate metabolism. Interactions between the various metabolic pathways are also believed to contribute to hyperglycemia. Glucose intolerance has also been found to parallel the severity of illness. Hyperglycemia has been associated with poorer outcome in critical human patients *(Van den Berghe, 2004)*, and studies have demonstrated the benefits of insulin administration in the critically ill population *(Van den Bergh, 2004)*.

The impact of hyperglycemia on outcome in critically ill cats has not been as well characterized. In a retrospective study, *Chan et al* (2006) reported that cats presented to the emergency service with hyperglycemia were significantly more likely to die or be euthanized than those without hyperglycemia. However, in this study, the degree of hyperglycemia did not appear to impact outcome. Critically ill cats have also been reported to be at risk for developing hyperglycemia associated with parenteral nutrition (PN). Hyperglycemia was documented to occur in 75% *(Lippert et al, 1993; Syring et al, 2001)* and 20% *(Crabb et al, 2006)*, respectively of cats receiving PN. More importantly, the development of hyperglycemia in cats receiving PN was shown to negatively impact survival *(Pyle et al, 2004)*. *Chan et al* (2006) reported that critically ill cats had higher circulating concentrations of glucose, lactate, glucagon, non-esterified fatty acids, and cortisol compared with healthy controls. Critically ill cats also had lower insulin and insulin:glucagon ratios compared with healthy controls. The phenomenon of hyperglycemia in critically ill cats is complex, remains incompletely understood and likely involves multiple pathophysiological mechanisms.

> Gastro-intestinal motility and mucosal integrity

Cats that are post-anesthetic, postoperative (especially abdominal surgery), hypokalemic, suffering from gastrointestinal, reticuloendothelial, or neuromuscular diseases, or on narcotic analgesics have a strong likelihood of gastrointestinal paresis. Several aspects of digestive physiologic and intestinal microbiologic characteristics of cats suggest a possible role of bacteria in these abnormalities. It has been suggested that increased numbers of bacteria in the feline intestine serve to enhance digestion of protein and fat *(Zoran, 2002)*. Ileus predisposes the patient to bacterial and endotoxin translocation, poor intestinal nutrient digestion and absorption, gastrointestinal ulceration and vomiting. The patient should be auscultated at least three times daily for bowel sounds *(Kirby, 2004)*. In addition, critically ill cats receive numerous medications that can cause anorexia, nausea and vomiting **(Table 3)**. These clinical symptoms contribute to the inappetance characteristic of critically ill cats.

> Feline hepatic lipidosis

Feline hepatic lipidosis (FHL) is the most common metabolic hepatic disease for cats; especially cats that are obese or stressed *(Zoran, 2002; Center, 2005)*. Although the etiopathogenesis of FHL is still incompletely understood, it is now clear that most cats (over 95%) have an illness or circumstance directly causing a catabolic state *(Center, 2005)*. Nutrients including taurine, arginine, non esterified FFAs and B-vitamins have been suggested, but not proven, to be involved in the pathogenesis of FHL *(Zoran, 2002)*.

Successful treatment of FHL is based on early intervention and adequate nutritional support. In cats that receive early aggressive nutritional support, the prognosis for survival approaches 90%, but in cats not receiving such treatment, the chance of survival is only 10 to 15%. The best diet for treatment of cats with FHL is unknown, but evidence clearly suggests that dietary protein reduces hepatic lipid accumulation and maintains nitrogen and energy balance in cats with FHL *(Biourge et al, 1994; Center, 2005)* (see chapter 4).

TABLE 3 - LIST OF SELECT MEDICATIONS WHICH MAY CAUSE ANOREXIA, NAUSEA AND VOMITING IN CATS

Adapted from Michel, 2006

Amoxicillin
Cephalexin
Chloramphenicol
Amoxicillin/clavulanate
Erythromycin
Tetracyclines
Trimethoprim/sulphadiazine
Cardiac glycosides
Non-steroidal anti-inflammatory drugs
Chemotherapeutic agents
Narcotic agents

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Obesity is a form of malnutrition often responsible for complications in the event of intensive care.

► Goal of nutritional support in critically ill cats

The immediate goal of providing nutritional support to hospitalized cats is not to achieve weight gain, which mostly likely reflects a shift in water balance, but rather to minimize further loss of lean body mass. Nutritional support will not reverse the factors causing proteolysis, gluconeogenesis or lipolysis associated with sepsis or stress. Therapy should therefore focus upon decreasing catecholamine secretion by correcting hypotension, hypoxia and pain, and decreasing the levels of catabolic polypeptide mediators by treating sepsis (e.g., antibiotics, fluid therapy). Nevertheless, while nutrition may not reverse the catabolic response, it enhances protein synthesis and may retard protein catabolism, and therefore may reduce the total burden of body protein loss if introduced early in the management of the acutely ill patient *(Atkinson & Worthley, 2003; Kirby, 2004; Chan & Freeman, 2006)*.

3 - Nutritional assessment

Nutritional assessment identifies malnourished patients that require immediate nutritional support and also identifies patients at risk for developing malnutrition in which nutritional support will help to prevent malnutrition. Moreover, nutritional assessment aims not simply to diagnose whether a patient is malnourished but whether the malnutrition will have an impact on clinical outcome. Currently used indications for nutritional support include a history of illness or weight loss, current poor body condition or acute loss of 5% body weight, or a history of anorexia or inappetence over 3 days (real or anticipated).

Nutritional assessment first determines the patient's nutritional status. This is a subjective evaluation based on the medical history and physical examination. Next the patient's caloric intake should be assessed. The patient's nutritional status and food intake are considered in conjunction with the severity of the patient's current illness, factors such as cardiovascular instability, electrolyte abnormalities, hyperglycemia, and hypertriglyceridemia and concurrent conditions such as renal or hepatic disease that will impact the nutritional plan.

Considering all this information will allow the clinician to determine what method of feeding is necessary, how aggressive they should be in initiating assisted feeding, and which route of feeding will be the safest, most effective and best tolerated by the patient *(Michel, 2006)*. An important fact to remember is that many critically ill cats present to the veterinarian after several days if not weeks of inadequate nutritional support. Therefore, provision of nutrition to critically ill patients should occur as soon as it is safe to provide nutrition. This will vary from patient to patient, but the tendency has been to wait too long *(Chan, 2006; Chan & Freeman 2006)*.

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Successful treatment of feline hepatic lipidosis is based on early intervention and adequate nutritional support.

► Determining nutritional status

In humans, a technique referred to as Subjective global assessment (SGA) was developed approximately 20 years ago as a standardized tool to assess the nutritional assessment of patients *(Detsky et al, 1987)*. Although no standardized scoring system currently exists in veterinary medicine, the principles of SGA can be applied to ensure the appropriate history, physical examination, laboratory data and diagnostic techniques are applied for the assessment of critically ill patients *(Michel, 2006; Elliott, 2008)*.

> History

The dietary history should record if the patient is or is not consuming food. It is important to record the total duration of inappetance, which is the number of days the cat was inappetant in both in the home prior to hospitalization, and the hospitalized environment. It is also important to differentiate between how much food the pet is offered, versus how much of the food the cat consumed at home and in the hospital. This could be particularly difficult if the cat is both an

indoor/outdoor cat, or is in a multi-cat free-feeding environment. The frequency and amount of vomiting and/or diarrhea should also be noted.

> Physical examination

The physical examination focuses on changes in body composition, specifically wasting of fat stores and muscle mass, the presence of edema or ascites, the presence of mucosal or cutaneous lesions, and the appearance of the patient's hair. Indications for nutritional support include the presence of injuries which prevent adequate oral intake (facial injuries, prolonged or unmanaged pain, injuries requiring surgical correction), and conditions of excessive protein loss (peritoneal drainage; open discharging skin wounds; hepatic or renal failure; protein-losing nephropathy or enteropathy).

> Body weight

Body weight provides a rough measure of total body energy stores and changes in weight typically parallel energy and protein balance. In the healthy animal, body weight varies little from day to day. However, additional challenges may arise in the critically ill patient. Edema and ascites cause a relative increase in extracellular fluid and mask losses in muscles or fat mass. Conversely, massive tumor growth or organomegaly can mask loss in fat or lean tissues. In addition, body weight can be falsely altered by dehydration or fluid accumulation. There can also be wide variation between scales, so it is important to use the same scale for an animal to avoid inter-scale variation. Finally, body weights are relatively small in cats and variations could be subtle and the scale must be precise *(Chan, 2006; Elliott, 2008)*.

Finally, a single body weight measurement by itself has little meaning. It is important to know if and how it changes.

> Body condition score

Several excellent body condition scoring systems have been developed for cats. The most common is a 5-point system **(Figure 3)** where a body condition score of 3 is ideal, 5 is obese, and 1 is cachetic (see chapter 1). The body condition scoring systems are designed to evaluate fat stores on the body. In critically ill cats, there is often a disproportional loss of lean body tissue, while the fat stores appear to be adequate. Therefore, careful examination of the muscle stores by palpation of the skeletal muscle mass over bony prominences, such as the scapula or vertebral column is also necessary. Indeed, *Freeman et al* (2006) have recommended the use of a cachexia scoring system to evaluate lean body mass, where a score of 0 is normal and 4 represents severe cachexia.

Figure 3 - 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

> Laboratory indicators of malnutrition

There are no biochemical analyses that will reliably identify malnourished cats or enable monitoring them during supportive alimentation. Currently used laboratory indicators of malnutrition include hypoalbuminemia, decreased blood urea nitrogen, hypocholesterolemia, anemia and lymphopenia. However alterations of these common indicators are often indistinguishable from those that can occur with concurrent disease. Albumin loss, for example, rather than undernutrition, may decrease plasma albumin levels *(Atkinson & Worthley, 2003)*. *Fascetti et al* (1997) reported that anorectic cats have significantly higher serum creatine kinase concentrations compared to healthy cats. Furthermore, the creatine kinase concentration significantly decreased within 48 hours of implementation of nutritional support. The availability and ease of quantification of creatine kinase (CK) activity make it a promising method of nutritional assessment and monitoring in cats.

Other markers of nutritional status including prealbumin, transferrin, total iron binding capacity, fibronectin, IGF1, retinal binding protein, ceruloplastin, α-1-antitrypsin, α-1-acid glycoprotein and C-reactive protein have not been evaluated in feline patients *(Elliott, 2008)*.

> Integrating the data

All steps in nutritional management should be documented completely and clearly in the medical record. The importance of clear documentation is exemplified by the study of 276 dogs in which a negative energy balance occurred in 73% of the hospitalization days. The negative energy balance was attributed to poorly written orders in 22% of cases *(Remillard et al, 2001)*. Accurate documentation facilitates communication between the various members of the veterinary care team and strengthens the importance of nutrition in the overall care of the patient.

► Assessment of voluntary food intake

In order to assess whether that patient's food intake is adequate, it is necessary to determine the caloric goal, to select an appropriate food and to write precise feeding orders for the patient. Precise documentation allows an accurate accounting of how much food is offered to the patient and an easier evaluation of intake based on how much of the food is consumed *(Michel, 2006)*.

► Determining the route of feeding

Nutritional support of critically ill patients can be administered via enteral or parenteral routes. Considerable debate and controversy has existed for several decades as to which method may be superior. The answer, or at least the current consensus, is that both methods are valuable and have important roles in managing critically ill patients. The goal of nutritional support should remain to utilize all tools that are available to prevent malnutrition in critically ill patients, while maximizing the benefits and minimizing the risks of the modality that is chosen.

The choice of the best route for assisted feeding is based principally upon evaluation of the patient and to a lesser extent upon logistical factors such as the availability of special diets and nutrient solution or access to 24 hour nursing care *(Michel, 2006)* **(Table 4)**. Whenever possible, the enteral route should be the first choice *(Chan, 2006)*. Enteral nutrition is preferable as it is the most physiological, easy and safe method to institute; it is also the least expansive *(Yam & Cave 1998)*. While the enteral route is commonly held as the method of choice, in practice gastrointestinal dysmotility or diarrhea may cause suboptimal results with failure to deliver the desired daily requirements *(Atkinson & Worthley, 2003)*. However, even if patients can only tolerate small amounts of enteral nutrition, this route of feeding should be pursued and supplemented with PN as necessary to meet nutritional needs. Critically ill cats that are completely intolerant to enteral feeding, should receive parenteral nutrition **(Figure 4)**.

TABLE 4 - PERTINENT INFORMATION TO EVALUATE IN THE NUTRITIONAL ASSESSMENT

Adapted from Michel, 2006

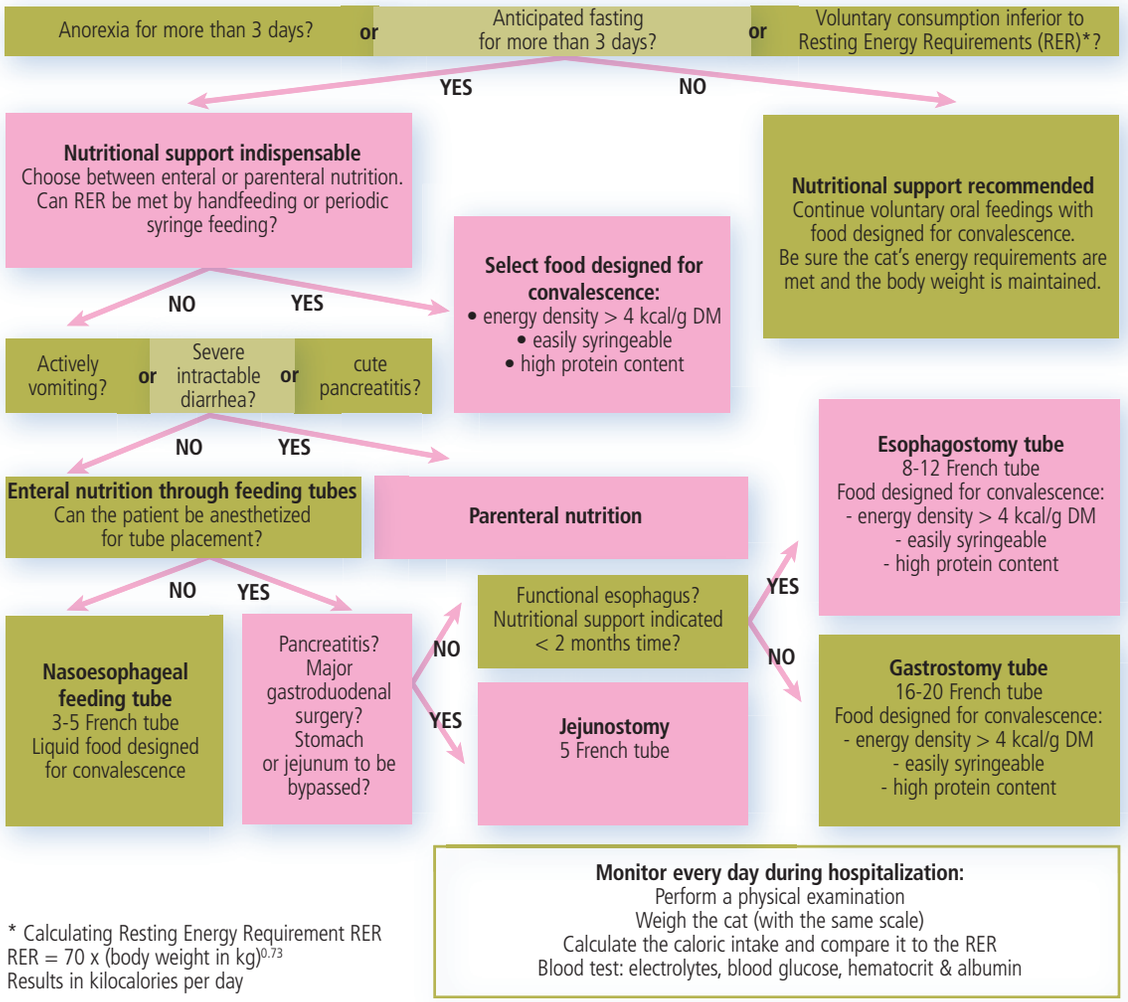
1. Assessment of gastrointestinal (GI) tract function
2. Assessment of the other organ systems that have an impact on the patient's ability to tolerate specific nutrients
3. Assessment of the patient's ability to tolerate placement of a feeding tube
4. Assessment of the patient's risk for pulmonary aspiration
5. Assessment of the ability to obtain vascular access
6. Assessment of the patient's fluid tolerance

The assessment of gastro-intestinal (GI) tract function should include evaluation of the patient for nausea and vomiting and indications of GI dysfunction such as ileus or malabsorption. It is important to consider if the patient is receiving any medications that might cause nausea or GI ileus and whether the patient has had any recent gastrointestinal surgery or injury that will require bypass.

The patient is further assessed for indications of other organ systems that may impact the patient's ability to tolerate specific nutrients. Renal or hepatic failure may affect protein tolerance. Infiltrative mucosal disease may affect the patient's ability to assimilate dietary fat.With the exception of nasoesophageal tubes, placement of enteral feeding tubes requires general sedation or anesthesia. Therefore veterinarians should anticipate the need to place an enteral feeding tube when the patient is undergoing diagnostic procedures or surgery. If an enteral feeding tube is to be surgically placed, the patient should be assessed for a coagulopathy. Patients should also be evaluated for underlying conditions or the use of medications that might impair wound healing. Even the placement of a nasoesophageal tube will require physical restraint and some patients with respiratory compromise may not be able to tolerate this simple procedure.

FIGURE 4 - INTEGRATING NUTRITIONAL SUPPORT: DECISION TREE

(Adapted from Delaney et al, 2006)



If PN is considered, it is necessary to determine whether venous access can be obtained and whether that access will be central or peripheral. In addition, the patient's fluid tolerance must be assessed *(Michel, 2004; Michel, 2006)*. The optimal delivery of PN is via a central venous catheter which requires close monitoring of the patient for metabolic complications. Therefore the patient receiving PN should be cared for in a facility that has 24 hour nursing care and the ability to perform serum chemistry tests.

The type of nursing care that the patient will receive should influence the choice of tube and feeding route. For example, if a cat is expected to go home with a feeding tube then it must be a type through which bolus feeding is possible unless the owner is capable of caging and monitoring their pet at home for continuous feeding.

The type of diet will influence the choice of tube type and site. If the only available food is blenderized then the choice is limited to using large bore tubes placed in the esophagus or stomach *(Michel, 2004; Michel, 2006)*.

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Patients must be stabilized before undergoing anesthesia, regardless of the urgency to implement nutritional support (Chan & Freeman, 2006a).

4 - Calculating nutritional requirements

Once the decision to implement nutritional support has been achieved, a stepwise process to calculate the energy requirements and to select the appropriate nutrient profile with respect to protein, carbohydrate, and fat is necessary. In addition to nutrients, the water requirement of the cat also needs to be evaluated.

► Energy

The calculation of the energy requirement of critically ill patients has been the subject of some controversy. Direct measurement of patient's energy consumption is not readily available. Consequently, several equations have been recommended to estimate the requirement. These equations utilize the resting energy requirement (RER), the basal energy requirement (BER), or the maintenance energy requirement (MER). The RER accounts for the energy required by the animal in a resting state and it includes physiologic influences and the assimilation of nutrients *(Elliott & Biourge, 2006; Michel 2006)*. The interspecies formula (1) is most commonly used by the authors. Formula (2) is an alternative equation that can be used for to estimate RER in cats.

Formula 1 RER = 70 x (current body weight in kg) $^{0.73}$ kcal/day
Formula 2 RER = 40 x (current body weight in kg) kcal/day

To avoid complications associated with refeeding critically ill patients (see below), the cat's current body weight should be used for the initial RER calculation, regardless of whether the cat is underweight or overweight. The caloric intake can then be adjusted on a day-to-day basis to ensure the appropriate amounts of calories are administered to maintain current body weight. With resolution of the critical illness, caloric intake is further adjusted to either achieve weight gain in underweight cats, or for obese cats, a healthy weight loss program can be implemented **(see chapter 1)**.

Some authors have recommended multiplying the RER with an illness factor (0.5 to 2.0) to account for hypermetabolism *(Bartges et al, 2004)*. Other authors suggest that the RER of critically ill dogs, determined with indirect calorimetry, indicates that their energy expenditure is only slightly increased from normal *(O'Toole et al, 2004)*. In addition, feeding excess calories can be associated with gastrointestinal complications, electrolyte imbalances, hepatic dysfunction, or cardiac abnormalities, complications commonly referred to as the refeeding syndrome *(Solomon & Kirby, 1989; Miller & Bartges, 2000; Armitage-Chan et al, 2006)*. Furthermore, overfeeding energy can result in increased carbon dioxide production which can challenge patients with respiratory compromise *(Lippert et al, 1993)*. Finally, a study showed an association between the use of illness factors and the development of hyperglycemia in cats administered parenteral nutrition *(Crabb et al, 2006)*. Therefore, these studies support the recent trend of formulating nutritional support in critically ill patients to meet the RER rather than the more generous illness energy requirements *(O'Tool et al, 2004)*.

TABLE 5 - PROTEIN REQUIREMENT IS USUALLY HIGHER IN CRITICALLY ILL CATS COMPARED TO HEALTHY CATS

Protein to calorie ratio is 110g/1,000 kcal versus 80 g/1,000 kcal in normal cats.
Proteins represent 40% RER versus 28% in normal cats.
Specificities of cats: - Higher protein requirements - Higher taurine and arginine requirements

► Protein

To abolish negative nitrogen balance in a severely hypermetabolic and hypercatabolic patient it may be necessary to supply protein in amounts in excess of normal minimum requirements *(Elliott & Biourge, 2006)* **(Table 5)**. Although nitrogen balance is often used to determine the protein requirements of critically ill people, this is not commonly measured in critically ill animals. In critically ill cats, protein should reach 30 to 50% of the calories *(Chan & Freeman, 2006)*. Protein requirements are usually estimated based on clinical judgment and the recognition that protein requirements are markedly increased during certain diseases (e.g., peritonitis, draining wounds, severe burns) or require adjustement with other diseases (e.g., uremia, hepatic encephalopathy). The dietary source of protein should be highly digestible and contain all the essential amino acids. Human liquid formulas should be used cautiously, if at all in cats. Human formulations typically do not meet the high protein requirements of the cat, and are deficient in essential nutrients such as arginine, taurine and arachidonic acid.

The branch-chain amino acids (BCAAs) leucine, isoleucine and valine (or their metabolites) may have a regulatory and anabolic role in protein metabolism by either increasing the rate of muscle protein synthesis or by decreasing the rate of protein degradation. Some, but not all, human studies have reported that BCAAs have a positive effect on nitrogen balance in the stressed patient *(Skeie et al, 1990)*. To date, studies to evaluate the benefits of BCCA in critically ill cats have not been reported. However, the metabolism of these amino acids in this species, suggest that BCAA's could have positive benefits *(Elliott & Biourge, 2006)*.

There are limited studies in critically ill or diseased companion animals supplemented with GLN. *Marks et al* (1999) were unable to preserve intestinal function in cats with methotrexate-induced enteritis that were fed a glutamine-supplemented amino acid-based purified diet. However, there are numerous studies evaluating the effects of enteral or parenteral glutamine in critically ill humans. Some studies report positive effects of glutamine supplementation on the gastrointestinal barrier and outcome, whereas other studies report no differences. Summarizing the numerous human studies certainly suggests that glutamine could have positive benefits on gastrointestinal health in critically ill cats.

► Carbohydrates

Cats do not have an absolute requirement for carbohydrates other than as an alternative source of energy. However, supplementation with carbohydrates may help to preserve lean body mass by down regulating gluconeogenesis. Excess simple carbohydrates should be avoided in critically ill cats as they can predispose to hyperglycemia *(Lippert et al, 1993; Chan et al 2002; Pyle et al, 2004)* **(Table 6)**. The subsequent release of insulin may lead to or exacerbate hypophosphatemia, hypokalemia, and other metabolic derangements *(Elliott & Biourge 2006)*. In addition, cats have difficulty metabolizing large loads of highly digestible carbohydrate. Therefore, carbohydrates as source of energy are not recommended for critically ill cats.

Conversely, the inclusion of fermentable fibers or prebiotics such as beet pulp or fructo-oligosaccharides may have several beneficial effects in critical illness. Fermentable fibers have a positive effective on the mucosal barrier by stimulating the growth of intestinal bacteria such as Lactobacilii and Bifidobacteria. These bacterial species are considered to be beneficial to gastrointestinal health as they decrease the growth of pathogens such as *Clostridia* and *E. coli*. In addition, they produce the short chain fatty acids butyrate, acetate and propionate, which provide fuel for colonocytes. Short chain fatty acids enhance sodium and water absorption, increase mucosal blood flow and increase gastrointestinal hormone release. These mechanisms contribute to the trophic role that short chain fatty acids have on the intestinal mucosa, stimulating enterocyte and colonocyte proliferation *(Elliott & Biourge, 2006)*.

TABLE 6 - THE CARBOHYDRATE INTAKE SHOULD BE LOWER IN CRITICALLY ILL CATS COMPARED TO HEALTHY CATS

Carbohydrate to calorie ratio is 40-60 g/1,000 kcal in normal cats.
Carbohydrates represent 15-20% RER versus 20-30% in normal cats.

► Fat

High fat diets (over 40% of calories) have been recommended for critically ill patients because free fatty acids rather than glucose provide the principal fuel in the catabolic patient. The preferential use of fat as a fuel may also help spare protein from catabolic processes for energy generation so that the protein can be used for anabolic processes. In addition, fat provides more than twice the energy density per unit weight than protein or carbohydrates, which helps to make the diet more concentrated **(Table 7)**.

TABLE 7 - THE FAT REQUIREMENT IS USUALLY HIGHER IN CRITICALLY ILL CATS COMPARED TO HEALTHY CATS

Fat to calorie ratio is 60-80 g/1,000 kcal versus 60 g/1,000 kcal in normal cats.
Fat represents 50-70% RER versus 50% in normal cats.

Polyunsaturated fatty acids (PUFA's) are essential for the maintenance of membrane integrity as constituents of membrane phospholipids and the provision of substrates for eicosanoids synthesis (protaglandins, thromboxanes, and leukotrienes). The eicosanoids regulate the production of several cytokines such as interleukin-1 and TNF-α and are involved in critical inflammatory and immune responses. The long chain omega-3 fatty acids such as EPA (eicosapentanoic acid) and DHA (docosahexaenoic acid) decrease the synthesis of inflammatory mediators (COX-2 inhibitor-like action, PGE_2 production inhibition, NF-ÎB nuclear translocation decrease, and cytokines production inhibition), and they have been shown to have clinical benefits in a variety of disea-

se states, including sepsis. Conversely, omega-6 fatty acids have a significant role in immunosuppression, tumorinogenesis, and inflammation *(Kerl & Johnson, 2004; Saker, 2006)*.

► Vitamins and minerals

Vitamins and minerals facilitate complex metabolic reactions and are key components of antioxidant activities *(Saker 2006)*. Electrolytes (phosphorus, sodium, potassium and magnesium) should be closely evaluated in diets formulated for the critically ill patient to prevent the refeeding syndrome *(Solomon & Kirby, 1989; Justin & Hohenhaus, 1995; Miller & Bartges, 2000; Armitage-Chan et al, 2006)*. Zinc supplementation may be beneficial in the critical patient to support the immune system and help promote wound healing. Critically ill cats may also have increased requirements for the water-soluble B vitamins. Vitamin B_{12} is particularly important for cats with pancreatitis or chronic intestinal disease.

► Special nutrients

The association of malnutrition with reduced resistance to infections has been observed for centuries. Numerous studies have evaluated the clinical effectiveness of specific nutrient supplementation in modulating the immune system *(Heyland & Dhaliwal, 2005)*. Immunomodulating nutrients that have been evaluated include glutamine, arginine, long chain omega-3 fatty acids, antioxidants (such as vitamin C, vitamin E, taurine, caroteinoids), and nucleotides *(Chan & Freeman, 2006a)*. However, the optimal combination and level of immune modulating nutrients to support the immune system of the critically ill cat is not yet known (see chapter 14).

Free radicals are unstable molecules generated by numerous exogenous and endogenous mechanisms. Hypovolemia, ischemia and reperfusion injury, common components of critical illness, can increase the production of free radicals. Free radicals cause oxidative damage to cellular components, which may ultimately contribute to organ dysfunction. The body counteracts oxidative damage by using free radical scavenging systems such as superoxide dismutase, glutathione peroxidase, catalase, vitamin E, vitamin C, taurine, and carotenoids. However, in critical illness, an imbalance between oxidant production and antioxidant protection can arise. Therefore it is prudent to supplement the diet of the critically ill patient with antioxidants.

In summary, the beneficial effects derived from adequate nutrititional support include: enhanced immune fonction, wound repair, response to therapy, recovery time and survival time **(Figure 5)**.

► Water

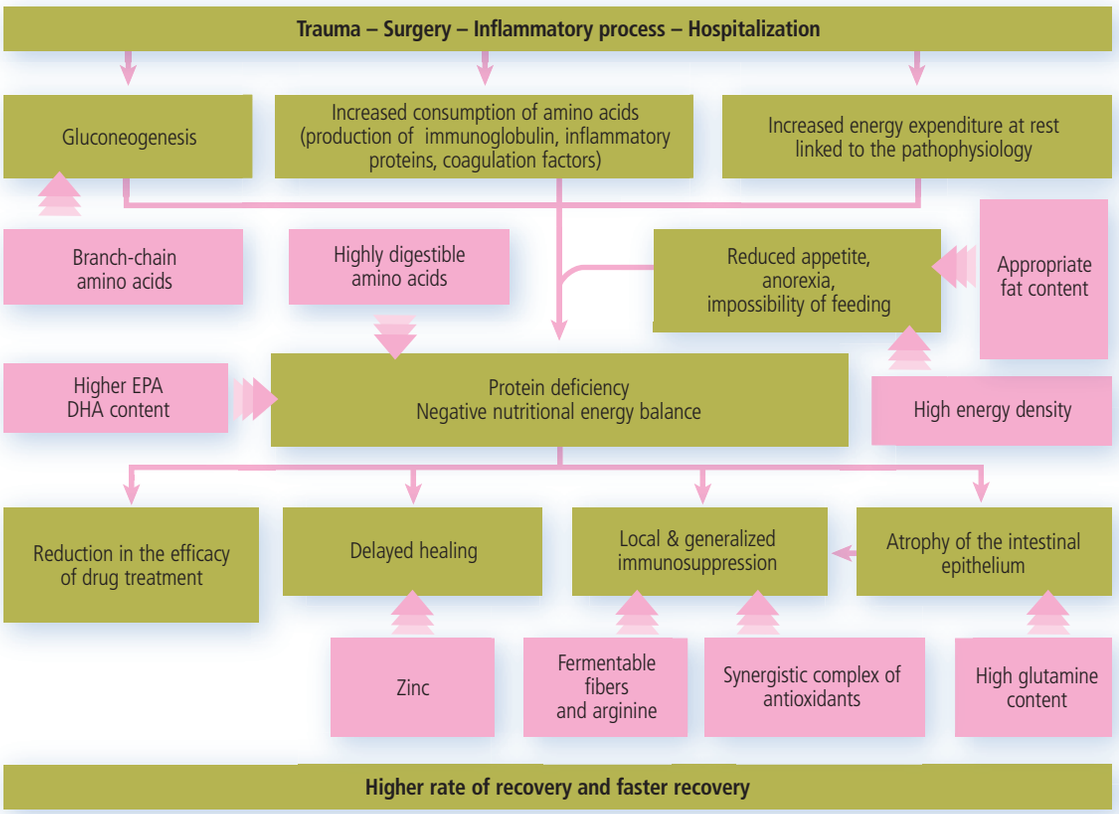
The water needs of cats reflect their evolutionary status as desert-dwelling carnivorous animals who evolved to obtain most of their water requirements from the consumption of prey. Cats also have a less sensitive response to thirst and dehydration than dogs.

Nevertheless, critically ill cats are generally dehydrated or hypovolemic and restoration of fluid and electrolyte balance, and circulating blood volume typically requires intravenous support. However, consideration should also be given to critically ill cats to ensure adequate intake of free water, which can be administered enterally or parentally.

5 - Enteral nutrition

A study investigated the percentage of prescribed enteral nutrition delivered to 23 cats and 2 dogs *(Michel & Higgins, 2006)*. This investigation reported a good rate of success for delivery of clearly prescribed enteral nutrition. In addition, consultation with the Nutritional Support Service improved the likelihood that prescribed nutrition would meet the patient's estimated RER.

Figure 5 - Nutritional keypoints to improve the speed of recuperation and to improve clinical success



► "Assisted" feeding

Cats are known for a tendency to have fixed food preferences and therefore may refuse a new food. When smell or food is associated with positive consequences, the food will be eaten again. Conversely, if the smell or food is associated with distress, such as an unpleasant experience or hospitalization, the food will be avoided in the future. This phenomenon is known as aversion and in cats, aversion sets in very quickly. It is recommended to resist the temptation to coax a cat to eat. Forcing food on a cat who clearly does not want it may risk inducing aspiration pneumonia and a learned food aversion.

The smell alone of a food associated with digestive disorders is enough to elicit aversion. Cats even go so far as to show aversion for their usual food if it is served in the presence of an air current bearing the odor of a food to which they have developed an aversion. Therefore, it is important to be careful when preparing foods for cats at the hospital. Odors may travel and could trigger an aversion reaction even in cats being fed their usual diet. It is best to prepare the cats'food in a place where food odors cannot reach the cats.

For cats that show some interest in food, several methods can be tried to increase the inclination to eat. One can offer food in a novel setting or have someone different to do the feeding. Stroking and talking to a cat with the food nearby may stimulate interest to eat **(Figure 6)**.

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***Figure 6** - Sometimes a cat will be stimulated to eat if a small amount of food is placed in the mouth or on the lips or paws.*

Cats need to feel safe and secure within their environment. To this end veterinarians and owners need to provide facilities for the main behavioral functions of eating, sleeping and playing and also ensure that the cat has the ability to control its own stress through the natural mechanisms of hiding and retreating. One of the problems with hospitalization is that the cat finds itself


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Figure 7 *- Moving the cats to larger dog cages which permits the separation of food, lodging and litter may restore the appetite of some cats.*

constantly on display and correspondingly vulnerable. Taking steps to provide the cat with a constant and predictable environment, both in terms of physical structure and scent profiles, will help to increase the cat's security. Hospitalized cats may be uncomfortable eating because the lack of space causes the spatial requirements of cats to be disrespected **(Figure 7)**.

Early satiety is common in anorectic patients, so it is recommended to divide the day's food up into as many small fresh meals as possible. This is particularly important in cats as their natural behavior is to eat a large number of small meals each day. They also eat day and night. Therefore, mimicking natural behavior in the hospitalized environment by providing multiple small fresh meals during the day and night may facilitate food intake.

It is important to keep in mind that "mouth feel" is very important to cats. Nutrients that increase palatability for most cats are moisture, fat and protein, and cats prefer foods with an acidic flavor and strong aromas. Adding water to a dry cat food or switching to a canned food may improve food acceptance. Most cats prefer their food at body temperature. Therefore warming the food prior to serving may encourage anorectic cats to eat. For cats showing interest in food but an unwillingness to eat warm food, it is suggested to try offering chilled food *(Michel, 2001)*. For cats that do not achieve adequate caloric intake using the above mention methods, enteral or parenteral feeding is indicated to achieve effective dietary management *(Michel, 2001; Elliott, 2008)*.

► Pharmacological appetite stimulation

Only a few drugs have been used as appetite stimulants in feline patients **(Table 8)**. There are a number of adverse effects associated with these medications. In numerous authors'opinion they have no place in the nutritional management of hospitalized critically ill patients. The only means of ensuring adequate caloric intake is through nutritional support (i.e. tube feeding or PN). Appetite stimulants could be used once the patient is recovering from its disease in the home environment *(Chan, 2006)*.

► Enteral feeding tubes

Enteral feeding can be achieved via nasoesophageal, esophagostomy, gastrostomy or jejunostomy devices *(Marks, 1998)*. Enteral feeding tubes are available in several sizes and designs, and are constructed of latex or silicone. Latex tubes are less expensive but generally require replacement within 8-12 weeks due to tube wear and tear. Silicone tubes typically survive 6-12 months and are less irritant at the stoma site. An array of feeding adapters can be attached to the enteral tube.

The use of these agents in cats can be restricted according to the licence applicable in each country.

TABLE 8 - APPETITE STIMULANTS
Adapted from Chan, 2006

Drug	Dosage	Comments
Benzodiazepine derivatives: - Diazepam - Oxazepam	 - 0.2 mg/kg IV - 0.5 mg/kg PO SID to BID	Sedation, contraindicated in cats with hepatic failure, effects wane with time when used in sick animals
Cyproheptadine	0.2-0.5 mg/kg PO BID	Antiserotoninergic, can cause excitability, aggression and vomiting
Mianserine chlorhydrate	2-4 mg/kg PO SID	Excitability, aggression and vomiting


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Figure 8 - Nasoesophageal tube placed in a cat.
Most critically ill patients will tolerate nasoesophageal tube placement, but some individuals may require sedation.

> Nasoesophageal tubes

Nasoesophageal tubes are an excellent option for short-term feeding (< 5 days) of hospitalized cats **(Figure 8)**. Placement is described in **Table 9**. The tip of the nasoesophageal tube should not enter the stomach, but rather, sit in the distal esophagus. If the tube traverses the esophageal-gastric junction, acid reflux is likely, causing esophagitis and contributing to vomiting and irritation.

TABLE 9 - NASOESOPHAGEAL TUBES

Verset et coll, 2008; adapted from Bosworth & Snow 2004; Chan 2006

Indications	Contraindications
• Anorexic animals with a functional lower digestive system • Short-term tube feeding (< 5 days) • Spontaneous feeding contraindicated or impossible: mandible fractures, post oral surgery	• Uncontrollable vomiting • Surgery on the mouth, pharynx, esophagus • Trauma or esophageal stenosis • Deglutition/esophagus transit disorder • Altered state of consciousness • Delayed gastric emptying • Hepatic duct surgery • Fractures of nasal cavities or rhinitis • Severe thrombocytopenia/pathy • Brain trauma or intracranial hypertension (increased intra cranial pressure due to sneezing)
Pros	**Cons**
• Inexpensive • Easy to place • No anesthesia required • Animals can drink and swallow around the tube • No wait time before use or withdrawal	• Short-term nutrition • Uncomfortable tube of small diameter • Liquid food and large volumes due to small diameter • Elizabethan collar interferes with resumption of spontaneous feeding
Preparation	
Equipment	**Cat**
• 3-5 Fr Pediatric feeding tube (PVC, silicon, Teflon) • Lidocaine spray • Lidocaine gel • Non-resorbant monofilament thread and needle and/or cyanoacrylate • Elizabethan collar	• Spray lidocaine in the nose • Animal sitting or in sternal decubitus position • Flexed neck
Insertion	
• Measure the placement length of the tube (from nasal meatus to 9th intercostal space) and mark the tube with indelible ink • Apply lidocaine gel around the tube • Insert the tube ventromedially and feed to the position of the insertion guide • Secured the tube with glue spot, suture or surgical staple at the nares laterally to the face and head • Verify the tube's position by radiograph • Place an Elizabethan collar	
Post insertion	
Supportive care	**Complications/withdrawal**
• Progressive refeeding • Prior to each and every use: Confirm placement by aspiration and check for gastric contents • Following each and every use: Rise with lukewarm water (5-10mL) to prevent obstruction	• Overfeeding (nausea, reflux, vomiting, diarrhea) • Aspiration pneumonia • Epistaxis, rhinitis, dacryocystitis • Gastro-esophageal reflux and esophagitis • Obstruction of the tube • Withdrawal: resumption of spontaneous feeding

Figure 9 - Esophagostomy tube in a cat.
Esophagostomy tubes can easily be placed under a light anesthetic with minimal equipment.

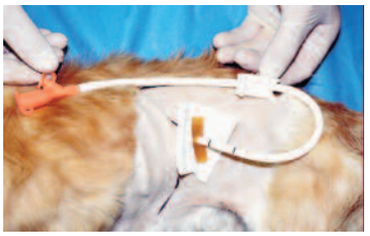


Figure 10 - Gastrotomy tube in an anesthetized cat.
A gastrotomy tube must remain in place for a minimum of 7-10 days to allow a seal to form with the abdominal wall.

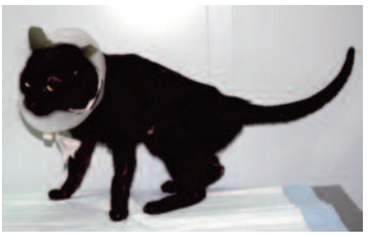
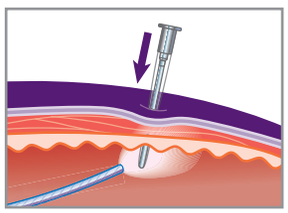
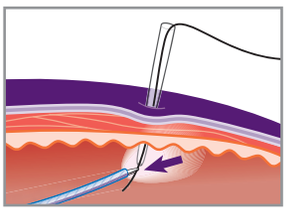


Figure 11 - Gastrotomy tube in a conscious cat.
Most patients tolerate the tubes quite well.

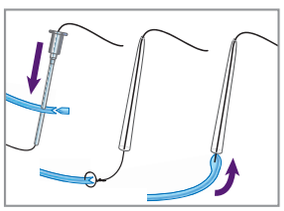
FIGURE 12 - PERCUTANEOUS ENDOSCOPIC GASTROSTOMY (PEG)



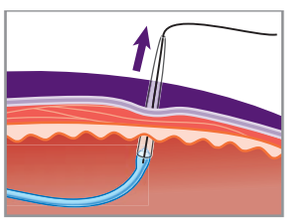
The endoscope is introduced into the stomach, which is dilated, then the skin and stomach are punctured using the trocar.



A guide is passed through the trocar and gripped with the endoscope forceps in the direction of the muzzle until it re-emerges.



The tube is fixed to the guide using attachment.



The guide and the tube are pulled towards the stomach until the end of the tube reaches the stomach wall.

Contraindications for nasoesophageal tubes include patients that have severe facial trauma involving the nares, protracted vomiting and/or regurgitation, semiconsciousness, or those patients that have laryngeal, pharyngeal, or esophageal physical or functional abnormalities *(Marks, 1998)*. Nasoesophageal tubes, are small, typically 3 to 5 Fr. Therefore, the selection of diet to feed via a nasoesophageal tube is limited to liquid or reconstituted powder diets. Some critically ill cats may not tolerate the large volumes required of such mixtures. *(Marks, 1998; Yam & Cave, 2003; Chan, 2006)*.

> Esophagostomy tubes

Esophagostomy tubes can easily be placed under a light anesthetic with minimal equipment **(Table 10)**. The only major associated complication is the potential for infection at the entry site and meticulous care of the surgical wound is essential to maintain the tube. In a study of 67 cats, esophagostomy feeding tubes were placed in 46 cats and percutaneous endoscopic gastrostomy (PEG) feeding tubes were placed in 21 cats. The authors reported that esophagostomy tubes were an excellent and less invasive alternative to the PEG tube *(Ireland et al, 2003)*. Critical care nutritionists believe that mastering the placement of esophagostomy feeding tubes is essential in the management of critically ill cats and this technique should be adopted in almost all practices *(Chan, 2006)* **(Figure 9)**.

> Gastrostomy tubes

Gastrostomy tubes are invaluable for the long-term nutritional support of critically ill patients **(Figure 10)**. Gastrostomy tubes may be placed surgically, or by percutaneous technique assisted with an endoscopic or blind placement apparatus. 16-20 Fr tubes are appropriate for cats. They must remain in place for a minimum of 7-10 days to allow a seal to form with the abdominal wall. These tubes can be easily maintained for many weeks to months in the chronically ill or anorexic patient *(Elliott et al, 2001; Luhn et al, 2004, Mesich & Snow 2004, Thompson et al 2004)* **(Figure 11)**. Peritonitis is a potential complication if the gastrostomy tube leaks or is removed early. The PEG technique is presented in **Figure 12**.

> Jejunostomy tubes

The jejunostomy tube by-passes the stomach and pancreas and can be used in case of severe pancreatitis, diffuse gastric mucosal disease, protracted vomiting or delayed gastric emptying. The jeju-

Table 10 - Esophagostomy tubes

Verset et coll, 2008; adapted from Von Werthern & Wess 2001; Bosworth et al, 2004; Vannatta & Snow 2004; Chan, 2006

Indications	Contraindications
• Enteral nutrition > 7 days • Prolonged anorexia • Post-op mouth and head surgery • Oral cavity disorders • Contraindications of nasoesophageal tubes	• Uncontrollable vomiting • Primary or secondary esophageal disorders (esophagitis, megaesophagus, trauma, stenosis) • Foreign body, surgery or esophageal tumor • Delayed gastric emptying • Hepatic duct surgery
Pros	**Cons**
• Well tolerated • Inexpensive • Easy to place • Large diameter tubes • Can use calorically-dense diets • Long-term nutrition (1-12 weeks)	• General anesthesia needed for placement • Surgical procedure
Preparation	
Equipment	**Animal**
• Endotracheal tube • Curved Rochester carmalt • 8-12 Fr 40 cm Pediatric feeding tube (PVC or silicon) • Non-resorbant monofilament thread and suture equipment • Elizabethan collar	• General anesthesia with placement of endotracheal tube • Right lateral decubitus • Clip and surgically prepare the left lateral cervical zone
Insertion	
• Measure the placement length of the tube (from 1/3 proximal of the esophagus to 8th or 9th rib), and mark with indelible ink • Elongate the side exit side hole on the tube with a small blade • Identify the position of the jugular, retromandibular and oral-facial veins • Introduce the carmalt in the mouth and direct it down the proximal esophagus with outward pressure, caudally to the hyoid and the entrance to the larynx • Rotate the tip of the carmalt dorsally, pushing the esophagus towards the skin • Palpate the tip of the carmalt over the skin • Incise through the skin into the esophagus over the tip of the instrument (the mucosa of the esophagus is more difficult to incise than the skin) • Gently force the tip of the instrument through the incision when the mucosa • Enlarge the incision slightly to allow the tip of the carmalt to open • Place the esophagostomy tube within the tips of the carmalt • Close the carmalt and remove it from from the oral cavity, with the attached tube • Disengagement of the tip of the carmalt • Curl the tip of the tube back into the mouth and feed it into the esophagus • As the curled tube is pushed into the esophagus, the proximal end is gently pulled outwards simultaneously • Redirect the tube within the esophagus and creat a subtle "flip" • Visually inspect the oropharynx to confirm that the tube is no longer present within the oropharynx • Re-scrub the incision site, place a pursestring suture followed by a "Chinese finger trap" • Apply a light trap around the neck • Confirm correct placement with radiography	
Post insertion	
Supportive care	**Complications/withdrawal**
• Monitor the wound and change the dressings for 3-5 days then every 2-3 days • Wait 24 h before use • Progressively refeed • Prior to each and every use: Confirm placement by aspiration and check for gastric contents • Following each and every use: Rise with lukewarm water (5-10mL) to prevent obstruction	• Overfeeding (nausea, reflux, vomiting, diarrhea) • Perforation of the jugular at placement • Aspiration pneumonia • Esophageal reflux, vomiting/regurgitation • Local infection at stoma site • Obstruction • Cellulitis if tube is prematurely removed

Table 11 - Determination of a refeeding program

Case A anorexic for <3 days: plan to meet Resting Energy Requirement (RER) in 3 days
Day 1: 1/3 of RER Day 2: 2/3 of RER Day 3: Full RER
Case B anorexic for >3 days: plan to meet RER in 5 days
Day 1: 1/4 of RER Day 2: 1/2 of RER Day 3: 2/3 RER Day 4: 3/4 of RER Day 5: Full RER

nostomy tube requires surgical placement with general anesthesia and laparotomy. New placement techniques have been described whereby the jejunostomy tube is introduced via a gastrostomy tube and directed down through the pylorus with an endoscope *(Heuter 2004; Jergens et al 2007)*. Due to the narrow diameter of the tube, and placement in the jejunum, feeding must be by a continuous infusion pump with a liquid diet. Therefore jejunostomy tubes are limited to in-hospital use. Peritonitis can occur if the tube is prematurely removed. Contraindications include ascites, peritonitis, immunosuppression and distal small bowel obstructions *(Heather et al, 2004)*.

> Feeding protocols

Nutritional support should be introduced gradually. Generally one-third to one-quarter of the daily caloric intake is administered on the first day. If no complications occur, the amount fed is successively increased to reach total caloric requirements by the third or fourth day *(Bartges et al, 2004; Elliott & Biourge, 2006)* **(Table 11)**. If necessary, the diet can be modified by blenderizing with water to ensure passage through the feeding tube. The total daily volume is divided into 4-6 feedings depending on duration of anorexia and patient tolerance.

Gastric dysmotility is a common abnormality in critically ill patients. Prokinetic agents appear to have a beneficial effect on gastrointestinal motility and feeding tolerance in critically ill patients *(Corke, 1999; Booth et al, 2002)*. The use of anti-emetic drugs should be considered in cats where vomiting and nausea are a problem **(Table 12)**. Metoclopramide, in addition to having some anti-emetic effects, may be beneficial in patients where delayed gastric emptying is a problem *(Michel, 2001; Mohr et al, 2003)*. *Chan & Freeman* (2006) recommend continuous infusions of metoclopramide at 1-2 mg/kg/day. More recently, potent anti-emetics belonging to the HT3-antagonist family of drugs (ondasetron, dolansteron) have been recommended, however efficacy trials are lacking. A new type of anti-emetic (maropitant, an NK-1 antagonist), has been introduced. However, clinical experience in cats is not yet available.

A common misconception is that animals fed via enteral tubes will not eat voluntarily, and therefore ad-libitum feedings are withheld. Anorexia typically resolves once the primary disease is addressed. Therefore, food can be offered to cats to assess their appetite, and to help to determine when to wean them from enteral tube feeding.

> Complications

Aspiration pneumonia

The most serious complication of enteral feeding is aspiration pneumonia. This can be a fatal complication in critically ill cats. Patients at risk of pulmonary aspiration include patients who have had a prior episode of aspiration pneumonia, patients with impaired mental status including those receiving sedatives and certain analgesics, patients with neurological injuries, patients with reduced or absent cough or gag reflexes, and patients receiving mechanical ventilation *(Michel, 2004; 2006)*. Nasoesophageal tube displacement from the esophagus into the trachea will cause aspira-

Table 12 - Select anti-emetic agents
Adapted from Michel 2001

Drug	Dosage	Comments
Metoclopramide	0.2-0.4 mg/kg IV, SC or PO TID 1-2 mg/kg/day IV CRI	Promotes gastric emptying and acts centrally on the chemoreceptor trigger zone (central effects are less potent in the cat than in other species)
Ondansetron	0.1-0.15 mg/kg slow IV push BID	Acts centrally on the chemoreceptor trigger zone ($5HT_3$ antagonists)

The use of these agents in cats can be restricted according to the licence applicable in each country.

tion pneumonia. The risk of aspiration pneumonia can be minimized by ensuring correct positioning of the feeding tube prior to each and every feeding.

Mechanical complications

Mechanical complications such as tube obstruction, premature removal or dislodgement are the common complications seen with enteral nutrition. Tube obstruction can be minimized by adequate dilution and blending of the diet prior to administration. The enteral formula should never be allowed to sit in the feeding tube and the tube should be flushed with warm water after every feeding or whenever GI contents are aspirated via the tube. Obstruction of esophagostomy tubes can be dramatically reduced, by enlarging the distal exit hole prior to placement. Techniques to facilitate removal of the obstruction include massaging the outside of the tube while simultaneously flushing and aspirating with water; instilling carbonated drinks, meat tenderizers or pancreatic enzyme solutions for 15 to 20 minutes; or gently using a polyurethane catheter to dislodge the obstruction. The final resort is tube removal and replacement.

While it is tempting to employ a feeding tube for medicating a patient, this practice should be used with caution. If possible, only liquid medications should be given through feeding tubes. Viscous medications should be diluted with water and tablets crushed to a fine powder before mixing with water. Only one medication should be administered at a time and with the exception of phosphate binders for renal disease, separately from enteral feedings to avoid drug-drug and drug-nutrients interactions.

Premature tube removal or dislodgement is best prevented by choosing a tube that the patient will be comfortable with and by using Elizabethan collars or body wraps as appropriate. Marking the tube where it exits the body at the time of tube placement with indelible ink will aid in monitoring whether a tube has migrated from its original position. Whenever the location of a tube is in doubt it should be verified radiographically. Iodinated contrast media can be infused through a gastrostomy or enterostomy tube to check for leaks into the peritoneal cavity *(Michel, 2004)*.

Feeding intolerance

Feeding intolerance is a common complication, especially in critically ill animals. Animals that vomit persistently and frequently (more than 3 times a day) probably should not be fed via the enteral route. Altering the feeding strategy is recommended for cats that vomit small amounts and infrequently (less than 2 times a day). For example, smaller volumes administered over a longer duration, more frequently can improve feeding tolerance. If bolus feeding is still not tolerated, feeding via continuous infusion could improve feeding tolerance. It is recommended to start at a very low rate, e.g. 2 mL/hour and slowly increase the rate based on patient response, until the daily caloric intake is achieved. In such cases, reaching caloric target may be delayed by a few days *(Marks, 1998; Michel, 2004; Chan, 2006; Chan & Freeman, 2006)*.

Metabolic complications

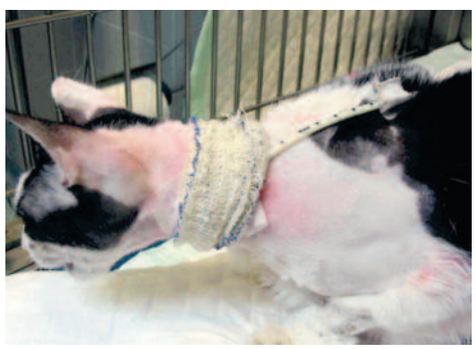
Different types of metabolic disturbances can occur with nutritional support.

- Patient's inability to assimilate nutrients

For example, a cat with impaired renal function might become azotemic on a high protein diet. This disturbance can be anticipated by a thorough nutritional assessment of the patient before formulating the nutritional regiment.

- Refeeding syndrome

The refeeding syndrome can develop in patients who have experienced severe muscle wasting as a result of prolonged starvation or catabolic disease *(Michel, 2004; Armitage-Chan et al, 2006)*. This is perhaps the more severe complication associated with nutritional support of critically ill patients and may develop after oral, enteral or parenteral nutrition although this remains a rare



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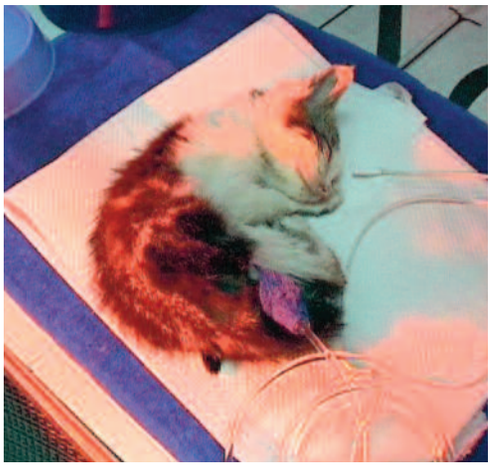
While it is tempting to employ a feeding tube for medicating a patient, this practice should be used with caution.



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Prevention of the refeeding syndrome requires stabilization of the fluid, electrolyte and acid-base status of the patient before starting nutritional support (Armitage-Chan et al, 2006).

occurrence. In people, this syndrome results in widespread systemic effects including depression of myocardial function, cardiac arrhythmias, hypoventilation, seizures and mental dysfunction, poor neutrophil function, muscle weakness, and hemolytic anemia.

Most of these effects occur secondary to hypophosphatemia however deficiencies of magnesium and potassium may also contribute. Hypophosphatemia develops due to the rapid increase in insulin release upon reintroduction of nutrition. Increased insulin activity stimulates anabolic processes, which require incorporation of phosphate into high-energy substrates such as adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (2,3-DPG). There is a transcellular shift of phosphate, which in the face of whole-body phosphate depletion results in hypophosphatemia. The reduction in ATP synthesis and consequent energy deficit, contributes to many of the clinical signs associated with the refeeding syndrome *(Solomon & Kirby, 1990; Miller, 2000; Armitage-Chan et al, 2006)*. Hemolytic anemia secondary to hypophosphatemia associated with the refeeding syndrome has been reported in cats *(Justin & Hohenhaus, 1995)*. Patients identified with severe hypophosphatemia usually respond to phosphate supplementation at a rate of 0.01-0.06 mmol/kg/hour *(Justin & Hohenhaus, 1995)*.

- Hyperglycemia

Hyperglycemia is another common metabolic complication that has only recently received attention in veterinary medicine. Possible consequences of hyperglycemia in critically ill animals include higher infection rates and increased mortality, however, it is not yet clear if insulin administration is indicated or influences outcome (see § 2,b,1) *(Chan et al, 2006; Crabb et al, 2006)*. The risk of hyperglycemia associated with nutritional support is more common with parenteral nutrition *(Crabb et al, 2006)*.

- Fluid overload

Diets used for enteral tube feeding are > 80% water, and water is used to flush the enteral tube upon conclusion of feeding. Therefore, fluid overload can occur in cats receiving nutritional support. Patients with pre-existing cardiac disease on high volumes of enteral tube feeding and receiving intravenous fluids are most at risk of fluid overload. Clinical signs consistent with fluid overloaded include dyspnea, pulmonary edema, and pleural effusion. Prevention requires thorough clinical evaluation to identify those patients most at risk, and to formulate an appropriate nutrition and fluid therapy plan to maintain hydration and yet avoid fluid overload *(Chan & Freeman, 2006)*.

> Monitoring and reassessment

Monitoring parameters for patients receiving enteral nutrition include body weight, serum electrolytes, the patency of the enteral feeding tube, the appearance of the stoma site, and clinical signs consistent with gastrointestinal intolerance, volume overload or pulmonary aspiration *(Chan & Freeman, 2006)*. The number of calories, and indeed the macronutrient composition of the diet selected may need to be adjusted according to the patient's changing needs and tolerance. In patients unable to tolerate the prescribed amounts, the clinician should consider reducing the amounts of enteral feedings and supplementing the enteral feeding with parenteral nutrition. With continual reassessment, the clinician can determine when to transition the patient from assisted feeding to voluntary consumption of food. The discontinuation of nutritional support should only begin when the patient can consume at least 75% RER, without coaxing *(Chan, 2006)*.

6 - Parenteral nutrition

Principal indications for parenteral nutrition include uncontrollable vomiting, regurgitation, acute pancreatitis, intestinal obstruction, severe malabsorption, prolonged ileus, and inability to guard the airway. Parenteral nutrition can be delivered through a central vein (central PN or

CPN) or a peripheral vein (partial PN or PPN). CPN is the provision of all of the animal's calorie and protein requirements. PPN only supplies part of the animal's energy and nutrient requirements *(Chan & Freeman, 2006; Delaney et al, 2006)*.

CPN is often the preferred modality for a cat requiring parenteral nutrition. A disadvantage of CPN includes the requirement for central venous access (jugular or femoral venous catheter), it is slightly more expensive, and it may be associated with more metabolic complications. CPN requires central venous access as the solution is hyperosmolar. The higher the osmolality of the solution, the higher the incidence of thrombophlebitis *(Chandler et al, 2000)*. Relatively few reports are available regarding the use of parenteral nutrition in cats *(Lippert et al, 1993; Chan et al, 2002; Pyle et al, 2004; Crabb et al, 2006)*. The major indication of parenteral nutrition in cats appears to be pancreatitis *(Chan et al, 2002; Pyle et al, 2004; Crabb et al, 2006)*.

► Components

Both CPN and PPN are a combination of a dextrose solution, an amino acid solution, and a lipid solution. The most commonly used amino acid solutions contain most essential amino acids for cats, except taurine. However, because parenteral nutrition is typically not used beyond 10 days, taurine deficiency is not a clinical complication in most circumstances. Amino acids solutions are available with and without electrolytes. Cats that have normal serum electrolytes typically receive amino acid solutions with electrolytes, whereas patients who have electrolytes disturbances may benefit from amino acid solutions without electrolytes so that the electrolyte disturbances can be individually corrected *(Chan & Freeman, 2006; Freeman & Chan, 2006)*. The osmolality of the amino acid solutions with and without electrolytes is also significantly different. Consequently, PPN, which requires the osmolality of the final solution to be less than 600 mmOsm/L, is typically formulated using an amino acid solution without electrolytes.

Lipid emulsions are the calorically dense component of parenteral nutrition and a source of essential fatty acids. The ratio of dextrose to lipid should be selected to reflect the hormonal milieu and metabolic condition of the liver. Lipid emulsions are isotonic. Typical lipid emulsions consist of soybean and safflower oil and provide predominantly long-chain polyunsaturated fatty acids, including linoleic, oleic, palmitic, and stearic acids. These solutions are emulsified with egg yolk phospholipids and their tonicity is adjusted with glycerol. The emulsified fat particles are comparable in size to chylomicrons and are removed from the circulation through the action of peripheral lipoprotein lipase. Infusions of lipid have not been shown to increase pancreatic secretion or worsen pancreatitis, excepted in cases where serum triglycerides are elevated, indicating a failure of triglyceride clearance. Although specific data on the maximal safe level of lipid administration in veterinary patients are not available, maintaining normal serum triglycerides levels in cats receiving parenteral nutrition seems prudent. *(Chan & Freeman, 2006; Freeman & Chan, 2006)*.

The parenteral solution should be formulated to contain 40 mEq/L of potassium to compensate for the insulin mediated transcellular potassium shift associated with refeeding. Similarly, the parenteral solution should be formulated to contain a minimum 5-10 mM/L of phosphorus. Water soluble vitamins can be provided by the addition of a multivitamin B complex preparation. These preparations typically do not include folic acid due to incompatibility with riboflavin in solution. Fat soluble vitamins, trace elements, and calcium are not generally included in the parenteral nutrition solution if the duration of treatment is expected to be less than 1-2 weeks. The addition of calcium is not routine because of the risk of precipitation of the parenteral solution, and calcium deficiency appears to be well tolerated in the short term. The dose of trace minerals to include in the parenteral nutrition is uncertain. Vitamin K should not be added to the parenteral nutrient solution, but should be administered subcutaneously once weekly.

TABLE 13 - WORKSHEET FOR CALCULATING PARTIAL PARENTERAL NUTRITION FOR CATS

Adapted from Freeman et Chan, 2006

1. Caculate the resting energy requirement (RER)
70 x (current body weight in kilograms)$^{0.73}$ = ☐ kcal/day

2. Calculate the partial energy requirement (PER)
PER = RER x 0.70 = ☐ kcal/day

3. Determine the nutrient composition
For animals under 3 kg, the formulation will provide a fluid rate higher than maintenance fluid requirements. Be sure that the animal can tolerate this volume of fluids
a. Cats weighing 3 - 5 kg
PER x 0.20 = ☐ kcal/day from dextrose
PER x 0.20 = ☐ kcal/day from protein
PER x 0.60 = ☐ kcal/day from lipid
b. Cats weighing 6 - 10 kg
PER x 0.25 = ☐ kcal/day from dextrose
PER x 0.25 = ☐ kcal/day from protein
PER x 0.50 = ☐ kcal/day from lipid

4. Calculate the volume of nutrient solutions required each day
a. 5% dextrose solution = 0.17 kcal/mL and 253 mOsm/L
☐ kcal from dextrose ÷ 0.17 kcal/mL = ☐ mL dextrose/day
b. 8.5% amino acid solution without electrolytes= 0.085 g protein/mL = 0.34 kcal/mL and 890 mOsm/L
☐ kcal from protein ÷ 0.34 kcal/mL = ☐ mL amino acids/day
c. 20% lipid solution = 2 kcal/mL and 260 mOsm/L
☐ kcal from lipid ÷ 2 kcal/mL = ☐ mL lipid/day

5. Calculate the total daily volume of parenteral solution
☐ mL total volume of PPN solution = ☐ mL 5% dextrose solution + ☐ mL 8.5% amino acid solution + ☐ mL 20% lipid solution

6. Calculate the osmolality
mOsm/L should be less than 600 mOsm/L for peripheral administration
☐ mL 5% dextrose solution * 0.253 mOsm/mL = ☐ mOsm
☐ mL 8.5% amino acid solution * 0.890 mOsm/mL = ☐ mOsm
☐ mL 20% lipid solution * 0.26 mOsm/mL = ☐ mOsm
☐ mL total volume of PPN solution
☐ mOsm of PPN solution
☐ mOsm/L of PPN solution = 1000*(☐ mOsm of PPN solution ÷ ☐ mL total volume of PPN solution)

7. Calculate the administration rate
This formulation provides approximately a maintenance fluid rate.
☐ mL/hour PPN solution = ☐ mL total volume of PPN solution/24 hrs

Foot notes
Calories supplied by proteins: 4 kcal/g
Calories supplied by carbohydrates: 4 kcal/g
Calories supplied by lipids: 9 kcal/g

► Compounding and prescription

Parenteral nutrition requires specific compounding practices to maintain sterility and to prevent precipitation of the components. The macronutrients should be combined in the following order: glucose then amino acids then lipids. For logistical and economical reasons, more than one day's supply of PN usually is typically compounded at one time, however, no more than a 3-day supply of parenteral nutrition should be compounded and stored (refrigerated) at a time. Parenteral admixtures should never be frozen or heated, and any unused portions should be discarded *(Campbell et al, 2006; Freeman & Chan, 2006)*.

The worksheets presented in **Table 13** and **Table 14** are designed to provide an admixture that is intended to last 24 hours when administered at a constant-rate infusion. Bags of parenteral nutrition should not be at room temperature for more than 24 hours.

► Administration

Parenteral nutrition requires a dedicated catheter (central or peripheral) placed aseptically **(Table 15).** Strict asepsis and regular catheter care should minimize the risk of bacterial colonization and a catheter-related infection. The choice of catheter type may vary depending on the desired formulation (osmolarity and composition), the bleeding propensity of the cat and the available venous access. Triple lumen central IV catheters are often used for CPN. These catheters allow the first port to be used for blood sampling and intermittent drug administration, the second port to be used for continuous medications and fluid adminstration and the third port to be soley dedicated to CPN *(Campbell et al, 2006; Delaney et al, 2006)*. CPN solutions should be administered through a 1.2 µm in-line filter, and as continuous rate infusions utilizing infusion pumps *(Chan & Freeman, 2006)*.

Hydration status, electrolyte abnormalities and acid-base disturbances should be corrected prior starting parenteral nutrition administration, as provision of nutritional support can cause alterations that may initially worsen these changes. CPN should be instituted gradually over 24 to 48 hours. If there are no complications, the rate of administration can be increased every 4 hours, until the goal rate is achieved *(Campbell et al, 2006)*. Most cats tolerate receiving 50% of total requirements on the first day and 100% on the second day. Cats that have been without food for long periods may require slower introduction (33% on the first day, 66% on the second day, and 100% on the third day). PPN does not require gradual introduction and can be initiated at 100% on the first day. It is important to adjust the cat's intravenous fluids when initiating parenteral nutrition to avoid fluid volume overload *(Campbell et al 2006, Delaney et al 2006; Freeman & Chan 2006)*.

Table 14 - Worksheet for calculating central total parental nutrition for cats

Adapted from Freeman & Chan, 2006

1. Calculate the resting energy requirement (RER)
70 x (current body weight in kilograms)$^{0.73}$ = ☐ kcal/day

2. Calculate the protein requirements
Standard 6 g/100 kcal
Decreased requirements (hepatic, renal failure) 3-4 g/100 kcal
RER ÷ 100 x ☐ g/100 kcal = ☐ g protein/day

3. Calculate the volumes of nutrient solutions required each day
8.5% amino acid solution with electrolytes = 0.085 g protein/mL = 0.34 kcal/mL
☐ g protein required/day ÷ 0.085 g/mL = ☐ mL of amino acids/day
Non-protein calories
The calories supplied by proteins are subtracted from the RER to get total non-protein calories needed
☐ g protein required/day x 4 kcal/g = ☐ kcal provided by protein
RER - kcal provided by protein = ☐ nonprotein kcal needed/day
Non-protein calories are usually provided as a 50/50 mixture of lipid and dextrose. However, if the patient has been preexisting condition (diabetes, hypertriglyceridemia), this ratio may need to be adjusted.
To supply 50% of nonprotein kcal with lipid
Volume of lipid required = (☐ nonprotein kcal needed/day * 0.5) ÷ 2 kcal/mL = ☐ mL of 20% lipid
To supply 50% of nonprotein kcal with dextrose
Volume of dextrose required (☐ nonprotein kcal needed/day * 0.5) ÷ 1.7 kcal = ☐ mL of 50% dextrose

4. Total volume of the solution
Total volume of TPN solution = ☐ mL 8.5% amino acid solution with electrolytes + ☐ mL 20% lipid solution + ☐ mL 50% dextrose solution = ☐ mL

5. Calculate the amount of potassium and phosphorus to add to the solution
The desired potassium concentration = ☐ mEq/L.
8.5% amino acid solution with electrolytes contains 60 mEq/L potassium.
Calculate the amount of potassium provided by the amino acid solution: = (☐ mL of amino acids *60 mEq/L) ÷ 1000 = ☐ mEq in ☐ mL Total volume of TPN solution = ☐ mEq/L.
The volume of potassium to add to the parenteral solution to achieve the desired potassium concentration = (desired potassium concentration ☐ mEq/L – actual potassium concentration ☐ mEq/L) * ☐ mL Total volume of TPN solution = ☐ mEq K to add.
The desired phosphorus concentration = ☐ mM/L.
8.5% amino acid solution with electrolytes contains 30 mM/L phosphorus.
Calculate the amount of phosphorus provided by the amino acid solution: = (☐ mL of amino acids *30 mM/L) ÷ 1000 = ☐ mM.
Calculate the amount of phosphorus provided by the lipid solution: = (☐ mL of amino acids *15 mM/L) ÷ 1000 = ☐ mM.
The amount of phosphorus provided by the parenteral solution = ☐ mM/L from amino acid solution + ☐ mM/L from lipid solution in ☐ mL Total volume of TPN solution = ☐ mM/L.
The volume of phosphorus to add to the parenteral solution to achieve the desired phosphorus concentration = (desired phosphorus concentration ☐ mM/L – actual phosphorus concentration ☐ mM/L) * ☐ mL Total volume of TPN solution = ☐ mM phosphorus to add.

6. Consider vitamin B supplementation

7. Administration rate
Day 1: ☐ mL/hour
Day 2: ☐ mL/hour
Day 3: ☐ mL/hour

Table 15 - Central and peripheral intravenous catheters recommended for parenteral administration in cats

Adapted from Campbell et al, 2006

Catheter use	Material	Lumens	Size	Length
Central jugular for CPN	Polyurethane	2-3	4-5.5 Fr.	8-13 cm
Peripheral lateral saphenous for CPN	Polyurethane	3	5.5-7 Fr	30 cm
Peripheral for PPN	Any	1	-	Any

CPN: central parenteral nutrition - PPN: partial parenteral nutrition

Table 16 - Potential complications of parental nutrition
Adapted from Freeman & Chan, 2006

	Type of complication	Methods to reduce the risk
Mechanical	Line breakage Chewed line Disconnected line Perivascular infiltration Catheter occlusion Phlebitis Thrombosis	Aseptic placement of catheter Aseptic handling of catheter and lines Use Elizabethan collars Change bandage and check catheter site daily for swelling, erythema, malpositioning of catheter
Metabolic	Hyperglycemia Hypoglycemia (when discontinuing parenteral nutrition) Hyper/hyopkalemia Hyper/hypochloremia Hyper/hyponatremia Hyper/hypophosphatemia Hyper/hypomagnesemia Hyperbilirubinemia Hypertriglyceridemia Hypercholesterolemia Refeeding syndrome	Use a conservative approach (RER) for the calculation of caloric requirements Initiate and discontinue parenteral nutrition gradually Monitor glucose and electrolytes daily
Septique	Clinical signs of sepsis in conjunction with a positive catheter tip or blood culture	Maintain a dedicated catheter Catheter composed of materials of low thrombogenicity Place and handle catheters and lines with aseptic technique Changing catheters at prescribed time Monitor body temperature, catheter site, general attitude If sepsis is suspected, parenteral solution and catheter tip should be cultured

Routine physical examinations including body temperature, heart rate, respiratory rate, twice daily weight measurements, assessment of hydration status, and attitude should be performed on all critically ill patients receiving parenteral nutritional support. To monitor for complications associated with the parenteral nutrition therapy, the packed cell volume, total protein, blood urea nitrogen, serum electrolytes (sodium, potassium, chloride, ionized calcium), venous blood gas and blood glucose concentrations should be monitored every 4 to 6 hours **(Table 16)**. Urine can be checked daily for glucosuria. Serum triglycerides and ammonia concentrations should be determined daily.

► Complications

Metabolic, mechanical and septic complications can occur in cats receiving parenteral nutrition.

Studies report the rates of metabolic complications in critically ill cats receiving parenteral nutrition to range from 28-320% **(Table 16)**. The rates of metabolic complications appear lower when less than full calculated energy requirements are provided *(Crabb et al, 2006)*. The most common metabolic complications described in cats are hyperglycemia, glucosuria, lipemia, hypernatremia, hypokalemia, azotemia, hypocalcemia, hyperchloremia, hypertriglyceridemia, hypophosphatemia, refeeding syndrome and throbocytopenia *(Lippert et al, 1993; Chan et al, 2002; Pyle et al, 2004; Campbell et al, 2006; Crab et al, 2006)*. These may necessitate adjusting the nutrient ratios, slowing the rate of infusion, or administering insulin, potassium or phosphate supplements. Hyperglycemia appears to be the most common metabolic complication *(Crab et al, 2006)*. Congestive heart failure can occur secondary to fluid shifts *(Freeman & Chan, 2006)*.

The rate of mechanical complications in critically ill cats receiving parenteral nutrition have been reported to be between 9-56% *(Lippert et al, 1993; Chan et al, 2002; Pyle et al, 2004; Crab et al, 2006)*. Reported mechanical complications include catheter dysfunction or dislodgements, thrombophlebitis, damaged or leaking administration lines, accidental breaking or occlusion of the administration line, and equipment failure. These mechanical complications were rapidly rectified when recognized and usually had little effect on the cat's outcome *(Campbell et al, 2006)*.

The rate of septic complications has been reported between 3 and 16% *(Lippert et al, 1993; Chan et al, 2002; Pyle et al, 2004)*. Intestinal atrophy that occurs with long-term parenteral nutrition may explain the increased occurrence of bacterial translocation from the gut and sepsis in animals receiving only parenteral nutrition *(Campbell et al, 2006)*. Bacterial infections of the administration line and sepsis can be minimized with sterile placements techniques, sterile parenteral nutrition compounding and regular line care by staff trained specifically in these tasks *(Campbell et al, 2006)*. Rapid removal of any catheter believed to be contributing to localized or systemic infection is advised. The range of potential septic complications includes positive blood cultures, infected catheter sites in febrile animals, positive culture of the catheter tip or the paren-

teral solution in febrile animals and/or an abnormally high neutrophil concentration *(Campbell et al, 2006)*.

Overall mortality rates in feline patients receiving parenteral nutrition have been reported to be between 19-52%, but this is likely influenced by the animal's underlying medical condition(s) *(Lippert et al, 1993; Chan et al, 2002; Pyle et al, 2004; Campbell et al, 2006)*. *Chan et al* (2002) found no differences in metabolic, mechanical or septic complications in cats administered parenteral nutrition centrally versus peripherally. In parallel, this study showed that concurrent enteral nutrition during PN administration was associated with improved survival.

► Discontinuing parenteral nutrition

Transitioning to oral intake or enteral nutrition should occur as soon as possible to avoid the problem of gut atrophy. In veterinary medicine, parenteral nutrition is typically administered for less than one week. It is important to ensure that the patient is tolerating oral intake or enteral nutrition and is ingesting sufficient amounts (at least 75% of RER) before discontinuing parenteral nutrition. Once the patient is able to eat, it should be offered food regularly to assess its appetite, or a feeding tube should be placed if the animal is anorectic. It is suggested to gradually reduce the rate of administration of CPN over a period of 12 to 24 hours, to allow time for appropriate endocrine equilibration in order to prevent hypoglycemia. PPN can be discontinued abruptly without this gradual decrease *(Campbell et al, 2006; Freeman & Chan, 2006)*.

The use of parenteral nutrition as part of the supportive care plan can be an invaluable addition in select animals. Given cats'unique nutritional requirements and metabolic particularities, future additional studies aimed at more closely examining PN formulations may lead to the development of a formulation more suitable for cats with a lower overall rate of complications.

Conclusion

Critical care nutrition is a rapidly evolving field. It is clear, and fortunate that the paradigm has changed from waiting until a cat decides to eat on it's own (and suffers severe body mass loss in the process) to proactively implementing nutritional support as soon as the patient's life threatening conditions are stabilized.

The consequences of critical illness culminate in significant changes that clearly alter not only nutrient metabolism, but also increase the risk of morbidity and mortality to the patient. Critical steps in management include early recognition of the need to feed the patient, adapting the caloric and nutrient intake to match the metabolic environment and continual monitoring to optimize the prescription and minimize the risk of complications. Aggressive nutritional management will not only increase the survival chances of the critically ill patient, but also aid rapid recovery and return to the home environment.

Fallacies regarding feeding during intensive care

F	A
"Nutrition is not a great problem. It is neither a priority nor an emergency compared with the other treatments and care protocols."	Nutritional support is not a substitute for emergency treatment to support the main vital functions. On the other hand, it must not be neglected. Status and nutritional requirements must be evaluated every day as part of a full examination of the cat during intensive care. Nutritional support must be part of the care protocol.
"The cat will be able to eat on its own in one or two days."	Time passes quickly in intensive care and the period the cat does not eat properly is always underestimated. Nutritional support takes time and may demand invasive procedures (e.g. esophagostomy or gastrostomy), which clinicians delay in the hopes that the cat will start eating again on its own. Anorexia is one of the most commonly observed clinical signs in intensive care units: treatment, anesthesia, surgery and the stress of hospitalization are all anorexigenic factors.
"Perfusion feeds the cat."	Although it does provide glucose, maintenance fluid therapy cannot be considered to be a form of nutritional support. While the aim is to correct blood volume, dehydration, and acid-base and electrolyte imbalances, its role is not to feed the cat. Only total or partial parenteral nutrition solutions administered in accordance with precise protocols can do this.
"If the cat does not want to eat, you can just initiate a parenteral nutrition protocol."	Parenteral nutrition is always tempting because it makes it possible to calculate precise intake with total certainty. Parenteral nutrition is not risk free, however, and it demands monitoring by qualified staff. Septic complications are especially common and the numerous required biological analyses are expensive.
"Hyperglycemia induced by parenteral nutrition is not a real problem. At least the cat receives the energy."	In humans, hyperglycemia is correlated with a negative prognostic outcome. In cats, it is correlated with the seriousness of the disease. There is a dearth of studies in this species for determining the influence of hyperglycemia on the prognosis and the necessity of controlling it with insulin therapy. The current recommendation is to avoid treatments that are likely to induce hyperglycemia.
"Cats fed through feeding tubes are not hungry. It's not worth giving them anything else to eat."	On the contrary, it is important to offer food to cats fed through feeding tubes. It helps assess how interested they are in foods and whether they have their appetite back. It helps clinicians determine the best time to withdraw the feeding tube.
"Feeding tubes are very practical for administering drugs."	While tempting, it is inadvisable to administer drugs through a feeding tube. Turning drugs into powder can change their absorption and digestive tolerance. Also, the absorption of some drugs is changed by the composition of foods (depending on their fat content). Lastly, drugs may interact when administered at the same time.
"Parenteral solutions can correct electrolyte imbalances."	The aim of parenteral nutrition is to provide an intake of nutrients bypassing the digestive system, not to correct electrolyte imbalances, which should be done independently using traditional fluid therapy solutions. It is however advisable to check the electrolyte content of common parenteral nutrition solutions. If they contain electrolytes, they can only be administered to animals with a normal electrolyte balance. Furthermore, the electrolyte balance must be monitored in these cats, to identify the appearance of any disruptions caused by the parenteral nutrition. If the cat's electrolyte balance is disturbed, it is advisable to use parenteral nutrition solutions containing no electrolytes and to correct the patient's electrolytes independently at the same time.

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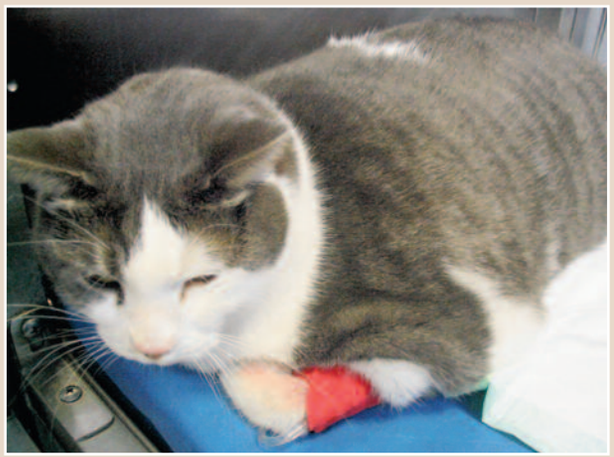

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Nutritional support is an integral part of treating hospitalized animals in a critical situation.

Key points to remember

The benefits of nutritional support in critically ill cats

Factors predisposing to malnutrition

Four risk factors are cited, although there may be more.

- Spontaneous consumption of the cat tends to fall or be interrupted during pathological episodes.
- Some traumas or lesions of the oral cavity may disrupt ingestion.
- Additional examinations or surgical interventions sometimes entail protracted fasting.
- Nutritional requirements increase in the event of acute and/or febrile diseases.

Expected benefits of nutritional support

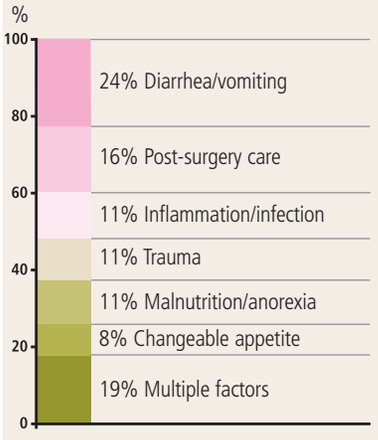
There is medical consensus on the importance of early nutritional support whatever the cause of the reduced appetite. Whenever possible, oral feeding is preferred ("If the gut is working, use it"). This per os feeding helps preserve the intestinal barrier. In the absence of spontaneous consumption, nutritional support may be provided by nasophageal tube.

Generally speaking, when instigated early nutritional support can:

- achieve clinical improvement and accelerate rehabilitation
- reduce hospitalization time
- reduce complications in the event of surgery
- improve the survival rate in critically ill cats

INDICATIONS OF CONVALESCENCE DIETS FOR DOGS AND CATS IN VETERINARY CLINICS

Source: Royal Canin survey (June-September 2006)



The convenience of the diet given to hospitalized cats is a major selection criteria that may gain time in critical care situations.

Select practical criteria for choosing food for critically ill cats

The use of food specially formulated to nourish animals in intensive care facilitates the work of clinicians and care teams.

Maximum palatability

Sick cats generally display a reduced appetite and weight loss. The food must help overcome this by being as palatable as possible.

Formulation adapted to increased nutritional requirements

High-energy concentration

High energy density is important for providing the highest quantity of calories in a low volume. This compensates for a reduced appetite in cats that feed themselves and facilitates administration in the event of enteral-feeding.

To increase the energy density, food for critically ill patients must be high in fat (> 40% of total calories). High-fat diets may present contraindications only in the event of acute pancreatitis and hyperlipidemia.

High protein content

Pathological conditions activate metabolism: tissue catabolism increases and must be compensated for by more intense tissue synthesis. Intake of 30-50% of total energy in the form of protein helps combat loss of lean body mass. This protein must have the following characteristics:

- high biological value to cover the requirement of essential amino acids
- high digestibility to minimize nitrogenous waste and so avoid overloading the liver and kidney functions.

High-protein diets may not be tolerated in hepatic encephalopathy or stage III/IV chronic kidney disease.

Rich in antioxidants

Hypovolemia and reperfusion injury increases the production of free radicals. A complex synergy of antioxidants (vitamins E and C, taurine, carotenoid pigments etc) help combat oxidative stress and facilitate optimal immune defenses.

Convenience

Wet foods are generally more acceptable to cats in the intensive care setting or convalescent cats with a reduced appetite. They can also be warmed to body temperature before feeding.

Wet foods are also better suited to different types of distribution: in a bowl, from the hand or through enteral feeding tubes. The texture must enable administration by syringe, in diluted or undiluted form. The food must be both easy to manipulate, regardless of how it is administered, and easy to split into precise rations.

Wet foods are suited to different types of distribution: in a bowl, from the hand or through enteral feeding tubes.

Convalescence rationing sheet

Step 1 • Calculate patient's resting energy requirement (RER)
RER = 70 x (body weight in kg)$^{0.73}$ kcal/day = = ☐ kcal/day

Step 2 • Characteristics of the convalescence diet
Name of the selected food:
Food energy density:
in kcal/g: ☐ [or in kcal/mL]: ☐
- **In case of diluted food*: determine energy density**
  Food: kcal/mL ☐ x food volume mixed: mL ☐ = ☐ kcal for total mix
  Water: mL ☐ + food volume mixed: mL ☐ = ☐ mL for total mix
  Total mix: kcal ☐ ÷ total volume: mL ☐ = ☐ kcal/mL for total mix
  *to assist the passage through a syringe or feeding tube

Step 3 • Calculate the total amount to give daily
(In gram [g] or in milliliter [mL])
If measuring by weight (g)
RER: kcal/day ☐ ÷ Food: kcal/g ☐ = ☐ g of food/day
For a liquid diet, if measuring by volume (mL)
RER: kcal/day ☐ ÷ Food: kcal/mL ☐ = ☐ mL of food/day
For a liquid mix, if measuring by volume (mL)
RER: kcal/day ☐ mix: kcal/mL ☐ = ☐ mL of mix/day

Step 4 • Determine the refeeding program
Case A: if anorexic < 3 days ==> plan to meet RER in 3 days:
D1: 1/3 of RER = food/day: g (or mL) ☐ x 0.33 = ☐ g (or mL)
D2: 2/3 of RER = food/day: g (or mL) ☐ x 0.66 = ☐ g (or mL)
D3: 100% of RER = food/day: g (or mL) ☐ x 1 = ☐ g (or mL)
Case B: if anorexic > 3 days ==> plan to meet RER in 5 days
D1: 1/4 of RER = food/day: g (or mL) ☐ x 0.25 = ☐ g (or mL)
D2: 1/2 of RER = food/day: g (or mL) ☐ x 0.5 = ☐ g (or mL)
D3: 2/3 of RER = food/day: g (or mL) ☐ x 0.66 = ☐ g (or mL)
D4: 3/4 of RER = food/day: g (or mL) ☐ x 0.75 = ☐ g (or mL)
D5: 100% of RER = food/day: g (or mL) ☐ x 1 = ☐ g (or mL)

Step 5 • Select the desired number of meals per day
Typically 4-6 meals evenly distributed throughout the day (as patient volume tolerance and staffing permits)
Number of meals per day: ☐

Step 6 • Calculate the amount to feed at each meal
Case A: If anorexic for < 3 days (plan to meet RER in 3 days)
D 1: [g (or mL) for day 1 ÷ number of meals per day] = ☐ g (or mL) per meal
D 2: [g (or mL) for day 2 ÷ number of meals per day] = ☐ g (or mL) per meal
D 3: [g (or mL) for day 3 ÷ number of meals per day] = ☐ g (or mL) per meal
Case B: If anorexic for > 3 days (plan to meet RER in 5 days)
D 1: [g (or mL) for day 1 ÷ number of meals per day] = ☐ g (or mL) per meal
D 2: [g (or mL) for day 2 ÷ number of meals per day] = ☐ g (or mL) per meal
D 3: [g (or mL) for day 3 ÷ number of meals per day] = ☐ g (or mL) per meal
D 4: [g (or mL) for day 4 ÷ number of meals per day] = ☐ g (or mL) per meal
D 5: [g (or mL) for day 5 ÷ number of meals per day] = ☐ g (or mL) per meal
Be sure to adjust the patient's intravenous fluids according to the amount of water being added through the diet.

Behavior

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The feeding behavior of the cat

The feeding behavior of the cat

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Dr. Horwitz graduated from Michigan State University College of Veterinary Medicine. After several years in general practice, she began to limit her practice to behavioral problems in companion animals. She received board certification from the American College of Veterinary Behaviorists in 1996. She has a private referral practice for behavior problems in dogs and cats and also consults for the Veterinary Information Network and lectures frequently in North America and abroad and is the editor and author of several books on behavior. She is president of the American College of Veterinary Behaviorists 2006-2008.

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An agricultural engineer with a Master's degree in managing innovation in biotechnology and the agro-food industry, Yannick Soulard joined Royal Canin's Canadian subsidiary in 1999 as a support technician for the sales team. He was given responsibility for formulating foods for North America until 2001. Back at the Royal Canin Research Center in Aimargues, France, he spent six years in palatability development. Today, he leads the Nutrition research unit.

Ariane JUNIEN - CASTAGNA
After graduating from Université de Technologie de Compiègne in 1996 (agro-food process engineering), Ariane joined Royal Canin in 1997, initially in production. She moved to the Research Center that same year, working on an industrial pilot. Since 2001, she has been in charge of palatability development projects.

Feeding behavior corresponds to all the motor sequences from the search for food, its recognition, acceptance and intake. It thus begins with exploration and ends with swallowing.

Although feeding behavior is well studied in domestication and production, only empirical data or anthropomorphic analysis is available for cats. Some recent scientific experiments, essentially performed by petfood manufacturers, are completing the scope of data available in pets.

The feeding and social behavior of cats differs greatly from dogs. Not only do their nutritional requirements differ, but the social structure of cats also results in different communication and feeding patterns both between cats and with their human caregivers. Meeting the nutritional needs of cats requires an understanding of their feeding ecology, nutritional needs and social communication and structure.

1 - Factors affecting the feeding behavior of the cat

► Hereditary determinants

> Sensorial aspects

Taste

The sensation of taste in a cat is present 5 days before birth *(Beaver, 1980)* and improves during life. The sensitivity differs between the 4 main types of taste perception, with the following hierarchy from the most to least stimulating (as demonstrated by the simple application of vinegar, salt, quinine, and sugar, on the tongue):

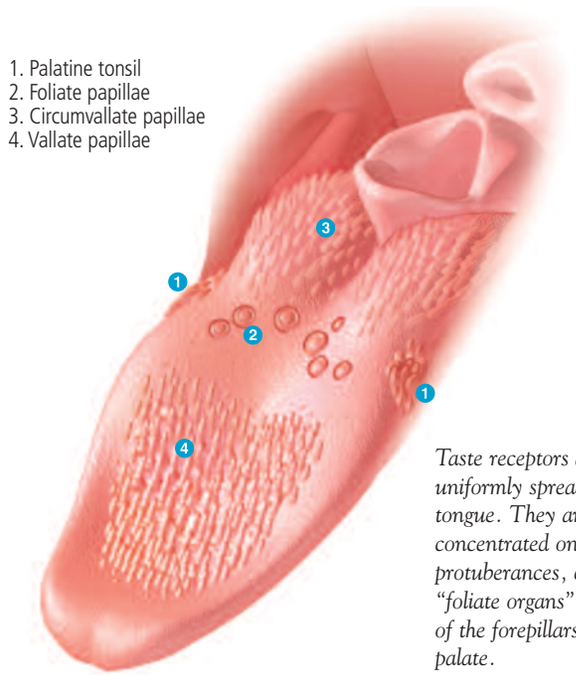
acid > bitter > salty > sweet

(Domestic cats are neither attracted to, nor show avoidance of the taste of sweet carbohydrates and high intensity sweeteners).

Our knowledge of taste has indeed evolved through the study of neurological signals in cranial nerves following the stimulation of the taste buds by different substances. Three cranial nerves are involved in taste. The facial nerves, in particular the chorda tympani, have undergone the most observations. This research has given rise to many theories. For example, *Boudreau* (1973,1977) presented a theory suggesting acid, amino acid and nucleotide taste systems specific to cats. This theory has not been confirmed by other authors.

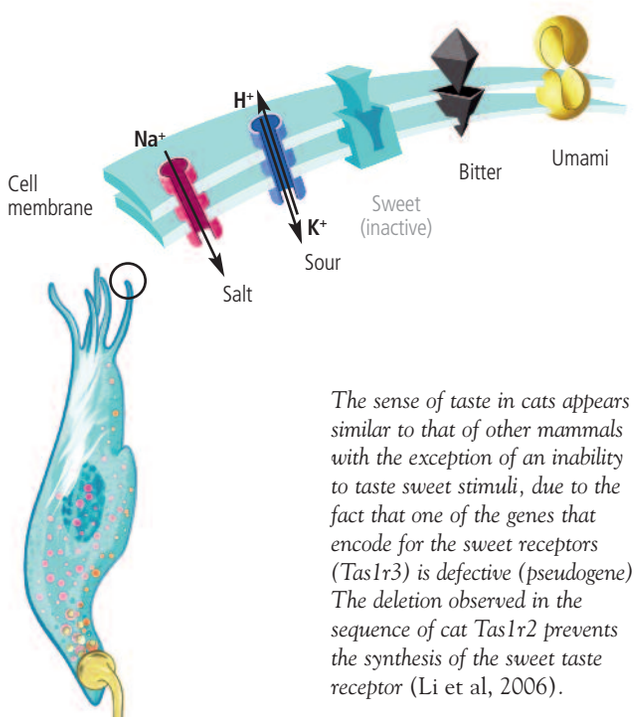
The number of taste buds is estimated at around 475 **(Figures 1 and 2)**. It is much less than dogs (1700) and man (9000). In dogs, gustatory cell turnover is around 4 days. No data is available in cats, but we may expect that it is similar. This data is interesting to evaluate appetite recovery after insult to the oral epithelium.

FIGURE 1 - LOCALIZATION OF THE TASTE RECEPTORS ON THE TONGUE OF THE CAT



Taste receptors are not uniformly spread over the tongue. They are mainly concentrated on two small protuberances, called "foliate organs", in front of the forepillars of the soft palate.

FIGURE 2 - DIFFERENT TYPES OF GUSTATIVE RECEPTORS



The sense of taste in cats appears similar to that of other mammals with the exception of an inability to taste sweet stimuli, due to the fact that one of the genes that encode for the sweet receptors (Tas1r3) is defective (pseudogene). The deletion observed in the sequence of cat Tas1r2 prevents the synthesis of the sweet taste receptor (Li et al, 2006).

Bitter taste
Bitter compounds easily trigger aversions. Bitter taste is due to a wide variety of components (tannins, alkaloids, malic acid, quinine, phytic acid, aminoacids such as tryptophan, isoleucine, leucine, arginine, phenylalanine, etc.).

Cats are very sensitive to bitter tastes *(Houpt, 2005)*. Cats are more sensitive than dogs to bitterness and detect it at lower concentrations. They can detect concentrations of bitter taste four hundred times smaller than levels detected by hamsters *(Carpenter, 1956; Houpt, 1991)*. This perception enables them to avoid many toxic substances (for example strychnine), which are often very bitter.

Sweet taste
Cats do not appear to care for sweet tastes: receptors have been deactivated. The corresponding gene exists but it has been switched off to a pseudogene *(Brandt, 2006)* through phylogenic adaptation *(Li et al, 2006)*. Cats tend to reject synthetic sweeteners like saccharine or cyclamate, since they are perceived as bitter *(Bartoshuk et al, 1975)*. The sweet taste of antifreeze appeals to dogs but not to cats. Rather, cats are typically poisoned by cleaning their paws after walking through the antifreeze.

Acid taste
This perceptiveness is widely used by petfood companies. Many commercially available cat food flavors indeed contain phosphoric acid. Excessive acid and phosphorus intakes must be avoided in cats with impaired renal function.

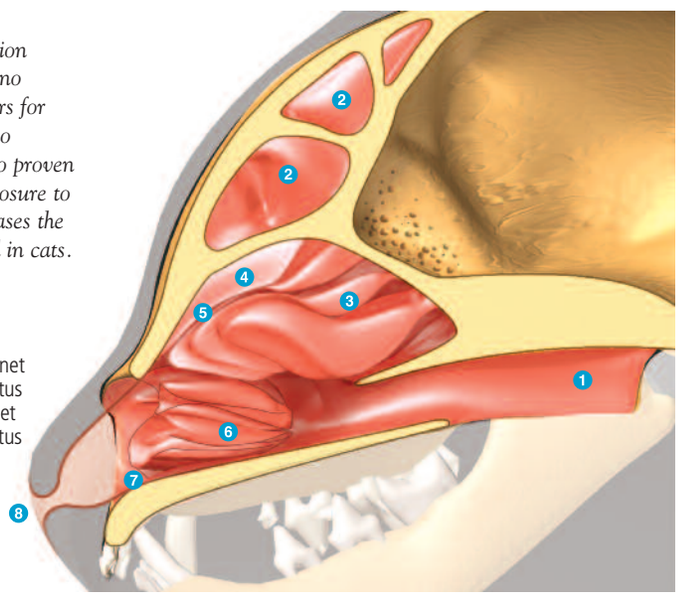
Salty taste
The perception is rather positive in cats and can enhance food or water consumption. Some water taste was hypothesized in early experiments, as taste receptors were thought to be reacting to distillated water. However, these electrophysiological responses were in fact the result of the adaptative neutrality of the cat's taste receptors to saline saliva.

Amino-acids
The taste buds connected to the facial nerve are highly sensitive to amino-acids: a single amino acid is able to stimulate the taste nerve fibers. These changes appear to be a specialization for feeding on prey, which is rich in protein *(Bradshaw et al, 1996)*.

FIGURE 3 - AIR CIRCULATION IN THE NASAL CAVITIES OF THE CAT

Unlike the perception of taste, there are no specialized receptors for smell. There are no published studies to proven that prolonged exposure to a given odor increases the detection threshold in cats.

1. Nasopharynx
2. Frontal sinus
3. Ethmoid sinus
4. Superior nasal cornet
5. Middle nasal meatus
6. Inferior nasal cornet
7. Ventral nasal meatus
8. Nostril



Oral sensitivity is not only gustatory, but somesthesia is important for granulometry and temperature detection through the lingual nerve. The ligaments of the teeth also participate. Any paradental disease or the effect of age, through modification of the resistance of the gums and teeth can strongly modify food perception and palatability.

It has been shown that the perception of food flavor is not simply the superposition of the various taste varieties but sensory messages are creating a brain image that is compared to innate or learned schemes *(Gallouin, 1987)*. However, no specific data exist for cats.

Olfaction

Olfaction is present at birth and matures by three weeks of age. The cat is less sensitive than the dog to smell. This difference in sensitivity is due to the num-

ber of olfactory cells, rather than their density in the mucosa. Cats have between 60 and 70 million olfactory cells (compared to 80-220 in dogs). In some animal studies, it has been estimated that only 1% of volatile compounds enter the nasal mucosa **(Figure 3)** however, no direct data exist in cats.

The cat is very selective and cautious. Olfaction is THE key factor to trigger food acceptance. Any anosmia will prevent food intake, and this anorexia will last as long as the cat cannot smell *(May, 1987)*. Renewal of the olfactory mucosa and appetite recovery requires four to five days.

The range of smells perceived by cats is large but some specific odors are particularly attracting for them:
- mineral origin: bleach
- plant origin: catnip, olive wood, valerian, asparagus, mint, papyrus, cloves, mimosa
- animal origin: pheromones (although they do not have any direct food related meaning, but only territorial or sexual), livers, meats, viscera, etc.

However, detection ability does not mean food preference and no clear data exist on individual variability.
Some unusual odors or pheromones often trigger a specific reaction, called the Flehmen reaction, during which the cat lifts its upper lip and breathes some air through the vomero-nasal organ (Jacobson organ) located in the hard palate.

Petfood manufacturers are of course working on volatile compounds that are able to attract both the cat (when approaching its bowl) and the owner (when opening the can or the bag of kibble). However, as can be expected, this area of research remains very confidential and unpublished.

Vision

Lott-Brown et al (1973) have shown that cats are not able to discriminate between 520 and 570 nm lengthwaves. They thus would be unable to discriminate white from yellow or green. It would be for the cat the same "tonality". Red and blue are conversely clearly differentiated.
As a result, we may assume that colors of food are more important for owners than for cats.

The cat's vision is panoramic and adapted to discriminate movements more so than tonal differences. This ability has clearly evolved to facilitate predation.

> Behavioral aspects

Pre-natal experience

The acquisition of certain preferences may occur very early in life, as early as during gestation. Fetuses are surrounded by amniotic fluid, which contains compounds they assimilate in utero *(Thorne, 1994)*. A cat's gustatory system is functional in the final days of gestation *(Tichy, 1994)*.

Suckling behavior

Thanks to a burrowing reflex which lasts until the 8th day after birth, the new born kitten chooses a nipple during the first two days of its life. This reduces competition between littermates and decreases the time to initiate suckling *(Foucault, 1992)*. Temperature (of the skin) and olfactory stimuli (from Montgomery glands secretion around the nipples) are the most important after birth

The suckling reflex appears from the 50th day of gestation and is gone by the 23rd day of life.

© Yves Lanceau/RC/British Shorthair

There is nevertheless a maturation process during which regulatory factors transition from oral stimulation by milk up to the 10th day, to peri-oral stimulation (whatever the food is). The effect of digestive filling appears from 3 weeks of age.

The time allocated to suckling changes during the first month according to a relatively constant scheme. Kittens spend 10% of their time suckling and get milk for the first 2 weeks. Suckling time increases quickly up to 60% at 3 weeks and then decreases to 10% at the end of the first month *(Foucault, 1992)*. They also spend time to suckle without drinking any liquid.

The evolution of the kitten – mother bond around food evolves quite significantly during this time. During the first two weeks, 75% of the suckling periods are initiated by the queen. During the two following weeks, the proportion falls from 50 to 5%. The mother then begins to avoid her kittens and allocates them only 20% of her time. Weaning is in fact beginning, with major behavioral and digestive changes.

During lactation, the composition of milk varies with the mother's diet. Kittens may develop certain preferences at this time in their lives *(Thorne, 1994)*. Few articles describe this for cats. Weaning has in fact been more throughly studied.

Weaning experience

When eating their first solid food, kittens choose what their mothers eat, even if this food is unusual for cats *(Wyrwicka & Chase, 2001)*. Dietary preferences are thus not all innate; they are acquired through social influences after birth.

Kittens whose mothers have been conditioned to eat bananas (usually unpalatable for cats) will eat bananas during weaning even if they have access to more conventional food for cats such as kibbles *(Wyrwicka & Long, 1980)*. Kittens imitate their mother's eating behavior down to the smallest detail. They begin by eating from the same plate, at precisely the same spot, as their mother takes its food. There is a correlation between the mother's dietary consumption and that of the kittens. In the above experiment, the kittens that ate the least amount of banana were those whose mothers ate the least. The influence of the queen can last after weaning and separation between kittens and their mother. Food preferences acquired during weaning in their mother's presence persisted in kittens until the age of 4 to 5 months *(Wyrwicka & Long, 1980)*.

Weaning is an important time in an animal's dietary history. The moment a cat eats its first solid food is probably crucial in terms of influence, especially if it happens in their mother's presence.

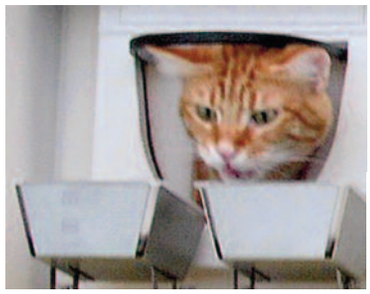
Kittens are more likely to eat a new and novel food when the queen is present than when she is absent *(Bateson, 2000)*. The illustration of the importance of the mother in food acceptance by kittens has also been illustrated in a trial from *Wyrwicka & Chase* (2001). Nineteen kittens from four litters were studied. Ten kittens ate in their mother's presence, while nine were without their mother during meals. The time it took kittens to accept a new food was very different between groups:

- for the kittens eating in their mothers'presence, it took an average of 5 hours for them to eat a new food
- in contrast, in the kittens separated from their mothers it took 4.8 days before they would eat a new food.

Therefore many dietary habits are determined before 6 to 8 weeks of age. The practical consequence is that food education must be done at this stage. A good idea is to select, at least for the first weeks after adoption, the food used by the breeder.

Individual and breed differences

Kittens fed by stomach tube have very limited gustatory experience compared to kittens fed normally. During conditioning tests in which success is rewarded with food, the kittens fed by stomach tube took longer to succeed and even refused to eat the reward *(Stasiak & Zernicki, 2000)*. Being deprived of dietary experience then influences future feeding behavior. All the early sensorial or digestive experiences create the individual variability. Learning leads to avoiding harmful or unpleasant foods and to preferably seek for nutritionally or sensorially gratifying ones.


© Royal Canin

One peculiar feature in cat palatability testing that offers the choice between two bowls, is that some tasters always choose one side, regardless of the diet inside the bowl. Some cats are thus left handed, other are right handed!

Sex has no recognized effect on food perception in this species, even if feeding behavior can be indirectly affected by acute territorial competition in female cats, and by breeding season in male cats.

Breed may have some influence, although it is difficult to prove it unequivocally. It may be an area of future research.

Age affects ingestion behavior but less than in dogs *(Peachey & Harper, 2002)*.The increase of dietary experience and the decline of olfactory and gustatory capabilities may enhance fussiness or even provoke preference inversion.

► Environmental factors

> Social environment

The cat is a solitary hunter, but tends to gather in feeding and breeding spots in wild urban groups. The territory is transient and variable throughout time and space, i.e. it is possible that the territory overlaps between two cats but at different moments. Hierarchy in cats depends on the place and time during the day: it is a relative dominance. Territory may easily trigger aggressiveness and fights.

In collective housing, it appears that some competition may occur. Fights are somewhat rare if food is available in large quantities.

Unlike dogs **(Table 1)**, household cats do not appear to show social facilitation of eating: they usually eat alone and do not seem to be affected by the presence of another cat *(Houpt, 2005)*. Some cats will even share the bowl with another cat, while others may sit calmly and wait for their turn. A female in estrus can have the right to get food first. However, other researchers feel that cats show hierarchical issues regarding the food bowl with higher ranking cats displacing lower ranking cats from the food source in a multi-cat home *(Knowles et al, 2004)*. In ad libitum experimental situations, social feeding (as defined by time overlap of at least one minute between meals), occurs in duo with only 20% of meals *(Mugford, 1977)*.

For owners of cats living outdoor, feeding is a privileged moment for contacts. Quite often, the feeder has better or, at least, the easier


© Yves Lanceau/RC/European cats

TABLE 1 - THE MAIN DIFFERENCES BETWEEN FELINE AND CANINE FEEDING BEHAVIOR

Cat	Dog
Strict carnivore	Omnivore
12 to 20 meals/day	1 to 3 meals/day
Feed during day and night	Feed during daylight
Regular eaters	Glutton feeders
No social value of the meal	Social value of the meal

relationship with the cat. *Geering* (1989) has shown that the act of feeding is necessary to reinforce the bond, but is not sufficient to keep it. Other interactions, like petting, grooming, playing, talking, are required to maintain a newly established link *(Bateson & Turner, 1989)*.

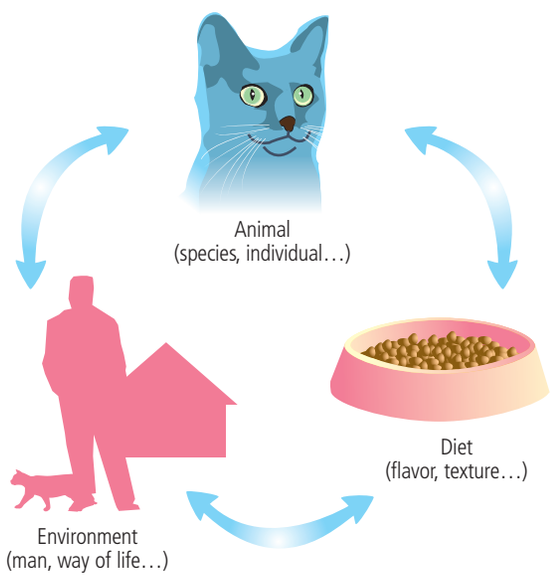
In the household environment, the rhythm of the supply of food often reflects the owner's lifestyle. Two or three meals are often fed during the day: in the morning before going to work, at the evening when returning, or even just before going to bed to keep the cat quiet!

Diet acceptance is largely influenced by the psychological, affective and material environment **(Figure 4)**. *Wolter* (1982) mentions various factors likely to influence the feeding behavior of the cat: tension between family members, change of light, sudden noise from stereo systems, different odors of cleaning product for the bowl, arrival of strangers, etc. This has nothing to do with food quality but an involuntary cat disturbance. Checking the feeding behavior during a recovery phase can lead to food refusal or lower acceptance. This situation is also observed when the owner has just bought a new food (new brand or new claim) and wants to check whether or not the animal accepts it. A very first analysis of perceived anorexia should review these unexpected but simple reasons! This disorder will be reviewed in the final section.

> Physical environment

Cats need to feel safe and secure within their home environment. To this end owners need to provide facilities for the main behavioral functions of eating, sleeping and playing and also ensure that the cat has the ability to control its own stress through the natural mechanisms of hiding and retreating. In tidy homes or those with built in furniture, places for cats to hide may be in short supply. This may create a situation where a cat might feel insecure and vulnerable without any escape routes or hiding places. Taking steps to provide the cat with a constant and predictable environment, both in terms of physical structure and scent profiles, will help to increase the cat's security; while the provision of access to high up resting platforms, secure bolt holes and hideaways may decrease the use of oral appeasing behaviors, such as over grooming and over eating. If all of the furniture in the house is built in it may be necessary to put up shelves for the cat to rest on, or clear out part of a cupboard or wardrobe to offer a safe hideout *(Dehasse et al, 1993)*.

FIGURE 4 - FACTORS CONTRIBUTING TO DIET ACCEPTANCE



► Influence of the food itself on feeding behavior

In the testing done on food choices and taste reactivity in cats *(Van den Bos et al, 2000)* two response sequences were noted and correlated to possible palatability reactions. A preference to consume an offered food was often preceded by a lick or a sniff of the feeding bowl, lip lick and face groom. Cats presented with food that was less desirable would lick or sniff the food and lick their nose. Whether the food was eaten was also partially dependent on the degree of hunger. In general cats will eat more of a desirable food regardless of hunger, but consumption of a less desirable food is often dependent on the hunger status of the cat.

Once a meal is consumed most cats will groom themselves regardless of perceived palatability. As direct gastric canulation leads to the same post-prandial behavior (without soiling lips and cheek), it is considered as an innate neurophysiologic reflex.

One of the most important features to consider is that cats will often eat and prefer a novel diet over a familiar one. The intensity of **neophilic behavior** depends on the foods' relative palatability and on the duration of exposure to the usual food. If the new food is less palatable than the usual food, the effect is shortlived. Twenty four kittens received the same food for 16 weeks, and then underwent a comparative test [two bowl test] for several days with the usual food and a new food of equivalent palatability. The first day, the kittens systematically chose the new food. After the second day, the difference was no longer significant between the two foods *(Mugford, 1977)*. The novelty effect lasted only a few days (rarely more than 5 or 6 days), after which dietary preference stabilized.

Neophilia is preference for a food never encountered by the animal or food that has not been recently encountered by the animal. This behavior is quite common in carnivores and has been identified in both dogs and cats. Neophilia enables animals to diversify their diet and achieve a better nutritional balance.

In the home, the preference for frequently changing the diet, a ritual that many owners participate in, is called **metaphilia** (from the greek, meta: "transformation"). This corresponds to an increase in consumption due to the renewal and alternation of known diets *(Rabot, 1994)*. This is clearly observable in the cafeteria regimen in practice. This behavioral trait has led some manufacturers to create packaging of multi-single portions containing various varieties.

When changing a pet's diet, one must be prepared for the possibility of neophilia and the associated increase in energy consumption during the first month after the new diet is introduced. The novelty effect is accompanied by temporary caloric overfeeding. In the first month, cats may eat up to100 kcal/kg. The effect then wanes and consumption stabilizes around 60 kcal/kg after two months *(Nguyen et al, 1999)*. Whenever a change is made to a pet's diet, owners should take care to measure out the food to ensure proper caloric delivery.

Breaking this natural neophilic trend, an owner can choose to always give the same diet. There is a risk of boredom with a perceived decrease in palatability (even it the food is complete and well balanced). One may relate that phenomenon to the human concept of "oral satiation" (always eating chocolate or eating oysters too often may decrease their palatability). On the other hand, choosing to frequently vary the diets beyond the carnivorous status of cats and to consider them as omnivorous by humanization, may lead to **neophobia** and again food refusal.

Some specific events can trigger fixation to one food and acquired **food aversion**. These disorders will be discussed below.

2 - Description of the feeding behavior of the cat

► Predation and hunting

Unlike the domestic dog, the body type of the domestic cat is not far from its wild ancestors. However, differences in prey sizes have led to significant differences, e.g: domestic cats use their incisors less, meals are more frequent and their way of consuming prey is also different: domestic cats begin with the head, large felids begin with the viscera.

> Hunting instinct or learned behavior?

Predatory behavior is innate: all cats probably know how to hunt, but certain aspects seem to be learned. Approach and pursuit are stimulated by littermates. Hunting behavior is more likely seen in kittens from a queen that hunts. Kittens learn to catch and to kill the same prey that their mother hunts *(Bateson & Bateson, 2002)*.

During weaning, there is an amazing training program for hunting displayed by the queen:

- 4th week: the queen brings meat pieces to the kittens
- 5th week: she eats dead prey in front of her kittens
- 6th or 7th week: she lets them eat the prey
- 8th week: she brings a live prey in order for the young hunters to learn to kill.

The first hunting sessions occur at 3 months. At 4 months of age, the young hunters are confirmed. The absence of predatory experience does not seem to interfere with motor abilities but often reveals prey selectivity issues. A kitten must indeed be taught that a mouse can be eaten. If it is not done before the age of 3 months old, the cat can starve even in the presence of the unknown prey! However, even cats that did not have access to prey when they were kittens can learn to become proficient hunters.

It has been speculated that feeding a cat may reduce its desire to hunt, but evidence to support this is lacking or controversial. Cats that are provisioned with food at home spend less time hunting than cats that are not provisioned with food, but both still hunt even if the number of actual prey caught and consumed is hard to quantify *(Fitzgerald & Turner, 2000)*.

Hunting session

Unlike dogs who hunt in packs, cats in the wild are solitary and opportunistic hunters. They catch small prey and eat alone. Observations show that they often fail in their attempts to catch prey: only 13% of tracked prey is actually caught *(Kays & DeWan, 2004)*, every success representing 3-5 attempts *(Fitzgerald & Turner, 2000)*. A cat brings home an average 0.7 prey a week *(Woods et al, 2003)*.

Hunting sessions can last 30 minutes, on distances between 600 and 1800 m in their territory. An obvious variability exists between individuals: for example, male cats hunt longer and further than female cats.

Cats spend two-thirds of their awake time to hunt in natural conditions. Hunting behavior is composed of several sequences:
- stalking the prey
- approaching and pursuing
- catching the prey by a central leap (their body will be low to the ground and they move slowly toward the prey, pausing prior to leaping to attack)
- killing by biting the neck, following an eventual fight
- consumption rarely occurs at the location of the catch (for the reason of quietness).

The domestic cat is a member of the Felidae family, Felis catus *and is a strict carnivore.*

© J.-P. Lenafant/RC/Norwegian Forest Cat

As the process progresses, the sequences are less and less modifiable by the cat's experience or it's'environment. The first steps (seeking, stalking and approach) are indeed flexible as a result of adaptation to different situations, while the last ones (e.g. attack and bite) are more stereotyped to secure efficient catch and kill, and thus individual survival.

Cats rarely bury their catch for postponed consumption. Cats eat rather quickly and then regurgitate furs and bones. Prey cleaning is rather poor, unless it is voluminous (such as pigeons or young rabbits). The cat breaks the bones and masticates with its large premolars. It can eat an entire mouse in less than one minute. When consuming a mouse, it starts at the head and eats

in the direction of the tail *(Case, 2003)*. It is often the logical consequence of the killing method, during which the neck is broken. It might also be related to an adaptative behavior, securing prey catch and intake.

Leyhausen (1979) (quoted by *Rabot*, 1994) has shown that the complete hunting sequence is in fact controlled by a system of progressive and different motivation phases:

- interest is awaken by auditory stimuli (scratching, grating), which enables the cat to locate precisely the prey. In veterinary practice, scratching the consultation table is indeed often the best way to draw attention from the cat;
- visualization of rapid movement triggers approach. Experience nevertheless allows the cat to recognize a motionless prey and to attack it;
- catch answers to more precise visual and olfactory clues and is triggered by tactile stimuli.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Feral cats hunt every 2 or 3 days, whereas domestic cats can hunt everyday.

Leyhausen's studies seemed to indicate that prey capture, killing and consumption were indeed independent actions. Capture and killing appeared to be also independent of hunger but if hunger pre-exists, predatory sequence is complete as hunger is the only reason that explains consumption.

Each stage induces in turn the following one, which permits the succession of all sequences by different stimuli. Hunger is not compulsory to trigger prey seeking but increases kill probability. Satiety does not inhibit sacrifice.

The domestic cat hunts quite often but rarely eats the prey. The system of independent phases proposed by Leyhausen would indeed explain that cats just fed can display all sequences without food intake. Some steps can be repeated and the owner can attend a cruel predatory play, during which prey is still alive while being handled in all ways. The fact of bringing back the prey to the owner can be falsely interpreted as a proof of the maternal like type of bond.

> The most common types of prey

Each catch represents only a small percentage of the cat's daily energy requirements (the caloric content of a mouse can be estimated at 30 kcal). It is possible to find up to 12 small preys in a feral cat's stomach. This represents an adaptative behavior to scarcity periods. Continental cats essentially hunt young lagomorphs and rodents. Birds come after in the list and reptiles even lower. Cats living on islands depend mainly on rats, mice and sea birds.

Cats are versatile and generalist hunters. They can easily move from one prey type to another depending upon ecological evolutions. They can even go to some domestic feeding during scarcity periods. On some islands, feline predation has been put as the cause of some species extinction, according to *Bateson and Turner* (1989). Studies focused on the effect of predation on wildlife are however limited and it is unclear whether the extrapolation of these data to the global feline population is accurate.

> Techniques to limit predatory behavior in domestic cats

Attempting to decrease predation by house hold cats is probably a worthy goal. Predatory behavior is a normal behavioral pattern in cats but often distressing to their owners. Although

6 of 10 cats (in the United States) and most pure breed cats are kept indoors and therefore cannot hunt, in Europe many cats (7 of 10) have an outdoor access so they can hunt and kill small rodents and birds. Owners often find this behavior objectionable especially when cats direct the behavior toward song birds and/or bring prey home.

Predatory behavior is best prevented by keeping cats indoors and obtaining kittens from queens that do not hunt (so as to get inexperienced individuals). In addition, keeping a quick release cat collar with a large bell on the cat may diminish their proficiency. *Nelson et al* (2005) compared collar mounted warning devices on reducing predation in cats in the UK and found that there was no significant difference in the prey return rate between cats wearing collars with one bell, two bells or a sonic device.

The cat has been domesticated for nearly 6000 years but has not lost his exceptional hunting skills thanks to the independency of predatory sequences. Cats can easily return to the wild and survive without human intervention.

► Domestic feeding

Cats spend from 1 to 2% of their awake time eating. When feeding a household cat, the food can be provided either in a controlled manner i.e. as meal feeding or as free choice feeding. Regardless of the type of feeding regime chosen, it is useful to establish regular feeding and eating patterns for house hold cats **(Table 2)**.

> The place of the feeding bowl

The territorial organization of the cat's life must be taken into consideration. Each spot has a defined dedication for the cat: feeding, resting, playing, eliminating. And these functions are not mixed. You would not eat in the middle of the train entrance or in your toilets. It is the same for a cat! **(Figure 5)**.

Bowls have to be small, to control intake and to encourage frequent refilling. Regular cleaning of the bowl is necessary, to avoid off smells and safety issues. In homes with multiple cats, each cat should be offered their own food bowl. Antagonistic interactions between cats may restrict some individuals from access to food and water bowls leading to weight loss and perhaps medical complications. In addition, because cats may not share space equally, food bowls should be allocated through out the environment, not all in one location. Care should be exercised to note where individual cats spend most of their time and place food and water bowls in those locations. Litter boxes should be placed at a significant distance from the feeding location.

TABLE 2 - FEEDING REGIMES IN HOUSE HOLD CATS

Method	Advantages	Disadvantages
Meal feeding The owner controls either the time the food is provided and/or the amount of food provided daily. Usually the cat is provided with 2-3 small meals daily at set times.	- Allows the owner to monitor food intake - Helps assess health - Allows all cats access to food - Increases bonding time	- Some cats may solicit food at other times - May not meet the cats internal schedule for eating
Free choice feeding The cat is provided with food at all times.	- Allows the cat to control consumption - The cat can eat multiple small meals daily	- Unable to monitor intake - May lead to over consumption and obesity - Allows no time for human-animal bonding
Combination feeding Free choice dry food, meal feeding wet food once or twice daily.	- Allows multiple small meals daily - Allows for bonding time	- Unless closely regulated over consumption can occur - Some individuals may not get enough to eat

> Meal feeding

When pet owners use a meal feeding method to feed their cats they either control the time the food is provided or the portion size provided. It is the best method for canned food so as to secure freshness and safety. Leaving leftovers for hours in the bowl indeed leads to bacteriological risks and palatability decrease due to organoleptic deterioration. Manufacturers have understood this problem and now propose single portions diets. Because cats eat multiple small meals when hunting, most household cats find

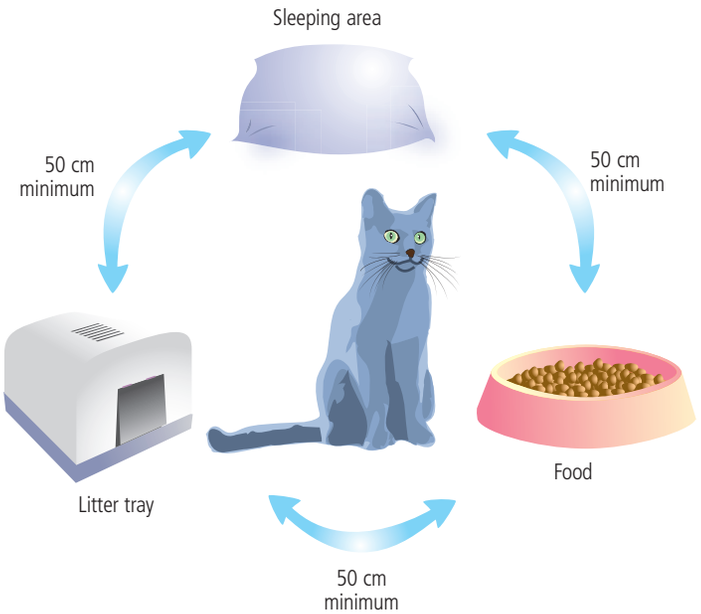
single meal feeding unsatisfactory if it is the only method chosen. If an owner chooses to feed its cat in a time controlled manner, at least two meals per day should be provided. However, an increased frequency of meals may help control hunger and decrease excessive food soliciting behavior. It is indeed amazing to see cats learning to detect when they can get extra food. They associate some events to a high probability to get reward e.g. during the advertising break of the evening TV movie or when the owner puts the kitchen in order (they can be warned by the noise of plates in the dishwashing machine!).

Meal feeding methods

- With **time controlled feeding**, the food is left available for a set amount of time and then picked up and not provided again until the next feeding time. For most cats, 30-60 minutes should be allotted for eating when fed in a time controlled manner *(Case, 2003)*.

- With **portion controlled feeding**, the amount of food provided is measured and placed in the bowl and once it is consumed, no more food is provided until the next meal. For a single household cat, portion control can help control weight while potentially allowing the cat to eat several meals through out the day, something that cannot occur with timed feeding.

FIGURE 5 - THE MINIMAL DISTANCE BETWEEN THE FEEDING PLACE AND THE ELIMINATION AND RESTING PLACES



The feeding station must be in a quiet place (not close to the washing machine), at the right distance from the litter box.

Meal feeding in either manner has several advantages. It allows owners to determine how much food the cat consumes in a 24 hour period. Food consumption is often a good marker of health and knowing how much the cat eats can help an owner determine how the cat feels. If multiple cats reside in the home it may allow the caregivers to assess each cats eating pattern and access to food and may help the owner to recognize health or social problems in the cats. Meal feeding also allows the pet and the owner to interact several times a day strengthening the human-animal bond.

Free choice feeding

In free choice feeding food is provided to the cat at all times so that the cat can eat multiple small meals in a 24 hour period. Domestic cats often eat multiple small meals through out the day. Depending upon observations, this number varies from 8 to 16. This is linked to the evolution of the cat to an opportunistic feeding pattern, nibbling small amounts of food on numerous occasions. This method relies on the cat ability to self regulate intake. This is the best option when the cat is fed with dry food. However, due to the increased palatability of commercial cat foods coupled with reduced exercise, cats may over eat and become obese. In addition, self feeding does not necessarily allow the human caregiver to determine daily intake especially in homes with multiple cats. With self feeding, a change in food consumption and resultant weight loss may not be noticed for some time perhaps imperiling pet health. Self feeding also limits the pet-owner interaction around feeding time.

Some pet owners may combine meal feeding and free choice feeding by providing set meals of small amounts of wet food and provide dry food in free choice. It creates a social re-enforcement of food intake, although this effect is much less important than in dogs. The cat is invited to eat wet food as a "plus" and the calorie content is added to the normal dry food ration spread over the day. In some cases the energy balance can be excessive. The practitioner must keep in mind that some cats may have difficulties to regulate their energy consumption when fed two different

types of food: a strict control of the quantities fed to the cat and of the nutritional balance of both types of foods is highly recommended.

> The role of the human in feline feeding

Because most household cats do not hunt to meet their nutritional needs, when they are hungry they target their pre-meal behaviors and food soliciting behaviors towards the humans within the home. These behaviors include vocalization, rubbing on nearby objects and on the humans. Often if the person moves in the direction of where the food is provided or stored, the cat may run in that direction or continue to wind between the legs actually impeding progress. It has been suggested that people who feed the cat have a better relationship with the cat perhaps because of these opportunities to interact *(Geering, 1989)*.

Owners often inadvertently assume all vocalization and attention is in fact a food soliciting behavior. They then respond by feeding the cat, resulting in a potent learning process. The owner's response is acting as a reward for vocalization and attention seeking behaviors which usually will increase in frequency and intensity. Not only can these behaviors be distressing to the owner, excessive food intake will also lead to obesity and related medical problems. Owners should learn to recognize when enough food has been provided and consumed, and not reward these behaviors with food. They then should find an alternate activity such as play or grooming once the nutritional needs have been met.

> Observations of feeding behavior: how the cat eats

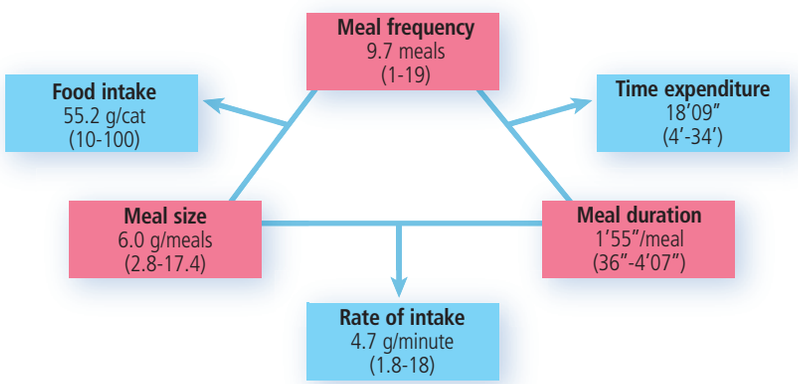
Many nutritional studies are based on the study of the factors affecting the amount of food that cats ingest. The regulation of ingestion is a complex and still poorly understood phenomenon. The frequency and size of meals represent two key parameters of feeding behavior.

Number of meals per day

Each cat has its own way to dispatch its meals throughout the day. A cat generally needs 3 weeks to get a stable life pattern. In an ad libitum situation, it ranges from 3 to 20 meals per day *(Kane et al, 1981; Houpt, 2005)*, like water intake *(Mac Donald et al, 1984)*. In cattery conditions, when cats are fed ad libitum with dry food, the dietary consumption is influenced by the night and day alternance: the dietary consumption at night is often inferior to consumption during the day, but during the night, the meals are larger and longer *(Kanes et al, 1981; Royal Canin Research Center: internal data, 2004)*.

FIGURE 6 - THE FEEDING PATTERN OF THE CAT OVER 24 HOUR

(Source: Royal Canin Research Center; internal data, 2004)



The feeding behavior of cats living together in groups was followed using an electronic scale with access controlled by an electronic chip. This system makes it possible to follow in real time each cat's consumption profile in terms of the number of meals, the meal size and the duration of the meal (between brackets: mean-extremes).
Data were collected with 8 adult domestic cats (2 to 3 years old), fed ad libitum with the same dry food over 17 days.

Meal size, meal duration and speed of eating

Meal size increases with palatability (especially the first meal) or when the feeder goes from meal feeding to ad libitum feeding. The average duration of a meal is almost 2 minutes **(Figure 6)**. The speed of eating is an important criterion for the owner's perception. It is in fact much more influenced by food structure than palatability. For dry kibbles, the eating rate increases from 2 to 4 grams per minute. For canned product, it lies between 4 and 8 grams per minute.

Studies done at the Royal Canin Research Center illustrate how the number of meals, quantity of ingested food and the speed of ingestion are significantly different for

different breeds in exactly the same environmental conditions and sharing the same nutritional history **(Table 3)**. The frequency of the meals is the most variable parameter between the different breeds studied with Bengal cats showing the highest frequency. Maine Coon cats tend to take the largest meals and Persian cats the smallest. Persian cats spend twice as much time per meal compare to the average of the other breeds studied (3'27" vs 1'49") *(Royal Canin Research Center: internal data, 2004)*.

TABLE 3 - FEEDING PATTERN DIFFERENCES BETWEEN PURE-BREED CATS AND DOMESTIC SHORT HAIR CATS
(Royal Canin Research Center: internal data)

Breed	Intake	Meal frequency	Meal size	Meal duration
Bengal	+	+	=	=
Maine Coon	+	+	+	=
Siamese	+	+	=	=
Persian	=	+	-	++
Birman	=	=	=	=

+ Statistically higher in purebreed cats compared to domestic short hair cats
– Statistically lower
= No significant difference ($p > 0.05$)

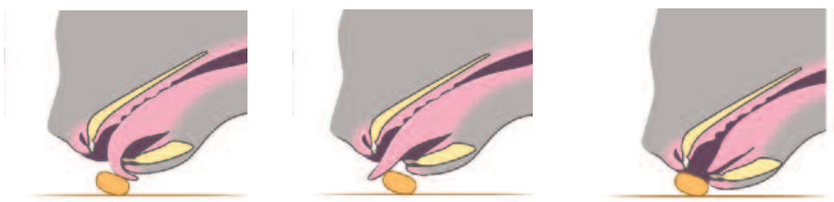
A group of 68 cats of different ages and breeds (European cats: 30; Persian/Exotic Shorthair: 8; Siamese/oriental cats: 8; Maine Coon: 9; Bengal: 7; Birman: 6) with free access to food for 18 hours were evaluated over an 8 day period. There was an average of 12.2 meals, with an average meal size of 5.3g/meal. On average, the cats ate 59.7g/cat/day and spent 23 minutes eating. These results mask great disparities between breeds.

Types of prehension

Prehension of food explains the apparent eating rate of cats. The cat has a small mouth and small teeth which are better suited to holding and killing prey rather than grinding and chewing food *(Case, 2003)*. The initial role of the canine teeth is to seize prey whereas the carnassials tear flesh.

Innovative studies conducted by Royal Canin in collaboration with the *École Nationale Supérieure des Arts et Métiers* (ENSAM) in France, demonstrated that cats exhibit three distinct methods of dry food prehension. The most common method is called labial prehension and involves the grasping of kibble using the incisors, without the use of the tongue. The second method is called supralingual prehension, which involves the cat using the dorsal side of the tongue to "lap up" their food. The third method is called sublingual prehension, in which the cat applies the ventral side of the tongue to the kibble, then turning it backwards **(Figure 7)**.

FIGURE 7 - PREHENSION MODES IN CATS



Supralingual mode | Sublingual mode | Labial mode

By filming cats from below as they eat on glass surfaces, Royal Canin has discovered that certain breeds of cats are more likely to demonstrate one type of prehension style over another. For example, brachycephalic breeds such as the Persian, have difficulty picking up kibble with their teeth, because of the structure of their head and jaw. In 80% of cases, Persians use their tongue to pick up a kibble rather than their lips or teeth. Mastication is somewhat poor in cats. Jaw joint configuration allows only vertical movement. They often break the kibble in one strike, or even immediately swallow in one gulp! This occurs commonly in cats with dental pain, who avoid breaking the kibbles with their teeth, rather they swallow the kibble whole and even vomiting quickly after.

The role of the tongue is very important when speaking about canned food. It acts like a spoon. Its rugose surface easily catches pieces of loaf or chunks.

Each of these parameters must be considered when feeding cats and creating environments conducive to good eating habits.

3 - Determinism and regulation of food consumption

► External stimuli: picking the appropriate food

Cats appear to be sensitive to the odor, form, texture and palatability of their diet (Table 4).

> Odor

Odor is key for cats: an off flavor arising from rancidity of fat can halt food intake regardless of the taste or nutritional value of the food. Odor is the major criteria of food selection. Experiments that alternated odor flow across the bowl of kibble have shown an increased numbers of meals and food consumption during the odor circulation phase.

Cats prefer food that is at room temperature or near body temperature (38 to 40°C), most probably because it contributes to volatilization of food odors. Temperature interferes with odor for volatilization of compounds. It is also something closer to prey temperature. In practice, increasing food temperature from 20 to 40°C can enhance food consumption up to 80%.

Prehension and mastication in the mouth leads to food re-warming. This can be important to get an improved perception of odors through retronasal olfaction.

> Shape

Since prehension occurs before food enters the cat's mouth, the ease of prehension is important to consider (see trials with Persians). For kibbles, shape determines the lines of breakage and convenience to guide toward the ancestral carnivorous drive, where it is broken in one strike before swallowing. Shape, by determining surface to volume ratio, also displays more or less flavors.

Table 4 - The successive steps of food consumption by the cat

Phases	Sense use	Characteristics of the food tested on the cat	Advancement paths to improve the palatability of the food
 **1 Selection**	Smell	Smell	Choice and quality of the ingredients, aromas and fats in the coating
 **2 Prehension**	Touch	Size, shape, texture	Technological process: grinding, cooking, drying
 **3 Chewing**	Taste	Taste	Quality of ingredients
 **4 Digestion**	Physiological reactions	Food security	Nutritional quality of the end product

> Texture

Some research has suggested differences in food preferences between domestic pet cats and free-ranging cats living on farms (*Bradshaw et al, 2000*). Farm cats preferred raw meat diets while house cats preferred harder or drier types of food (e.g. kibbles). These data may reflect learned preferences and/or neophobia of a food choice that is provided infrequently as was the raw meat to house cats. Cats used to a certain texture or shape of dry kibble may refuse new diets that vary in either one of these dimensions.

The food most frequently offered to cats comes primarily in two forms, dry cat food and moist (canned or pouch) cat food. Cats like the "cracking texture" of dry kibbles and the high moisture content (75-80%) of canned food however, rehydration of dry food is not appreciated by cats, unlike dogs.

Dry cat food has certain advantages for the human caregiver:

- it is easier to store, to keep for a longer period of time
- it can easily be fed free choice without concerns of spoilage
- it may offer dental hygiene properties. The chewing and grinding may help prevent plaque and calculus development (see chapter 10) and dry diets have been specifically formulated to increase their dental cleaning properties.

Some cats show a preference for certain shaped kibble morsels and have preferences for mouth feel and surface to volume ratio of the food *(Crane et al, 2000)*. Cats reject broken kibbles.

Canned cat food can either be a complete and balanced diet or just a supplement that is primarily meat. Canned foods are blended and contain additional water; in some cases the moisture of the product reaches 85%. It can result in a low caloric density and thus promote higher intake on a long term basis Many cats find canned foods extremely palatable due to the high water, fat and protein content *(Case, 2003)*. Product texture is very important to determine eating patterns:

Minced products are continuously swallowed, the cat staying crouched and never lifting its head. The speed of eating is high and owners may perceive that this is a reflection of palatability, whereas the reason is more mechanical than sensorial!
Jelly products lead cats to take large gulps of meat. They have to chew a bit and lift their head simply to swallow. Some owners may have the perception that their cat is more reluctant to eat. Others may feel that the cat is appreciating the food, tasting it quietly, thanking them by looking at them and licking their lips!

© Royal Canin

The texturometer is used to measure the kibble's resistance to the force of the cat's teeth and jaws. Interchangeable modules imitate the shape and size of teeth according to the size and age of the cat.

Semi moist foods: most of these products are marketed as treats for cats and are not meant to be used as the sole dietary source of nutrition. They are softer in texture than dry food, but they are not as moist as canned food. They do not require refrigeration and have long shelf lives. Some ingredients, used as preservatives of the water level, may even negatively affect palatability.

Homemade diets are not usually recommended since cats have specific dietary requirements that may be hard to meet.

> Taste and the composition of the food

Food palatability is the very first key factor of success for petfood acceptance, for both cats and owners. Despite a lot of publications concerning feline food preferences or aversions, cat's preferences are more nutrient-orientated than ingredient-orientated. Quality and freshness of raw materials are nevertheless important.

An important technological know how (enzymatic hydrolysis, fermentation, etc.) has been developed, leading to the commercialization of very efficient natural flavors, homogeneously coated onto the kibbles in order to drastically increase their acceptance **(Figure 8)**. However, there is little information that the authors can provide in this text as the data remains strictly confidential among palatability experts in petfood companies.

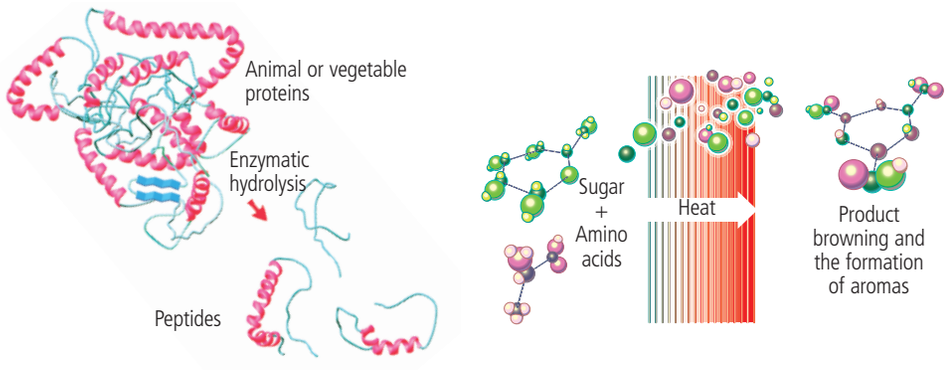
Proteins (especially hydrolysed proteins from meats, and sometimes plants such as soyabean) as well as fat are both palatable for cats. Some ingredients like yeasts and specific acids are also appreciated by cats.

The selection of fat is important, and above all their protection against oxidation. Fat can also interfere with palatability through some texture effects. Short and medium chain fatty acids (caprylic acid, coconut oil, etc.) are sometimes associated with altering the palatability of the food

FIGURE 8 - MAIN TECHNOLOGIES USED IN THE DEVELOPMENT OF AROMAS

1. Hydrolysates are often obtained from heated, acidified poultry proteins. Enzymes are used to breakdown protein into palatable compounds.

2. Maillard reactions are used to aromatize various products (coffee, biscuits, roasted meats, etc).



(Mac Donald et al, 1985) but this effect can be hidden when the ingredients and the surrounding formula are appealing for the cat.

Palatability has too often been blamed for feline obesity. However, the food's energy concentration is more important than palatability. An inactive, neutered cat that has access to food with a high-energy concentration will inexorably gain weight. Prevention is about maximizing activity and optimizing the composition of the food.

A cat has more difficulty limiting its food consumption if the kibbles are very rich in fat. Cats fed ad libitum with a food containing 20% fat develop greater adipose reserves than when the fat level is halved, regardless of the animal's sex: male or female, intact or neutered *(Nguyen et al, 1999)*.

► Elements of the regulation of hunger

Global palatability of the food is crucial, but hunger is a sine qua non condition for the cat to eat.

> General principles

Energy supply is controlled by homeostatic regulatory processes for food intake and body expenditure or both. Nutrient supply to the body must be constant. However, food intake is a discontinued and periodic behavior. A medium and long term regulation system thus exists; with the involvement of body storages (essentially fat). Everything is done homeostatically to prevent loss of tissues and weight loss.

Controls of food intake can be classified by several pathways:
- **behavioral pathways**: habits and learning such as sensorial or metabolic conditioning
- **nervous pathways**: mastication effecting oral satiation, stomach filling effecting physical satiation
- **metabolic pathways**: short term glucostatic theory, long term lipostatic theory

Glucostatic theory in cats

A low level of glucose in the hypothalamic cells triggers hunger *(Rowland, 1985)*.

Lipostatic theory

The endocrine role of adipose cells has been studied during the past few years. Many cytokines have been identified that act on insulin metabolism, inflammation, etc. Among these, leptin, the satiety hormone discovered in 1994, has been clearly involved in appetite regulation *(Bouret et al, 2004)* however, there are few studies in cats.

One satiation signal cannot act alone to control body balance which is the result of a series of separated control points, acting on a different time scale. Animals control their food consumption through 3 major food compounds:
- water
- sodium (all other mineral are consumed in relation to caloric density)
- energetic nutrients

If formulation is correctly done and if the feeding distribution well adapted to behavior requirements, energetic regulation is then efficient.

It has been suggested that the sensorial properties of a food become more important than metabolic ones for deprived cats. This could be an adaptative protective behavior during which cats seeking desperately for food become more discriminating to avoid poisoning risks in excessive hunger states. For well-fed cats, both palatability and nutritional values are acting in the regulation process.

From a practical standpoint, the only valid clue of efficient regulation is the stability of body weight. Significant inter-individual variability does exist. When analyzing publications and the possibly contradictory conclusions, it is important to perform a critical evaluation of what kind of regulatory processes are explored in relation to the beginning (animal reaction), the duration (constant modification) and termination (new equilibrium status).

> Energy regulation

Many experiments on caloric dilution of food content have been performed. Some contradictory conclusions have been drawn, that are often linked to the methodology employed (e.g. the addition of cellulose, water, clay etc).

Under very stable conditions, the cat seems able to control its food intake in relation to caloric density (more precisely in relation to dry matter caloric density). This process starts within 2 to 3 days and requires at least 3 or 4 weeks *(Rowland, 1981)*. Meal size is most affected, secondarily meal frequency. However cafeteria feeding (i.e. changing and varying daily dry matter content and palatability) disturbs this natural ability. This is typically what happens in the home when the owner frequently alternates canned and dry foods, brands, varieties, etc.

> Protein regulation

In cats, contrary to humans or dogs, protein has been shown to increase food intake *(Servet et al, 2008)*. Therefore, limiting the amount of protein (with a fiber substitution) is an original strate-

Why do some cats like fish so much?

In its original environment – the cat is adapted to deserts – where there is limited availability of fish. So where does this attraction for fish flesh come from - even to the extent that certain cats take great delight in raiding garden ponds, and feasting on gold fish and young koi?

Fish is a source of protein. Historically, cats have always been very opportunistic and quickly realized that there was obvious benefit in hanging around the quays when fishing boats returned to port because they could eat the remains from cleaning and gutting of the fish. In the time of sailing boats, voyages took a long time and boats took on board provisions of cereals - unfortunately accompanied by mice and rats that fed on them. Cats were therefore taken on board as well in order to control the population of these undesirable rodents and, once their mission was accomplished, the sailors would therefore show their gratitude by giving them fish.

In Asia, similar to human food, ocean-products are very commonly used in catfood.

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gy to limit spontaneous food/energy intake. These observations might be useful in the design of a diet to manage feline obesity (see chapter 1).

It has been suggested that some specific amino acids, such as tryptophan can affect general behavior (agression, excitability or territoriality modulation) in dogs *(Bosch et al, 2007)*. There may be a relationship between tryptophan intake by the brain and the level of carbohydrate in the diet. However, changes of the level of carbohydrate in the diet are often linked to concommittant change in the protein level, which can also affect behavior. The mechanism how the intake of nutrients that act as precursors of neurotransmittors (choline for acetylcholine, tyrosine for catecholamines, and tryptophan for serotonin) effect food composition is unclear and obviously needs more scientific work.

> Physical satiety

It has been proposed that the receptors for physical satiety in cats may be more efficient in regulating food intake than the energy pathways. In the single meal feeding situation, the cat is able to achieve its daily needs, even within 5 days following a transition from ad libitum to one hour distribution *(Thorne, 1982; Finco et al, 1986)*.

Ranking of control pathways is logically linked to the action level: physical satiation in the short term and caloric satiation in the medium term. The link is the fact that dry matter is both responsible for filling the stomach and for providing energy.

From a developmental standpoint, experiments on new born kittens *(Hinde, 1975)* would suggest that oral satiation is acting first before the development of gastric satiation: in other words, milk intake is less important than suckling movements.

Sleep is increased after meals. The effect is noticeable 3 hours after intake. Latency is variable: the quicker it appears, the longer it lasts. It is medidated by endocrine pathways and depends upon nutrients, duodenum pH, and gastric emptying.

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Nepeta cataria *(catnip plant)*
The catnip plant is usually well appreciated by cats. It is a generic name that applies to various plants sold for cats.

4 - Disorders of ingestion behavior

In the owner's mind, feeding behavior is associated with health, well being and pleasure, especially in mature markets where anthropomorphism is strongly present. This is probably why so many clients regularly question veterinarians about the relationship of food intake to some disturbances.

We will distinguish qualitative troubles (plant eating, pica and wool sucking, fixation on one food, learned aversion) from quantitative troubles (hyperorexia and anorexia).

► Qualitative disorders

> Grass and plant eating and catnip

Cats frequently eat grass if they have access to it and/or they may ingest house plants. Plant ingestion may be considered as a natural phenomenon which makes vomiting easier and thus the expulsion of hairballs. It becomes a behavioral issue when addiction occurs, i.e. if a cat systematically seeks a specific plant.

The **catnip plant** *(Nepeta cataria)* often induces a reaction in cats. Not all cats respond to catnip: 30-50% of cats do not respond at all and the response appears to be inherited and modified by both age and experience *(Beaver, 2003)*. When exposed to catnip a cat who responds will usually smell it, lick it, chew or eat it. The cat may hold the catnip in their paws if it is fresh. Cats will often roll in the plant. Some cats become quite animated and leap and play. The sequence is accompanied by head shaking, rubbing of the cheek

and chin against the plant and profusely salivating. This may be perceived by an unexperienced owner as an estrus-like behavior. The response lasts 5-15 minutes and cats may be refractory to catnip exposure for about an hour. This is a sort of satiation phase following the excitment. The active component, or at least the most powerful one, is a nepetalactone, a terpenoid with a special attraction effect to female cats *(Sakurai, 1988)*.

Valerian *(Valeriana officinalis)* produces similar effects to catnip. Cats roll on roots, urinate over it and exhibit signs of great excitement. After chewing the plant, the cat will roll for 10-15 minutes on the floor, rub against objects and exhibit estrus-like behavior.

Actinidia (including chinese gooseberry): when presented with this plant, the cat stops eating and even stops sexual activity. On detection of the smell, they will seek its origin and roll on their backs in a state of total ecstasy.

Olive wood
Most cats chew and lick olive wood objects and rub at them. Olive flesh is not attractive to cats, it is more the nut.

This attraction to plants may become annoying and more importantly, as many house plants are poisonous, can have serious consequences when ingested. In addition, most owners find the consumption of houseplants objectionable and punish the cat for doing so if they catch the cat in the act. This can often result in a cat that is frightened of the owners. Treatment aims at providing acceptable plant material for ingestion by creating a cat garden of grasses (sold in many petshops) and plants that are acceptable and safe for consumption by the cat. Other plants should be placed out of reach either high off the ground, secured in another room or outdoors. In some cases making the plants aversive using hot-pepper solutions sprayed on the leaves or a water sprayer if the cat gets too close diminishes the behavior.

> Pica and wool sucking/chewing behavior

Pica

Pica refers to the voluntary ingestion of non dietary, non nutritional items and can include clothing, electric cords, wool, fabric, cardboard, plastic and many other items. Some cats may actually ingest the items and intestinal blockage is possible.

It represents between 5 to 10% of behavioral problems in cats. Often pica occurs in young, active animals and in some cases a genetic predisposition is suspected but has not been proven *(Beaver, 2003)*. It is important to keep in mind that kittens actively explore orally their environment up to 6 weeks of age and voluntary intake of unedible items can occur without being pica. Beyond that, special attention is due.

The origin of pica is in fact not very well known. Some mineral or vitamins deficiencies had been incriminated in the past, but the tremendous formulation improvement of cat food has eliminated this possible theory. Massive parasitism may be a similar contributing factor in farm cats.

Medical conditions such as feline leukemia and feline immunodeficiency should be investigated since they may contribute to abnormal behaviors. In dogs, exocrine pancreatic insufficiency has been associated with pica, but that has not been noted in the cat *(De Braekeleer et al, 2000)*. In other situations a lack of an enriched environment, dental problems, teething, attractive odors on objects and attention seeking have all been considered as contributory factors for pica.

Pica is thought to first be exhibited in situations of conflict and/or anxiety for the pet. In cats the initial situations may be social situations between cats, changes in social interactions with family members, moving house, etc. Over time the problem behavior occurs in other situations and more frequently until it interferes with function. Diagnosis of a compulsive disorder is based on exclusion of other causes for the behavior.

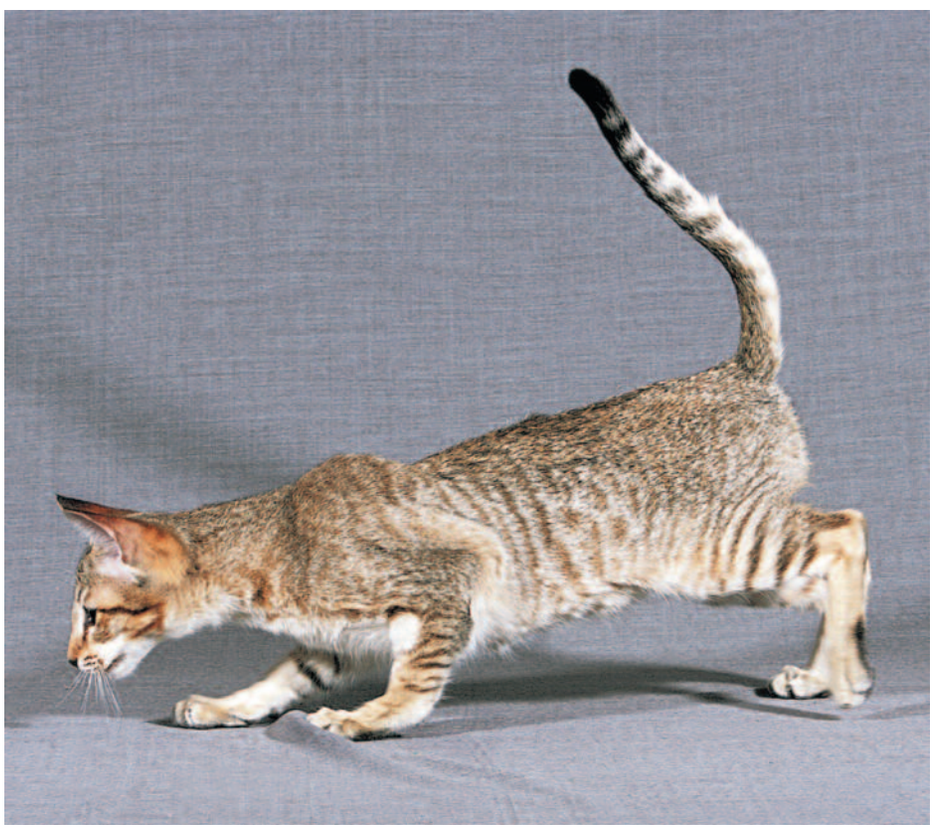
Wool sucking

Wool sucking has to be distinguished from true pica. This behavior is considered to be a compulsive disorder *(Luescher, 2002)*. Wool sucking occurs when a cat takes clothing items, usually woolens (but other fabrics may be chosen) and sucks or chews. Some kittens are naturally sucking their littermates or their own skin: later, this habit can extend to other species, cushions, or the owner's clothes. Under natural conditions, kittens can suckle their mother up to 6 months of age. In domestic conditions, weaning is earlier (6 to 8 weeks). *Houpt* (1982) hypothesized that it was the result of a suckling deprivation as a consequence of early detachment, however, nothing has yet been definitively proven. The strong or excessive affective link with the mother and with the owner (in oriental breeds) may also be part of the explanation.

Treatment

Treatment of pica and wool sucking includes a mix of the following strategies:
- in some cases merely keeping the pet away from items is useful.
- making items aversive with unpleasant smelling or tasting detergents: garlic or red pepper mashes, aloes, quinine, strong perfumes (avoid chlorinated agents which attract cats)
- redirect the cat to other items: increasing feeding opportunities through the use of feeder type toys may help.
- keeping the materials out of reach *(Houpt, 2005)*, when possible
- offer derivations to the cat, such as toys, possibilities to go out for a walk or a hunt
- behavior modification, creating a predictable and reliable environment avoiding anxiety sources
- restructuring the interactions with the owner, by discouraging over-attachment syndrome (regular and increasing separation phases from the owner, compensated by physical contacts initiated only by this latter while ignoring cat solicitations: it is hard to get observance but it is efficient)
- in some cases use psychotropic medication e.g. a Selective Serotonin Reuptake Inhibitor (SSRI) such as fluoxetine or a tricyclic antidepressant (TCA) such as clomipramine *(Luescher, 2002)*.

Because Siamese and Burmese cats are over-represented up to 8 months of age; a genetic predisposition toward wool sucking is suspected but not yet proven.



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> Fixation on one type of food and neophobia

Neophobia is the opposite of neophilia and corresponds to avoidance of a new food compared to the usual food. Also called "fixation of food habits", neophobia has been identified in cats. This behavior is part of a food selection strategy.

Omnivorous animals consume foods that provide a balanced diet and avoid taking the risk of eating new unknown foods. However, carnivores in the wild display more neophilic than neophobic behavior *(Thorne, 1982)*. Neophobia is more common when meals are served in unusual conditions *(Thorne, 1982)* or if the animal is under stress *(Bradshaw, 1991)*.

It is not uncommon for a cat to become fixated on a particular type or flavor of food and reject all others. Often this can be prevented by offering a diversity of flavors and textures of appropriate complete and balanced diets when the cat is young. Willingness to try new foods and food preferences may be influenced by the queen and the weaning conditions: kittens fed since weaning with the same cere-

al-based food preferred this type of food to more palatable canned food with tuna *(Wyrwicka & Long, 1980)*. Neophobia, the lack of recognition of food as being edible *(Bradshaw et al, 2000)*, exists in varying degrees. The more regular the diet, the more persistent is the neophobia.

In some cases it may be medically necessary to switch a cat to a new diet. If the diet texture and shape are the same as the previous one, the cat may accept it readily by adding it step by step in the new food while decreasing the proportion of the old food over a week of time. For some cats, offering the new food and old food side by side will also help the transition. In other situations, a cat may need to be transitioned from a canned food to a dry food or vice versa. This is often difficult since many cats seem to have preferences for certain shapes and/or textures of food. Increasing the smell may enhance eating for some cats and this often can be accomplished by warming the food.

A few days are required to overcome neophobia and for an animal to experiment with the new food *(Cheney & Miller, 1997)*. To overcome neophobia towards a new flavor, cats should not be exposed to the smell alone; they must also taste it. In a study on cats, *Bradshaw* (1986) showed that neophobia disappeared after the third day of presentation of food flavored with lamb. Neophobia reappeared three months later if the cat was not regularly exposed to the new flavour. One solution devised to overcome neophobia towards a flavor involves using drinking water as a support. Although neophobia toward new foods is common in many species, neophobia toward flavored drinking water is indeed rare.

Introducing a new diet under unusual circumstances or when a cat is stressed (by pain or illness, by being away from its owner, in a veterinary clinic etc) is more likely to result in neophobia (through an aversion learning process) than if the new food is introduced under familiar, positive circumstances. It is recommended to always introduce a new diet under the least stressful conditions for the pet and use a food transition program.

THREE APPROACHES WHICH MAY HELP OVERCOME NEOPHOBIA

1 - Offer the new diet each day for at least three days (offering fresh food each time). Persistent exposure, even if the cat initially refuses the new food, may help overcome neophobia.
2 - Try putting a small piece of the new food in the cat's mouth, so that the cat can taste the new food.
3 - If the diet is a wet food (can or pouch), try smearing a little of the food onto the cat's front legs. Most cats will lick off the food and this can habituate the cat to a new food.

> Learned taste aversions

Aversion is a strategy used by animals to avoid foods that are unsuitable for them. It is a form of negative conditioning. If the smell of food is associated with distress, with an unpleasant experience (hospitalization, forced or hidden drug administration) or with a digestive problem (poisoning, allergies), the food will be avoided in the future. This phenomenon is known as aversion *(Cheney & Miller, 1997)*.

In cats, aversion sets in very quickly. A single meal associated with unpleasantness leads to a refusal to eat. Such aversion can persist for 40 days *(Bradshaw et al, 1996)* or more *(Mugford, 1977)*. The smell alone of a food associated with digestive disorders is enough to elicit aversion. Cats even go so far as to show aversion for their usual food if it is served in the presence of an air current bearing the odor of a food to which they have developed an aversion *(Mugford, 1977)*. Be careful when preparing foods for cats being boarded at the hospital. Odors may travel and could trigger an aversion reaction even in cats being fed their usual diet. It is best to prepare the food in a place where food odors cannot reach the cats.

► Quantitative disorders

> Polyphagia

It is crucial to remember that feeding is an affective and rewarding act for the owner. It is the moment of the day during which the owner can get attention from the cat. However owners have to understand that the dietary behavior of cats is different from humans. For humans, the kitchen is often a social place. Cats like contact and will therefore go to the kitchen just to share social interactions. These requests for interaction are misinterpreted by the owner as begging for food. Owners do not recognize food soliciting behavior as an attention seeking behavior, not hunger and provide the cat with too much food which it willingly consumes. Most cats

TABLE 5 - CREATING GOOD FEEDING AND EATING HABITS IN CATS

1. Pick a diet appropriate for the life stage (kittens, adult cats, elderly cats), physical activity and environment
2. Provide food in an appropriate bowl in a safe, secure, quiet location
   a. When multiple cats reside in the home each cat should have their own bowl
   b. If social conflicts between cats are evident then some cats may need to be fed in separate locations
3. Calculate the appropriate amount needed to meet the nutritional needs of each cat in the home
4. Feed close to the same time each day
5. Avoid excessive solicitations for food if nutritional needs have been met
   a. Substitute play time, exercise, grooming or attention rather than supplementing dietary intake

TABLE 6 - CAUSES OF POLYPHAGIA
From: Masson, 2004

Transient			Persistant	
Reactional		Induced	Weight gain	Weight loss
Physiological	Psychological	Orexigen drugs	Dysregulation	Metabolic
Gestation Lactation Cold temperature Sustained exercise	High palatability	Megestrol Acetate	Hypothalamic lesions (unusual)	Diabetes mellitus Hyperthyroidism Malassimilation Chronic kidney disease
	Owner solicitation	Glucocorticoids		
		Anticonvulsivants		

are obese because they are provided with a highly palatable, energy rich diet in excessive of their metabolic needs. Starting out with a good feeding routine and pattern may help prevent obesity **(Table 5)**.

It is important to remember that neutering is responsible for decreasing energy expenditure. The balance between energy intake and energy requirements is usually disturbed after neutering.

Pathological and medical reasons

If the cat consumes excessive amounts of food without gaining weight then a metabolic problem (such as hyperthyroidism, pancreatic insufficiency, diabetes mellitus), massive parasitism or sometimes brain tumors, should be considered and a full medical evaluation obtained.

Some drugs such as diazepam, megestrol acetate and corticosteroids may also induce polyphagia **(Table 6)**.

"Hypersensitivity/Hyperactivity syndrome"

Some European behaviorists recognize a syndrome of excess food intake which may be due to lack of self control. Kittens scratch, bite, run everywhere and play constantly. Owners are impressed by the amount of food eaten without becoming fat. Some cats gulp their food, eat it quickly and then regurgitate it. This syndrome is due to a lack of mother regulation between the 5th and 6th week. This often happens when adopting young kittens from an outdoor life, that are not handled and not well fed during this crucial period of their life *(Beata, 2007)*.

Social problems

A cat may consume large quantities of food if it is anxious due to overcrowding, tense social relationships between cats in the home and lack of privacy while eating. Some kittens coming from large litters can maintain the habit to overeat to compensate for competition to the access of food, even when they are later in a single cat household, without competition.

If the problem of excessive food consumption is due to social problems between cats within the home, some simple environmental manipulations can be useful. Food and water bowls should be provided in all areas of the home, after paying special attention to which cats frequent what areas and where they spend their time. Some cats may be more agile than others and the provision of food bowls on elevated locations may allow them to eat with privacy. If one cat consistently eats more than its share of food, then set feeding times and separating cats for feeding may allow all cats to eat their required allotment.

Anxiety

The cat that is permanently looking for food may meet the European criteria for bulimia which can be a symptom of permanent anxiety. The excessive eating and food seeking are a substitution activity for frustration or conflict. If anxiety is the source of overeating then the individual conditions causing anxiety must be addressed (changes in schedules or territory organization, etc.).

These treatments are beyond the scope of this article but are detailed in other sources *(Horwitz, et al, 2002)*.

Excessive food solicitation behaviors and overfeeding

When cats become hungry they may engage in bothersome food solicitation behaviors. These can be especially problematic if the cat does not have access to the outdoors to hunt, or if food is provided in a meal format or set amount daily to prevent obesity. In an attempt to get noticed, food solicitation behaviors include vocalization, climbing, jumping, running, even destruction or agressivity (especially when meal feeding is chosen vs ad libitum distribution, creating some food frustration). Often these behaviors occur during night time hours, waking their owners. In an attempt to placate the cat many owners will get up and feed the cat. Unfortunately, although the cat will stop bothering the owner after being fed that time, the act of feeding the cat when they are noisy will result in the behavior continuing since the cat has been successful, i.e. they received food. The reward (food gift) is indeed reinforcing the undesirable behavior.

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Figure 9 *- Examples of food dispensing toys.*

Owners need to be counseled on how to avoid giving into demands for additional food. First, they must realize that not all vocalization (even that which occurs in the food preparation area) is a request for food. In some cases, it is just a request for interaction such as petting, grooming or play. A lot of owners wrongly interpret some marking behaviors (such as rubbing against the legs) like begging and they fill the bowl! They will effectively think they were right because they see the cat grabbing some kibbles in a very short meal. This will install a nibbling feeding habit in the cat that can eventually facilitate the development of obesity. If the owner responds to these solicitations with food, then food solicitation behavior can become a ritual, helped by the same reinforcement process explained in the previous paragraph.

Feeding the cat on a set feeding schedule allows owners to control food intake. The daily amount provided should be calculated so that the proper amount is fed daily. In some cases providing the food in a food dispensing toy **(Figure 9)** will slow down the rate of consumption and perhaps increase satiety thereby helping to decrease food solicitation behavior.

Daily play sessions limit the risk of obesity. Research has indicated that cats may quickly tire of a toy and the intensity of play diminishes within a few minutes. However, the presentation of a new toy stimulates the return of play *(Hall et al, 2002)* **(Figure 10)**. Exercise can also be increased by placing food bowls at distant locations requiring the cat to walk longer distances to obtain food.

Figure 10 *- Cats need to be stimulated by new toys to encourage play behavior.*


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Globally, two methods are employed to stop excessive food solicitation behaviors:

1. to ignore the cat and stop feeding the cat on demand, a process called **extinction**. When the owners attempt to do so, the cat will usually escalate their attempts for a few days, before it decreases. This intensification phase is hard to manage for owners. They

must be aware of such process and must hold out. With time, they will finally see a decrease in the demands. To facilitate success in this intensification phase, the owners can also either confine the cat to an area where they cannot hear it, or interrupt the behavior with a noise stimulus that discourages the cat from continuing.

2. to provide food in a way that is not connected to the owners using **a timed feeding system.** Electronic feeders that operate on a timer can be programmed to provide food at a set time each day and the cat may learn to wait until that time to be fed. In other cases, the feeding time must be slowly manipulated to teach the cat to eat at a later time each day.

Habits have to change to stop the reinforcement process. The owner may change the meaning of some daily situations or clues to play, petting, walking etc.

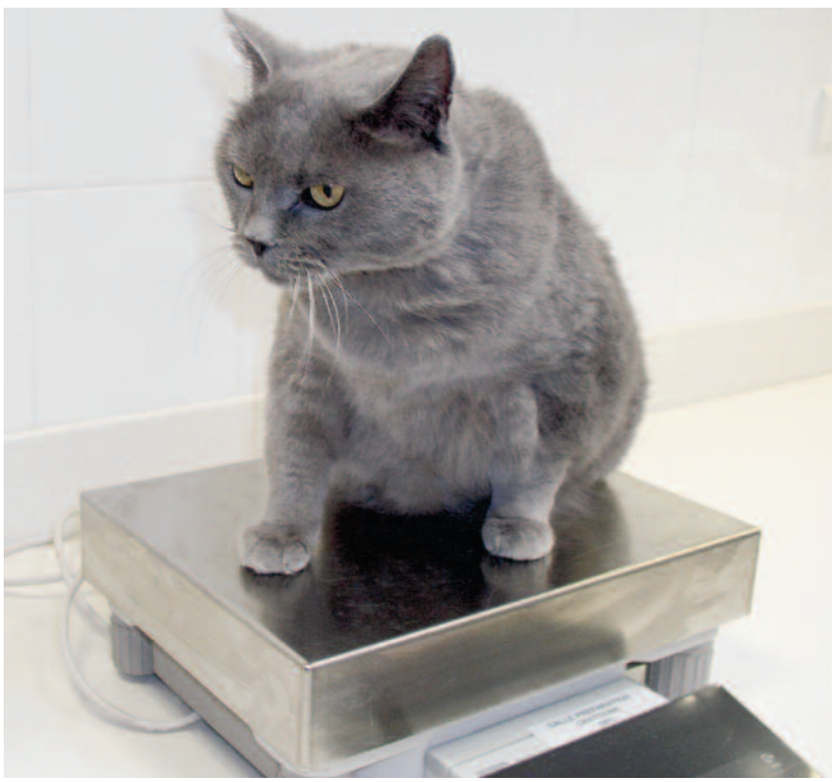
> Finicky eating patterns

Many pet owners complain that their cat is finicky and eats poorly. While many medical problems can influence hunger and subsequent food intake, these will not be considered here. Only the behavioral issues will be discussed, although all cats with suspected diminished appetite should undergo a complete medical and dental evaluation.

In certain cases a cat may refuse food from time to time simply because they are overfed, not hungry and/or exercising self-regulation of intake. Many new owners are unaware of the nibbling pattern of cat feeding behavior. Other cats may show finicky behavior due to excessive rotation of dietary choices. In other cases the cat has learned that waiting and not eating will result in a different, perhaps more desirable food choice being offered. It is important to take time to explain that too many changes in food varieties or giving treats can be harmful for cats.

The first step is to evaluate the actual amount of food provided daily and the actual amount consumed by the pet. This must also include all treats and human foods provided to the pet. The pet must be weighed: cats that are of normal weight and maintaining their weight over time are usually consuming adequate nutrition to maintain body weight. Body condition score should also be assessed. If the cat is obese then finicky behavior is not a nutritional problem, rather an emotional and behavioral one.

Body weight of a finicky cat should be assessed. If the cat is obese and if no disease is suspected, you can hypothesize that the cat may obtain food from additional sources (perhaps from a neighbor, another pets food etc).



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Once any underlying medical and dental problems have been identified and treated, behavioral treatment strategies can be employed. Daily caloric needs should be evaluated so that they can be met. The appropriate amount of food that should be provided daily to meet the animal's nutritional needs should be calculated for the owner. Often this is less than the owner has been feeding and this simple reassessment can help the owner understand that the cat is consuming adequate amounts of food. For many animals, setting a feeding routine is useful. The food should be provided at the same time daily in a quiet location and with each cat having its own bowl. Limiting treats can also help increase the desire to eat the provided commercial preparation.

Feeding diets that have increased levels of fat will allow for more nutrition with each mouthful. Excessive attention at meal times should be avoided since this can increase finicky behavior if it becomes an attention seeking tactic. Regular fol-

low up both to weigh the pet and discuss progress with the owner should be scheduled to assess improvement and keep the treatment program on track.

> Anorexia

Anorexia is defined as a diminished appetite. It is associated with many disease processes, trauma and psychological disturbances. In complete anorexia the animal does not eat at all. In partial anorexia the animal may eat some food but not enough to meet its metabolic requirements. Although it is often the reason for consulting the veterinarian, anorexia can result from either an organic or behavioral pathology. It can be due to:

- illness such as fever syndromes or cancer (anorexia may appear before tissue destruction and is the result of tumor metabolites).
- any parodontel disease (creating pain), face or jaw trauma (leading to an inability to eat)
- loss of olfaction: anorexia will last as long as the olfactory mucosa is not restored (renewal needs 4 to 5 days after the destructive agent has been removed)
- psychological stress (depression in reaction to the absence of the owner, even loss of close companions) or physical stress (e.g. excessive handling) *(Beaver, 2003)*: anorexia is accompanied by behavioral escape and withdrawal, house soiling, inhibition of play and exploration.
- anxiety triggered by social stress (antagonistic relationships between household cats, schedule changes, new household members (human or animal)
- anxiety that occurs with transportation, boarding or hospitalization (which can lead to specific learned aversion associated with the diet given during the event).

Cats that are anxious may hide and refuse to come out to eat. In this situation, the anorexia may simply be due to a lack of access to the food bowl. In some individuals anorexia may last only a few days, resolving when the stressful event ends or within a short period of time (2 to 3 days after boarding, house move, or transportation). Often these individuals do not need intervention other than providing easily accessible food and water bowls, possibly located where the cat is hiding. They then compensate by a huge meal. Forcing the cat to come out of hiding to eat is counter productive and may increase rather than decrease anxiety and the resultant loss of appetite.

In multiple cat homes partial anorexia may be ongoing especially if the social situation creates anxiety, stress and aggressive encounters between cats. If food and water bowls are not placed through out the environment, some cats may be unable to access them except at odd times. Even then, they may risk being attacked by other cats within the home for entering their territory. Understanding how the cats use the space provided to them and where various cats spend their time within the space provided can indicate where food, water bowls and litter boxes should be placed. Owners may need to be educated on aggressive interactions between cats. Not all aggressive interactions are overt (hissing, growling, chasing and fighting) but in many cases the actions are covert such as staring, blocking access or displacing the cat from resources **(Table 7)**.

In cats that are anorexic for more than 4 to 5 days, early intervention is suggested. Meal feeding in quiet, dark locations may help some individuals. The use of pheromone diffusers may calm some cats and increase food consumption both in the home and in the kennel or hospital situation, by their appeasing effects. *Griffith et al* (2000) found that both well and ill cats exposed to the pheromone showed increased interest in food and eating and increased grooming. In the second phase of the same

Table 7 - Social stress in the domestic cat and its effect on behavior

Problem	Effect	Solution
Too many cats in the home	Social stress leads to problems with eating or access to the feeding bowl	One food bowl per cat in various locations
To little space for so many cats	Aggressive interactions and/or hiding possible	Create additional vertical space
Aggression between cats	Chasing, injury, hiding, weight loss due to lack of access to food or anxiety	Create separate territories for cats, perhaps with barriers Have adequate resources through out the environment
House soiling	Owner distress, relinquishment of cats	More litter boxes in multiple locations (hygiene?)

study, cats exposed to the pheromone and a cat carrier showed significant increase in food intake over 24 hours compared to cats exposed to pheromone alone. Providing secure quiet locations, hiding spots within the cage or kennel and pheromones may therefore help increase eating in some hospitalized and kenneled cats.

When anorexia becomes profound, medical intervention is required. In the early stages some individuals may respond to benzodiazepines which may stimulate appetite. Diazepam however has only a transient effect (3 to 4 days) and acute hepatoxicity is often a serious risk. Mianserine has a quick orexigenic effect, but leads to some desinhibition to be controlled *(Coupry, 2007)*. Food should be nearby after administration in case the cat shows interest in eating. Cyproheptadine has also been used in some cases to stimulate appetite. Progestins and anabolic steroids have been tried in the past but, due to potential adverse side effects, they are not recommended and rarely used. Should anorexia persist, enteral feeding tubes need to be employed to allow for supplemental nutrition until the cat recovers and begins to eat on its own. Forced feeding presents however a disadvantage: digestion and absorption are indeed incomplete compared to voluntary eating (food intake stimulates the cephalic phase of digestion which can account for up to half of the gastric acid production).

To summarize, the following simple actions can help solve the problem *(Rabot, 1994)*:
- pay attention to any causes of uncomfort (dirty bowl, noisy place, strong smell of litter box, feeding spots with frequent passage, air flows)
- warm the food to 38-40°C (instead of receiving the canned portion directly out of the refrigerator)
- move the bowl to a quieter place (by looking at the cat activity program and locating preferred spots) or separate each cat (to avoid rivalry), at set times
- introduce a novel and very palatable food (the effect only lasts 2 to 3 days), in a sudden way, or spread over several days by increasing proportions into the daily ration
- attend meals for strongly dependent cats or put some food on the fingers to make them linked (especially in the case of reactional depression, but beware of the risk of ritualization)
- ensure renewal of canned food (to avoid oxidative and bacteriological damage).

One must remember that the efficacy of these recommendations may vary between cats and situations. Felines are rarely deceived and often stubborn.

5 - Water drinking in cats

Perhaps because of their evolutionary history, cats tend to have a relatively low intake of water. *Felis lybica*, the European cat ancestor, lived in the desert and was able to concentrate its urine to avoid water losses. Today's cat has kept this ability, but with the risk of forming bladder calculi. Although a cat can be food deprived for several weeks, a few days of water deprivation are enough to put its life in serious danger.

In a multiple cat home food and water bowls must be spread through out the environment so that all cats may access them easily without encountering cats that they have a conflict with. In many cases this will resolve the anorexia and the cat will begin to eat normal amounts of food.

Animals have three sources available to meet their water needs:
- water offered for drinking
- water in the food
- water created by the metabolism of nutrients *(Beaver, 2003)*. Water is produced by substrate oxidation (fat providing the greatest quantity but carbohydrates providing the best output).

► Some pathophysiological considerations

Water needs for cats vary from 55 to 70 mL/kg BW/day. The requirement is in fact related to the dry matter intake: 2mL per gram of dry matter eaten.

> Intrinsic regulation of drinking behavior

Thirst is the sensation which triggers water intake. The signal comes from the lateral hypothalamus, close to the hunger center. Regulation is complex and closely linked to variation of plasma osmolarity, controlled by vasopressin.

Drinking satiation is first triggered by oral stimulation on a short term basis (one hour). Gastric distension interferes later, acting mainly on the frequency of intake. Finally, cellular hydration controls water satiation through complex interactions.

Cats are not as sensitive to water loss as the dog and may not drink additional water until they have lost as much as 8% of their body water *(Case, 2003)*.

Water intake varies depending upon water losses:
- physiological losses: urination (40mL/kg/day), feces and respiration, lactation
- pathological losses: diarrhea, vomiting, edema, skin injuries, diabetes mellitus, renal failure, etc…

A reduction of blood pressure and blood volume also provoking thirst, through the renin-angiotensin-aldosterone system.

> External factors that influence drinking behavior

The composition of the food

Water intake is affected by food type and moisture content. Cats fed a canned food drink virtually no water since they meet most of their water requirement with their food intake. It is the same with fish or meat fed animals.

Dry food contains only 7-8% water, requiring the animal to consume more water to meet their daily needs. It has been shown that dry food increases fecal water loss but decreases urinary loss *(Jackson & Tovey, 1977)*. However, it is important to mention that, while intake is strongly modified, the general water balance is not modified by the moisture content of the food. Urinary calculi are more strongly linked to the urinary mineral composition and urinary pH than to the moisture content of the diet. The only risky situation occurs when there is a transition from canned to dry diet.

Caloric density does not affect water intake. Increasing the dietary protein level results in increased water intake (due to the increased diuresis required to eliminate urea). Carbohydrates decrease water intake, due the higher output of metabolic water from carbohydrate metabolism. Sodium chloride increases water intake. Hypernatremia (> 160 mEq/L) triggers thirst and water consumption in cats.

Temperature

The drinking behavior of the cat is much less influenced by temperature and effort compared to the dog. This can be readily explained as salivary and perspiration losses are not significant in the cat. To facilitate water intake the temperature of the water must not be too cold (not less than 10°C).

Food supply

This factor has been better studied in dogs than in cats. In a restricted regimen, the rate of water intake increases to 2.5 mL per gram of dry matter eaten. A one hour per day feeding pattern leads to a decrease of food and water consumption, compared to the ad libitum situation. In this latter context, water intake is linked to the meals. This is a learned process.

► Practical considerations to encourage a cat to drink

Like food intake, cats drink throughout the entire twenty-four hour period. They drink 12 to 16 times a day but water intake each time is small: 10 to 12 mL. Tremendous variation exists between individuals: this is linked to the sum of physiological effects described above.

To help promote optimal water intake, cats should be provide with fresh, clean water daily from easily accessible water bowls. Owners must pay attention that their cat can have access to water at any time. It is dangerous to provide only one bowl in one room, which could remain closed for a period of time, thus preventing the animal to drink enough. A second bowl elsewhere in the house is recommended, particularly when leaving the cats unsupervised e.g. for a weekend.

Spoiled water is rejected by cats. Glass, metal or porcelain bowls are preferred to plastic ones. The location of the water bowl is important: it has to be put at least 50 cm away from the food bowl and the litter. This distance is sometimes critical when the cat is hospitalized. Water must be palatable: cats are extremely sensitive to odors and some can display preferences for water taken from toilets, sink, etc. Some cats prefer electronic water fountains that aerate the water on a regular basis. One way to increase water palatability is to add meat juice, some milk or some salt. Feeding either a canned food or a liquid food is another alternative.

► Drinking disorders

> Adipsia or hypodipsia

Any cause of hyponatremia (such as severe hepatic disease, congestive heart failure, acute kidney failure, nephrotic syndrome) can stop water intake. These causes of adipsia are in fact compensatory mechanisms.

Conditions of the oral cavity (gingivitis, abscess, tumors, ulcers, fractured jaws, foreign bodies, etc.) may reduce drinking, due to either mechanical or painful reasons.

Adipsia may be simply the result of poor water quality (e.g. water left too long in a dirty bowl). It is nevertheless important to remember that water intake will be still nil as far as all water needed will have been supplied by the food!

> Polydipsia

The average water consumption of a cat depends on the dry matter ingested: around 2mL of water is required for each gram of dry matter consumed.

Any change of drinking behavior must be carefully evaluated. Water intake becomes pathologic beyond 100 mL/kg/day. Any cause of polyuria (> 50 mL/kg) will logically lead to polydipsia **(Table 8)**.

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Plasma osmolarity facilitates the identification of what is primary polydipsia and what is compensatory *(Remy, 1986)*:
- if plasma osmolarity is greater than 310 mOsm/L, polyuria is primary and urinary loss creates polydipsia
- when plasma osmolarity is below 290 mOsm/L, polydipsia is primary and the low osmotic pressure leads to polyuria.

Intake of salty foods (fish scraps…) leads to polydipsia, and then to polyuria.

Polydipsia may be a reaction to stress or a substitution activity of a permanent anxiety. Hypercortisolemia triggers excessive water intake *(Landsberg, 2003)*. Situations of conflict situations must be identified and corrected.

Hypercalcemia linked to secondary hyperparathyroidism can stimulate thirst.

Table 8 - Differential diagnosis polydipsia
From: Masson, 2004

Cause and intensity	Urinalysis		Blood analysis		
	Osmolarity	Abnormal elements	BUN	Glucose	Other
Chronic kidney disease +	⇩	Protein	⇧	N	
Pyometra +	N	Protein	⇧	N	
Diabetes mellitus ++	⇧	Glucose	N	⇧	
Diabetes insipidus +++	⇩		N	N	
Hyperadrenocorticism ++	N		N	Slight ⇧	Hypercortisolemia ⇧
Hyperthyroidism ++	N		N	N	
Liver failure ++	N	Bilirubin	N or ⇧	N or ⇩	SGPT ⇧
Gastro-enteritis +	⇧		N or ⇧	N	
Hypercalcemia +	N		N	N	Calcium ⇧

N = no change

Hepatic failure can lead to polydipsia through decreased renin degradation and increased angiotensin activity.

Conclusion

The data presented provides an understanding of the normal eating patterns of domestic cats. Some of the information is empirical. Others come from research, in both the natural condition and in the laboratory. Extrapolation from other species and large felids should be avoided.

The data can help veterinarians and pet owners make relevant choices for feeding routines and food types. The domesticated way of life, with increased social relationships and and evolutionary predator behavior must be considered when designing feeding protocols.

Medical problems can often contribute to changes in the selectivity and regulation of food ingestive behavior. Obesity is a major feline health problem. Proper client education and feeding regimes can help prevent and control excessive weight gain. The opposite problem of the fussy or finicky cat is only a problem if the cat is loosing weight. The real issue is in the owner's mind and belief.

Behavioral problems related to feeding and drinking can be due to anxiety, inappropriate provisioning of the cats within the home, learned eating patterns or compulsive disorders. A complete medical and behavioral evaluation should enable the clinician to determine the cause of the problem and therefore prescribe appropriate intervention.

Although the integration of the cat into the family can bring well being and happiness to everyone, the veterinarian will also have to explain to owners to avoid "thinking too human" when taking care of the cat, especially when feeding.

Frequently asked questions about the feeding behavior of the cat

Q	A
Do cats need to have several different flavors?	No, as long as they have a well-balanced diet, cats do not need flavor variety from day to day.
Why are cats fussier than dogs?	In fact, cats are not fussier than dogs. This commonly held belief is untrue. A poorly reared dog may be very hard to please. For some dogs, refusing food is a way of asserting their position in the family. Cats on the other hand, attribute no "social" value to food. If they refuse to eat, it's either because they're sick or because they have a genuine dislike of the food. The competition that exists in a pack always lead dogs to gulp down a maximum amount of food in the shortest possible time, i.e. dogs display "gluttonous" behavior. Cats, as solitary hunters, can take their time to dissect and savor their prey. Their behavior can be described as "tasting".
Are cats sensitive to sweet and salty taste?	Cats are different from dogs and humans. Cats have no preference for sweet tasting foods. This is due to their strictly carnivorous nature. Cats are also less sensitive to salt and have a higher NaCl or KCl detection threshold. Since salt is found naturally in their prey, cats have not been selected for this gustatory capacity present in other mammals, especially herbivores.
Every time I go to the kitchen my cat follows me and cries, what does he want?	Often the most frequent location and time for the cat to interact with the owner is around feeding so they may also choose that location or time to solicit attention. If the cat has been fed and consumed the proper amount to meet their nutritional needs, then they should not be fed when they vocalize. Feeding the cat every time it vocalizes will be seen by the cat as a reward for their behavior and therefore vocalization will increase. Try substituting play, grooming or social interaction rather than feeding the cat when it is not feeding time.
I have two cats and one is overweight and one is not. How can I provide an appropriate diet for each cat?	Each cat may need a different diet to meet their nutritional needs. One solution is to use timed meal feeding. Several times a day each cat is provided their diet and given a certain amount of time to consume their food. To facilitate each cat eating the appropriate food, the cats should be separated during feeding time. Once feeding time is over, the bowls should be put away until the next feeding session. In other situations, the thinner cat may be more agile than the larger cat and can have their food bowl in an elevated location that the heavier cat cannot access.

Q	A
How should I react when my cat refuses to eat the prescription diet?	Transitions to a new diet are best done slowly. The new diet can be offered next to the old diet to help the cat become familiar with the new food. In some cases it might help to mix the food together. If the texture of the two foods (old and new) are very different, this may be a problem for some cats. Using a similar texture food if possible may help the transition.
How can I prevent my cat from hunting birds?	Although unwanted by humans, predatory behavior is a normal cat behavior. Keeping the cat indoors will prevent predation. If that is not possible, some cats will be deterred by wearing a quick release cat collar that is equipped with large bells to warn the birds of their impending approach. Naturally, removing temptation in the form of bird feeders and bird houses is prudent.
I need to increase the amount of liquid (water) that my cat ingests every day. How can I do that?	Water consumption will vary according to the food type provided. Cats on dry kibble diets will drink more water than cats on moist, canned food. Water consumption can be increased by adding water to the canned food or providing water that has been enhanced with fish flavoring. Some cats prefer water that is fresh and aerated and will drink more water if provided water from a running faucet or a pet drinking fountain.

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Palatability and nutritional precision are interconnected

Palatability is essential if the cat is to take in what it needs. The best-balanced food in theory is useless if the cat turns its nose up at it. Even more so when its health demands a special diet that is theoretically not favorable to palatability: limited sodium, fats and proteins. There are various solutions for overcoming this obstacle and retaining an adequate palatability level.

Palatability is not a luxury: it's a vital obligation

The fundamental aim of nutrition is to provide all essential nutrients every single day in a sufficient quantity to cover all needs. The first of these needs is energy, in whatever form the calories are provided.

The formulation of feline diets is above all based on energy density: the ration volume offered to the cat must be compatible with its capacity of digestion:

- too low a volume does not give the cat a feeling of satiety
- too high a volume may not be consumed properly or may cause digestive problems.

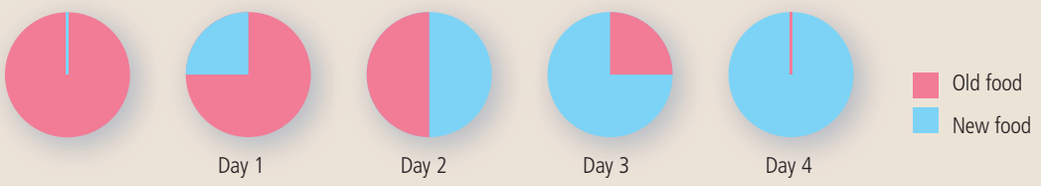
Palatability helps the cat overcome certain kinds of stress

For many cats, a loss of appetite is one of the first signs of stress. If the food is not sufficiently palatable and if the period of stress is prolonged, there will be a risk of chronic underconsumption and the appearance of nutritional deficiencies. The cat will lose weight, the quality of its hair will deteriorate and its immune defences will be weakened.

Examples of situations in which the cat's appetite is disturbed

- Changes of environment: when a kitten or an adopted cat arrives in a new home, moves house or is put in a cattery during the holidays.
- Changes to diet: some cats tend to reject a new food (neophobia). This phenomenon is especially observed when the food is offered in unfavorable environmental conditions or when cats have been given the same food for a very long time. Conquering neophobia entails realizing the most gradual dietary transition possible **(Figure 1)** in conditions that are ideal for the cat's well-being, thus preventing the development of an aversion that would be even more difficult to overcome.

FIGURE 1 - TECHNIQUE TO ENSURE GOOD DIETARY TRANSITION



It is advizable to change a diet gradually. For example, mix 25% of the new food with 75% of the old food on day 1. The next day mix together equal quantities and on day 3 mix 75% of the new food with 25% of the old food. On day 4 you can give the cat only the new food.

How is palatability evaluated?

Palatability is measured through objective studies to assess the cat's behavior in the presence of one or several foods. It is mostly interesting to try to estimate the cat's preferences and the way the food is ingested.

The cat's preference for a given food

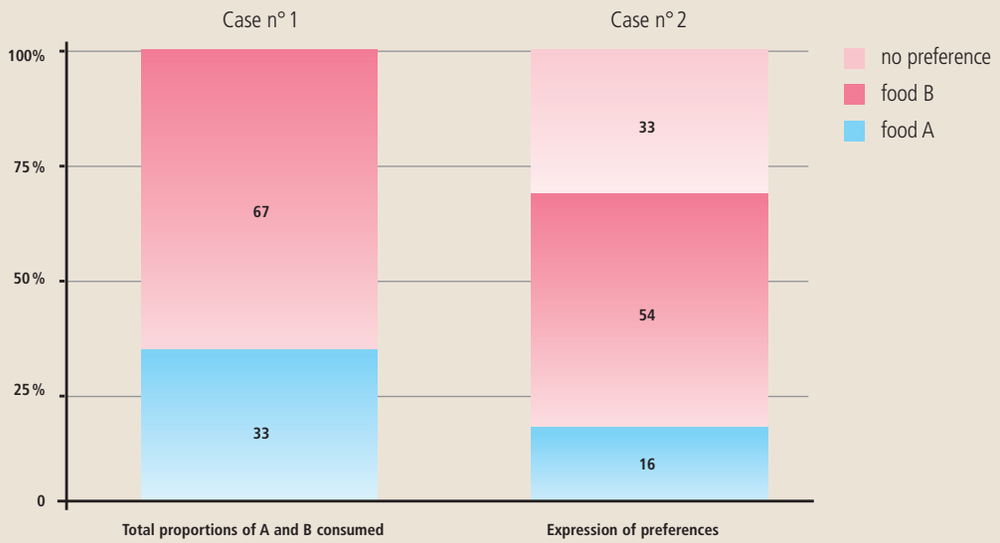
This can be realized by measuring the respective consumption of two different foods freely available to the cat **(Figure 2)**. The cat's selection criteria are subsequently analysed. The reliability of the result depends on the number of cats used and the duration of the study among other things. The selection of the most discriminating cats helps increase the sensitivity of the tests.

The way the food is ingested

This reflects the attractiveness of the food for the cat. The quantity of food spontaneously ingested within a given time or the time needed to ingest a given quantity are important data. Videos showing the prehension method and any consumption difficulties provide some useful additional data.

The information obtained at the cattery is confirmed by studying cats owned by private individuals when evaluating palatability in diverse environmental conditions and taking into account such notions as the owner's appreciation of the look of a product and his or her attitude when serving the food, the variable conditions of serving a meal, etc.

FIGURE 2 - TWO DIFFERENT WAYS TO EXPRESS THE RESULTS OF PALATABILITY



The results can be expressed in two ways:
- Case n°1: the graph only indicates the proportions of foods A and B consumed by all cats.
- Case n°2: 16% of cats preferred food A (i.e. they consumed at least twice as much of food A as they did of food B), 54% preferred food B and 33% showed no preference.
The second method best reflects the differences, because it takes into account the number of cats that show a clear preference.

Does palatability diminish with time?

All food products tend to deteriorate with time. Guaranteeing good palatability during the whole shelf life of a product entails slowing down the aging of the product.

Quality of fats

The conservation of the fats in a food demands close monitoring, particularly those in the kibble coating. In contact with the oxygen in the air, the fat molecules generate the production of unstable molecules – free radicals – that cause oxidation. Liquid fats at ambient temperature (poultry fats, vegetable oils) are the most sensitive to oxidation, because they are unsaturated. Keeping food in the light at a warm temperature accelerates the process.

The role of antioxidants is to block the free radicals before they provoke chain reactions that lead to the appearance of peroxides, then secondary oxidation compounds, aldehydes and ketones. All of these compounds are potentially toxic. It is rare for the cat to consume a food that contains deteriorated fats however, as it is very sensitive to the rancid smell emitted by oxidation. The use of truly effective antioxidants is indispensable to conserve palatability and protect the health of the animal.

Development of the aromatic profile

Expertise on palatability is not restricted to the development of aromas that are particularly attractive to the cat. These aromas are essentially volatile, so they can be easily picked out by the cat's sense of smell. That means they risk evaporating in the ambient air. As a result, the kibbles internal odors come to the fore. The cat does not necessarily find this different aroma profile as pleasant.

Another risk is the deterioration of aromas with time. What starts out being a pleasing flavor may ultimately turn into a negative palatability factor.

The research carried out on palatability entails following the development of these substances to verify their behavior as the product ages. Palatability must remain satisfactory throughout the life of the product, right up to the best before date on the pack.

To limit the risk of the loss of palatability after the pack has been opened, it is important to select the right size of pack for a particular cat's daily consumption. A 4 kg cat that eats an average 50 g of kibbles per day, consumes the equivalent of

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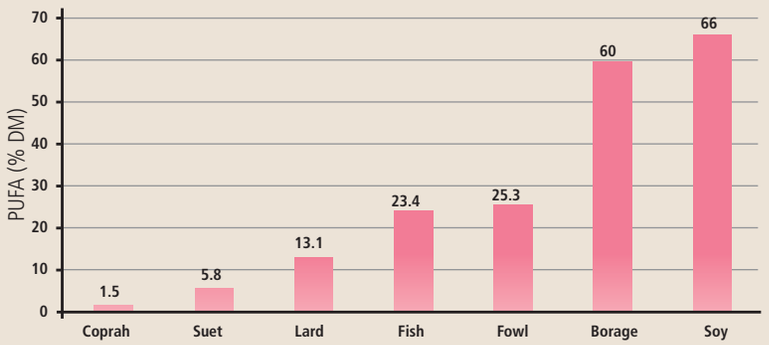
The quality of fats is monitored in the ingredients and in the final product. The freshness and the resistance to oxidation of oils and fats are major criteria for good palatability.

FIGURE 3 - COMPARISON OF THE QUANTITY OF POLYUNSATURATED FATTY ACIDS (PUFA) IN DIFFERENT OILS AND FATS



The higher the PUFA content and the longer the fatty acid chains, the greater the fat's sensitivity to oxidation if not adequately protected.

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The role of all the antioxidants is to stabilize the fat in the product and the kibble coating to preserve palatability and the health of the cat.

a 1.5 kg (3 lb) bag in a month. The aromas will be conserved well during that period as long as the bag is stored in a dark place in a hermetically sealed container at a stable temperature. It's better not to select a larger bag as this would require a longer period of storage.

Working on conserving the nutritional qualities of the product

The preservation of a product's organoleptic qualities entails vigilance at various levels.

The choice of ingredients

Palatability must be a key factor to take into account from the moment of formulation. The thermal treatment used to separate proteins and fats from a meat has an impact on palatability for example. Likewise, a given source of fat will be favored depending on its resistance to oxidation **(Figure 3)**.

The process

All the technology involved in kibble grinding, cooking, drying and coating is oriented to preserving the original qualities of the ingredients. The time between manufacture and packing is minimized.

Antioxidation

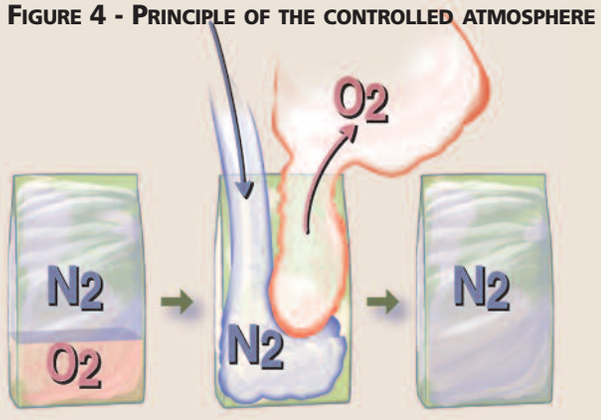
To prevent the oxidative reactions from beginning, it is preferable to use chelated trace minerals (especially iron and copper). Once chelated, their bioavailability is increased and they are unable to catalyze oxidation reactions in the food.

All fats in the food must be fresh and protected before they are transported and used: substances used in cat food are the same as those used in food for human consumption. They are selected on the basis of their safety and efficacy.

Packaging

To rule out the loss of aromas and oxidation the food is kept in an airtight pack totally devoid of oxygen, a technique called modified atmosphere packaging (Figure 4). The air is replaced by a neutral gas (nitrogen) during packaging. The food conserved in this way is protected as the bag is closed. After opening, the aromas are preserved properly by keeping the bag away from light and humidity at a constant, low temperature.

FIGURE 4 - PRINCIPLE OF THE CONTROLLED ATMOSPHERE



The air is made up of around 20% oxygen and 80% nitrogen. The modified atmosphere in the bag is 100% nitrogen, which prevents oxidation phenomena from taking place.

Immunity

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Nutrition and immunity

ABBREVIATIONS USED IN THIS CHAPTER

α **LA**: alpha linolenic acid
APC: antigen presenting cell
APR: acute phase response
ARA: arachidonic acid
CAM: cell adhesion molecule
CD80/CD86: costimulatory molecules
COX: cycloxogenase
DGLA: dihomo-γ-linolenic acid
EPA: eicosapentaenoic acid
FHV: feline herpes virus
HETE: hydroxyeicosatetraenoic acid
HPETE: hydroperoxy-eicosatetraenoic acid
IFN: interferon
Ig: immunoglobulin
IL: interleukin
iNOS: nitric oxide synthetase
LOX: lipoxogenase
LPS: lipopolysaccharide
LT: leukotriene
MHC: major histocompatibility complex
NF-κB: nuclear transcription factor
NK: natural killer cell
NO: nitric oxide
NOS: nitric oxide synthase
PAMPS: pathogen associated molecular patterns
PG: prostaglandin
PPAR: peroxisome proliferator-activated receptor
PUFA: polyunsaturated fatty acids
SIRS: systemic inflammatory response syndrome
TGF β: transforming growth factor
Th_1: lymphocyte Th_1
TLR: toll-like receptors
Th_2: lymphocyte Th_2
TNF-α: tumor necrosis factor
TX: thromboxane

Nutrition and immunity

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Nick Cave graduated from Massey University (New Zealand) in 1990 and worked in private practice for 7 years before completing a residency in internal medicine and Masters in Veterinary Science at Massey University. He then completed a residency in clinical nutrition and studied for a PhD in nutrition and immunology at the University of California, Davis, and became a diplomate of the American College of Veterinary Nutrition in 2004. He is now senior lecturer in small animal medicine and nutrition at Massey University.

There are few, perhaps no, diseases in which the pathogenesis does not in any way involve the immune system. The involvement may be primary as in hypersensitivities, secondary as in infectious diseases, or in more obscure and surprising ways such as in the effect of obesity on immunity. Immune function ranges from simple, innate, barrier defenses, through to complex, highly adaptive, antigen-specific multi-cellular responses.

From basic to complex, the immune system is, like any other body system, dependant on the appropriate supply of nutrients and sensitive to nutritional deficiencies and imbalances. But unlike other body systems, the rapid changes in nutrient requirements associated with cellular replication, cellular synthesis, and highly energetic activities makes the immune system very responsive to both long term and short term nutrition. Given the vital role that the immune system has both for the benefit, and in certain diseases the detriment of the animal, it is important to understand how nutrition affects immunity in health and disease. This chapter aims to explore some of the most important aspects of how nutrition affects immunity in cats.

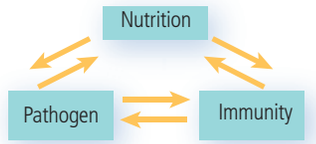
1 - Nutrition and immunity – Complex interactions

As indicated in **Figures 1 and 2**, nutrition directly affects the immune response. This can be in three general ways:
1. enhancement or exaggeration of the response
2. suppression or limitation of the response
3. changing the nature of the response

FIGURE 1 - NUTRITION AND IMMUNITY

The interaction between nutrition and immunity is complex and incompletely understood. An important basic concept is that the interaction is bi-directional.

FIGURE 2 - NUTRITION, PATHOGEN AND IMMUNITY



If one takes into account the specific pathogen or tumor cell that is initiating the immune response, the interaction becomes even more complex.

Whether a change is good or bad depends upon the specific disease state, and the individual patient. Attenuation of an immune response may be beneficial in hypersensitivity diseases (e.g. atopic dermatitis) or in overwhelming systemic immune activation (i.e. systemic inflammatory response syndrome or SIRS). Likewise, enhancement of an immune response may be desirable for prevention or elimination of infection, or immunity to tumor development.

In contrast, modulation of immunity can be detrimental or even fatal to the host. Immunosuppression in the face of infection can lead to prolonged morbidity or even overwhelming sepsis. Enhancement of immunity may lead to increased self-damage in states already characterized by excessive or poorly regulated immune activation (e.g. SIRS, hypersensitivity diseases). Clearly then, one diet cannot fit the needs of all.

To understand how nutrition can affect immunity, once must first understand the nature of immunity.

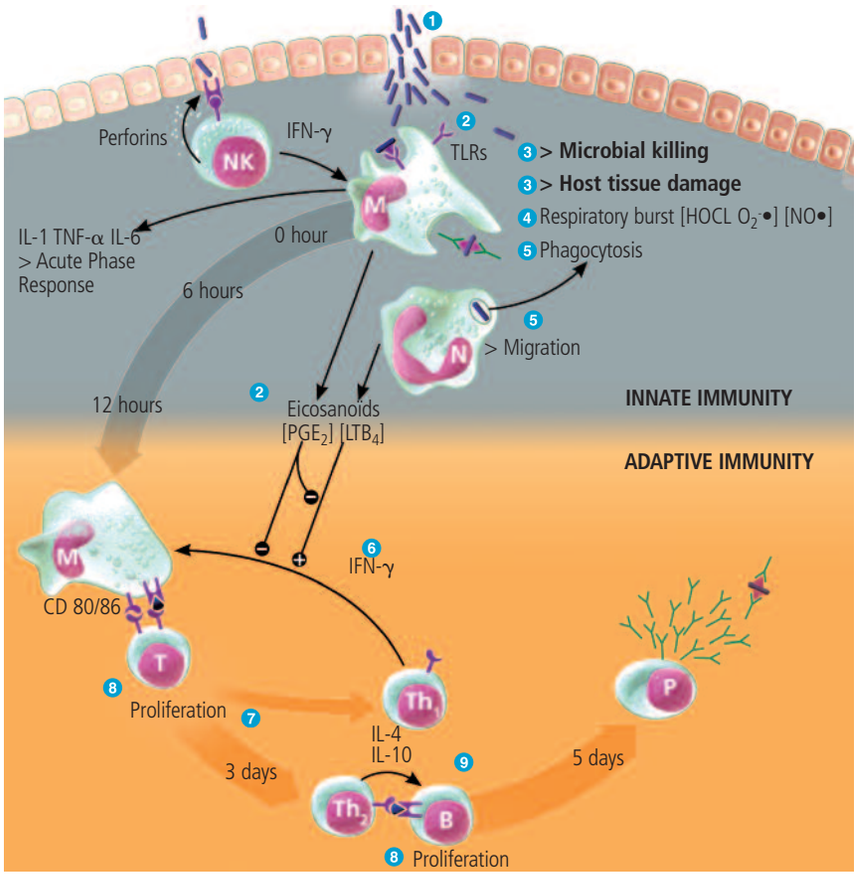
2 - The immune system

► Function

The immune system, in all its complexity, has evolved for the defense against infectious organisms from viruses, bacteria, and fungi, to large multicellular parasites. Immune responses range from non-specific barrier-type functions, to phylogenetically advanced, complex, adaptive responses that may involve destruction or elimination of the pathogen **(Figure 3)**. A perfect response to infection would result in elimination without self damage. Immune responses are never perfect however, and damage to the host always occurs, ranging from undetectable to disproportionate, and at its most extreme, fatal.

Remembering this basic concept is essential in interpreting the effect of nutrition on immunity.

FIGURE 3 - FEATURES AND FUNCTIONS OF INNATE AND ADAPTIVE IMMUNITY
Key points of nutritional modulation



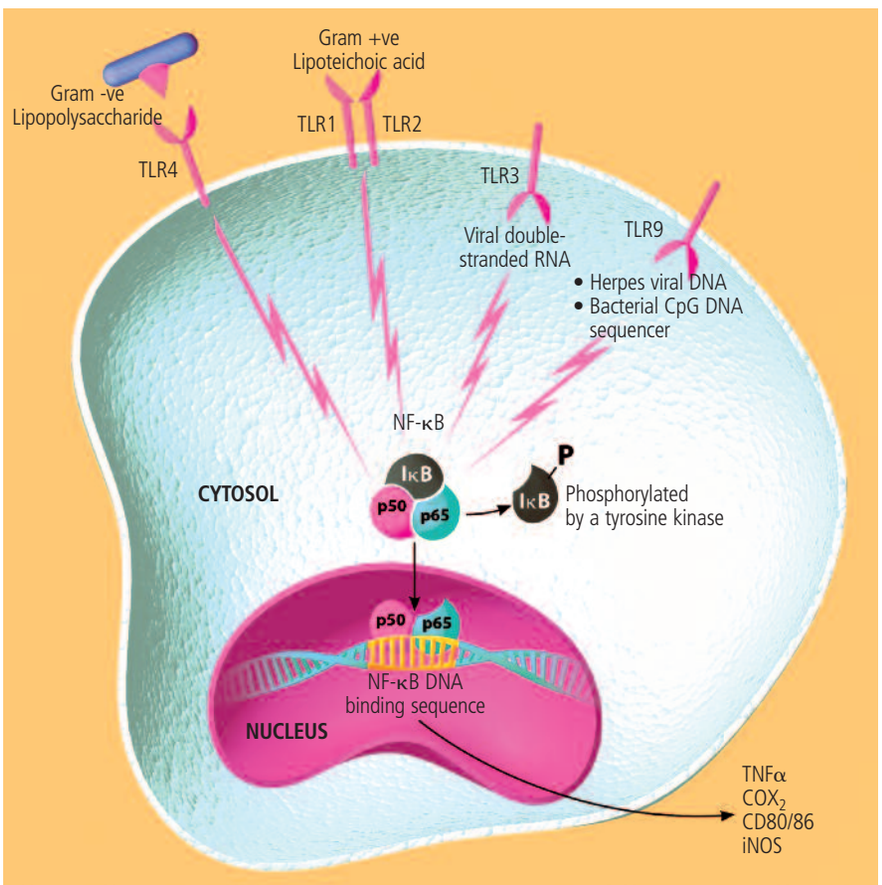
Site of effect: nutritional modification

1. Vitamin A, protein-energy malnutrition
2. Polyunsaturated fatty acids (PUFA)
3. Antioxidants, protein-energy malnutrition
4. Antioxidants, arginine, glutamine, genistein, carotenoids
5. Glutamine, genistein, iron
6. Lutein, genistein
7. Leptin, vitamin E, PUFA
8. Nutrients presented in **Table 2**, lutein, genistein (in cats?), copper, zinc
9. Lutein, vitamin A, iron

Table 1 - Key Components of Innate Immunity

Component	Examples	Functions
Epithelial secretions		Exclusion of infection, transport of antimicrobial molecules
Epithelial barriers		Exclusion of infection
Antimicrobial molecules	Defensins, lysozyme	Microbial killing
Natural antibodies	IgM	Opsonization, complement fixation
Phagocytes	Neutrophils, macrophages	Phagocytosis and killing of microbes
Killing cells	NK cells	Lysis of infected or neoplastic cells, activation of macrophages
Coagulation proteins	Thrombin	Physical confinement of microbes
Complement		Microbial killing, opsonization, chemotaxis, leukocyte activation
C-reactive protein		Opsonization

Figure 4 - Ligands and effects of Toll Like Receptors (TLR) signaling



One common signaling pathway after engagement of TLRs is the activation of the nuclear transcription factor NF-κB. The activated NF-κB dimer then diffuses into the nucleus where it promotes the transcription of a variety of pro-inflammtory genes.

► General aspects of immune responses

> Innate

Anatomical and physiological mechanisms that contribute to immunity and that are in place regardless of previous exposure, are referred to as "innate". Many of these mechanisms are phylogenetically ancient (e.g. lysozyme, phagocytes), whilst others are complex and have only evolved in vertebrates, becoming refined in mammalian species (e.g. natural killer cells) **(Table 1)**.

In mammals, the initial role of innate immunity is to exclude micro-organisms where possible. When infection occurs, the innate responses to the pathogen result in any, or a combination of:

1. elimination of infection
2. limiting the initial progression of infection (the "speed-bump" for initial infectious agents)
3. stimulation of adaptive immunity through the production of the early inflammatory response to infection. Thus innate immunity provides the "danger signals" that alert and activate adaptive immune responses.

Recognition of microbes

Cells of innate immunity have evolved receptors that recognize phylogenetically conserved molecules. These molecular patterns have been termed **pathogen associated molecular patterns** or "PAMPS". Examples of PAMPS are lipopolysaccharide (LPS) from gram negative bacterial cell walls, lipoteichoic acid from gram positive bacterial cell walls, and double-stranded RNA from viruses. The PAMP receptors include scavenger receptors, mannose receptors, and the family of Toll-like receptors (TLR) *(Akira, 2003)*. To date there are 10 known mammalian TLRs, although the expression of all 10 types has not yet been described in cats. Most TLRs are membrane proteins, although the TLR 9 binds to its ligand intracellularly (bacterial DNA). Binding of a TLR with its ligand results in the generation of the nuclear transcription factor NF-κB, which diffuses into the nucleus and binds to specific sites on the DNA of the host cell, leading to the transcription of a variety of pro-inflammatory genes. In macrophages and neutrophils these genes include cytokines (TNF-α, IL-1, and IL-12), adhesion molecules (E-selectin), cycloxogenase (COX), nitric oxide synthase (iNOS), and on macrophages the co-stimulatory molecules CD80 and CD86.

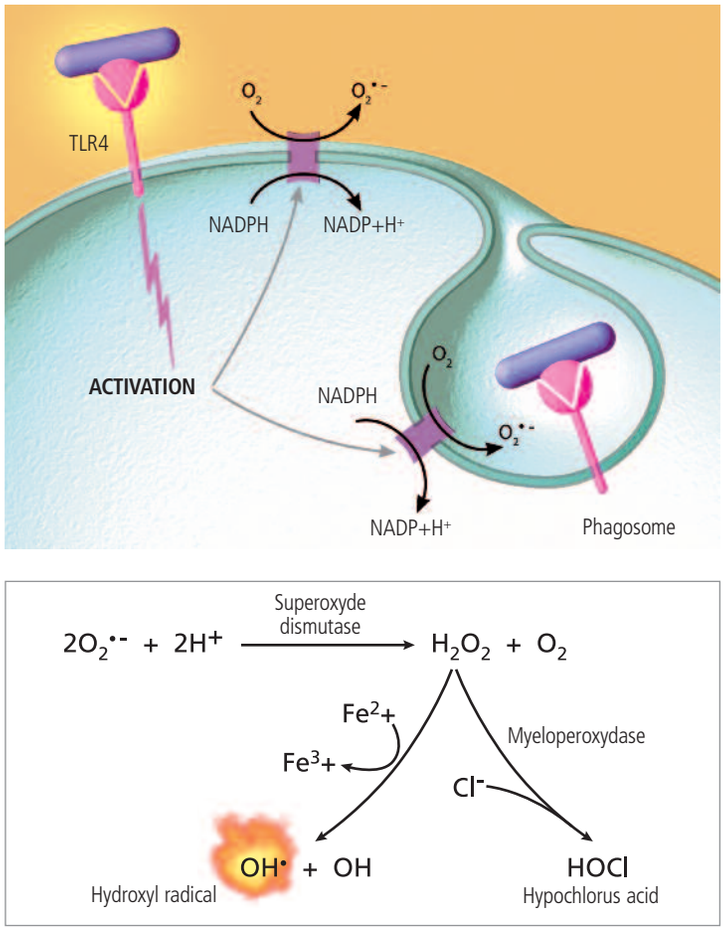
The net effect of TLR signaling in leukocytes is migration into inflamed tissues, enhanced killing of microbes or infected cells, and the production of inflammatory cytokines and chemokines to signal and activate the cells of the adaptive immune response **(Figure 4)**.

Killing of phagocytosed microbes

Phagocytosed microbes remain within the membrane bound phagosome in the cytoplasm. Once internalized, these phagosomes then fuse with preformed lysosomes, which contain several proteases (e.g. elastase). In addition, activation of the phagocyte (e.g. by signaling through TLRs) results in assembly of the multi-subunit machinery of the NADPH-oxidase in the phagosome membrane, and within the plasma membrane. This enzyme complex catalyses the reduction of diatomic oxygen (O_2) to the superoxide radical ($O_2^{\bullet -}$). The $O_2^{\bullet -}$ is then enzymatically dismutated to produce hydrogen peroxide, a potent oxidant that may be partially responsible for microbial killing. However, the presence of myeloperoxidase within the phagosome utilizes the peroxide to produce a more potent antibacterial, **hypochlorous acid** (HOCl). This process of producing powerful oxidants following activation and phagocytosis by neutrophils and macrophages rapidly utilizes large amounts of available oxygen and is termed the **respiratory burst (Figure 5)** *(DeLeo et al, 1999)*.

Following activation of the phagocyte, the inducible form of **nitric oxide synthetase** (iNOS) is also expressed, resulting in the production of the free radical **nitric oxide** (•NO), which reacts with superoxide to form the toxic metabolite peroxynitrite *(Eiserich et al, 1998)*. These various oxidants are not only confined to the phagosome, but are also released extracellularly to contribute to microbial killing in the immediate vicinity. Inevitably, this results in collateral oxidative damage to surrounding tissues.

FIGURE 5 - RESPIRATORY BURST AND HOCL PRODUCTION



A: NADPH oxidase is assembled at the outer and phagosome membranes to produce extra and intracellular superoxide (O_2^-).
B: Superoxide will then be dismutated to H_2O_2 which will react with a transition metal (Fenton reaction) to form the highly reactive hydroxyl radical (OH^-), or to be converted into hypochlorus acid ("bleach").

To protect themselves from massive autogenously derived oxidative damage, phagocytes require greater concentrations of cytosolic (aqueous) and membrane (lipophilic) antioxidants, which are degraded and rapidly replenished during the respiratory burst. The most important antioxidants in this regard appear to be glutathione, ascorbate, tocopherol, and taurine. Feline neutrophils contain high intracellular concentrations of taurine. In fact, taurine constitutes 76% of the free amino acid cytosolic pool, compared with 44% in lymphocytes *(Fukuda et al, 1982)*. Elimination of HOCl by the conversion of taurine to taurine chloramine protects cells against endogenously created oxidants. It has been also suggested that the taurine chloramine may also act as an intracellular signaling molecule that limits further $O_2^{\bullet -}$ and •NO production.

However, in cats maintained on taurine deficient diets, suppression of both phagocytosis and respiratory burst activity by neutrophils occurs, consistent with its role primarily as an antioxidant *(Schuller-Levis et al, 1990)*.

Natural killer cells

Natural killer cells (NK cells) are large granular lymphocytes, distinct from T and B lymphocytes. NK cells are responsible for the identification and killing of virally infected and neoplastic cells,

without prior exposure (sensitization). NK cells lyse target cells by releasing granules of the enzymes perforin, which creates pores in cell membranes, and granzyme, which enters the perforated cell and induces programmed cell death (apoptosis). Activated NK cells are also important secretors of IFN-γ, and are thus important activators of macrophages in the vicinity, increasing their phagocytic and respiratory burst capabilities.

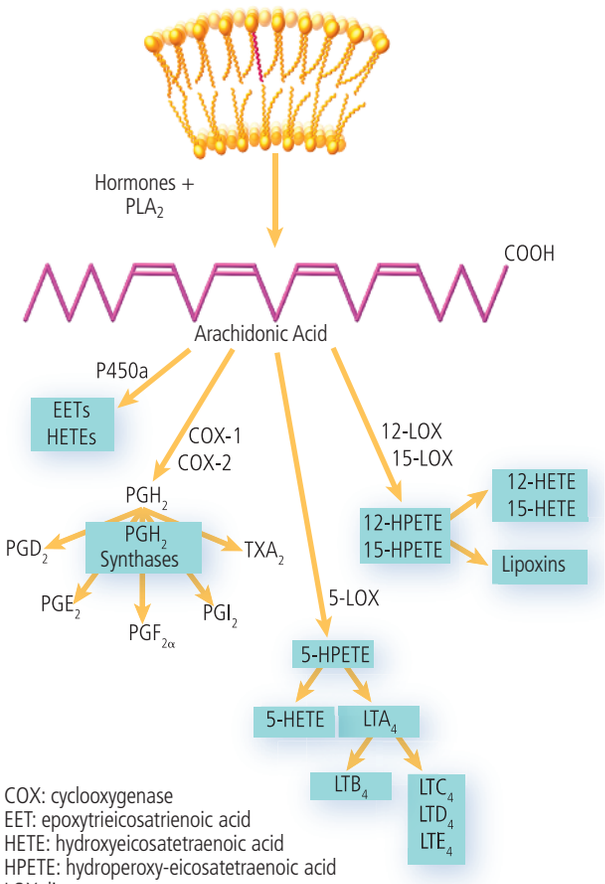
> Adaptive immunity

Adaptive immunity is stimulated by infection, and by signaling from the innate immune system. With subsequent re-exposure to the infectious organism, the magnitude, specificity, and speed of the response increases, hence the term **adaptive immunity**. Adaptive immunity is the domain of the T and B lymphocytes, whereby humoral (antibody) responses or cellular responses are generated against specific molecules termed **antigens (Figure 3).**

> Eicosanoids

Eicosanoids are a group of lipid messengers synthesized from the 20-carbon polyunsaturated fatty acids (PUFA) dihomo-γ-linolenic acid (DGLA; 20:3n-6), arachidonic acid (ARA; 20:4n-6) and eicosapentaenoic acid (EPA; 20:5n-3). Eicosanoids include prostaglandins (PGs), thromboxanes (TXs), leukotrienes (LTs), lipoxins, hydroperoxy-eicosatetraenoic acids (HPETE) and hydroxyeicosatetraenoic acids (HETE).

FIGURE 6 - THE PRODUCTION OF EICOSANOIDS FROM FATTY ACID PRECURSORS RELEASED FROM CELL MEMBRANE PHOSPHOLIPIDS BY THE ACTION OF PHOSPHOLIPASE A2



COX: cyclooxygenase
EET: epoxytrieicosatrienoic acid
HETE: hydroxyeicosatetraenoic acid
HPETE: hydroperoxy-eicosatetraenoic acid
LOX: lipoxogenase
LT: leukotrienes
PG: prostaglandins
TX: thromboxanes

The fatty acid precursor for eicosanoid synthesis is released from cell membrane phospholipids, usually by the action of phospholipase A2, which is activated in response to a noxious cellular stimulus **(Figure 6)**. Generally, the membranes of cells in cats on most commercial diets contain 5 to 10 times more ARA than EPA; thus ARA is usually the principal precursor for eicosanoid synthesis, giving rise to the 2-series PGs and TXs, and the 4-series LTs *(Plantinga et al, 2005)*. However, the exact proportion of other 20 carbon PUFA in cell membranes is determined by the relative proportions of them, and their shorter 18 carbon precursors in the diet of the animal.

PGE_2 has a number of pro-inflammatory effects including inducing fever, increasing vascular permeability and vasodilation and enhancing pain and edema caused by other agents such as histamine *(Harris et al, 2002)*. PGE_2 suppresses lymphocyte proliferation and natural killer cell activity and inhibits production of tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-2 and interferon (IFN)-γ In these respects then, PGE_2 is also immunosuppressive and anti-inflammatory. PGE_2 does not affect the production of the Th2-type cytokines IL-4 and IL 10, but promotes immunoglobulin E (IgE) production by B lymphocytes. Therefore PGE_2 supports a Th2-biased adaptive response, and inhibits Th1 responses.

LTB_4 increases vascular permeability, enhances local blood flow, is a potent chemotactic agent for leukocytes, induces release of lysosomal enzymes, enhances the respiratory burst, inhibits lymphocyte proliferation and promotes natural killer cell activity. LTB_4 enhances production of TNFα, IL-1 and IL-6 by monocytes and macrophages, and enhances Th1 cytokine production.

To add to the complexity, PGE_2 inhibits 5-lipoxogenase, thereby interfering with production of LTB_4, and ARA also gives rise to anti-inflammatory lipoxins. Thus, eicosanoids are pro- as well as anti-inflammatory, and together they regulate inflammation. The overall effect will depend upon the timing of production of the different eicosanoids, the sensitivity of target cells, and the concentrations of the different eicosanoids produced.

3 - Nutritional requirements for immunity

► During the development period

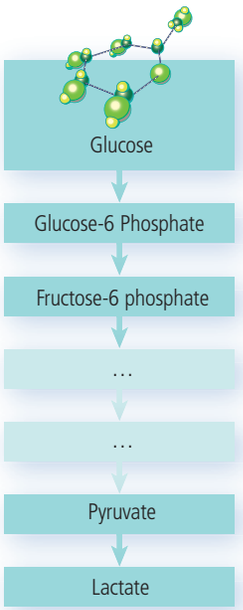
The first and perhaps most significant effect of nutrition on immunity occurs during the development of the immune system *(Cunningham-Rundles et al, 2005)*. Cells of the immune system develop in utero, but this is followed by an important period of maturation soon after birth, continuing to develop throughout life. Deficiencies of zinc, protein, essential amino acids, vitamin A, and copper are only some of the many nutritional variables that can impair development of the immune system in young, growing animals. Micronutrient deficiencies affect the adaptive immune responses, and innate responses **(Table 2)**. Thymic and splenic lymphocyte numbers can be greatly reduced by maternal deficiencies, most notably zinc. Serum antibody responses in young animals to vaccination can be affected by maternal deficiencies of nutrients such as of zinc, iron, copper, selenium, and magnesium.

The net effects of malnutrition during development are altered microbial colonization of mucosal surfaces, impaired responses to commensals and pathogens, increased susceptibility to infection, and decreased ability to resolve infection once established. Such defects may last well beyond the initial period of malnutrition and alter an animal's immunophenotype for life.

Table 2 - The effects of specific nutrient deficiencies on immunity

Primary nutrient deficiency	Immunological defects	Clinical manifestation
Zinc	Thymic atrophy, lymphopenia, altered T-lymphocyte differentiation, reduced Th1 cytokine production, decreased antibody production	Diarrhea, increased susceptibility to infection from skin commensals
Copper	Lymphopenia, reduced lymphocyte proliferation	Neutropenia, anemia
Selenium	Decreased, increased viral virulence??	Increased susceptibility to infection, increased organ oxidative damage
Iron	Decreased humoral responses, decreased phagocytosis and respiratory burst, reduced T-lymphocyte proliferation	Anemia, increased susceptibility to infection
Vitamin E	Increased IgE, increased PGE_2 production	Increased atopic disease signs? Increased organ oxidative damage
Vitamin A	Mucosal barrier defects (squamous metaplasia), Lymphopenia, depressed antibody production, decreased Th2 responses, depressed neutrophil and macrophage maturation	General increased susceptibility to infection - especially respiratory infections, diarrhea
Protein	Impaired cell mediated responses, decreased cytokine production	General increased susceptibility to infection
Protein – energy malnutrition	Thymic atrophy, reduced lymphoid tissue mass (lymph nodes), decreased circulating T-lymphocytes and B-lymphocytes, Impaired cell mediated responses, decreased cytokine production, reduced neutrophil migration	General increased susceptibility to infection from exogenous and endogenous sources, increased morbidity and mortality, diarrhea (villous blunting, chronic enteritis)

FIGURE 7 - ANEROBIC GLYCOLYTIC PATHWAY



► Essential nutrients for fuel

> Glucose

Glucose is essential for monocytes, neutrophils, and lymphocytes. Following activation of macrophages and neutrophils, or stimulation of lymphocyte proliferation, glucose oxidation increases dramatically, although it is only partially oxidized, with lactate being the predominant end product **(Figure 7)**. Glutamine is another vital fuel for both cell types, and at rest, may account for more than 50% of ATP production by these cells. Like glucose, glutamine is only partially oxidized, with glutamate, aspartate, and lactate as the end products, and only a small amount being oxidized completely to CO_2, H_2O, and NH_3. Although fatty acids and ketones can be oxidized for ATP production, cellular activation and proliferation of leukocytes does not increase the rate of usage of either substrate *(Newsholme et al, 1987; Newsholme & Newsholme, 1989)*.

Incomplete oxidation of glucose and glutamine occurs despite the presence of mitochondria and functioning citric acid cycles. This is consistent with the need for these cells to operate in areas of low oxygen availability (e.g. ischemic tissue, or unvascularized spaces). The high rates of glucose and glutamine utilization is partly to provide intermediates for the biosynthesis of purine and pyrimidine nucleotides which are required for the synthesis of DNA and mRNA by these cells, and partly to maintain high rates of metabolic flux through the pathways to allow for rapid large changes in utilization that follows activation.

> Glutamine

Plasma glutamine concentrations affect the susceptibility of cells to different apoptosis triggers: where glutamine-starving cells are more sensitive to apoptosis *(Oehler and Roth, 2003)*. In contrast, glutamine may protect activated T cells from apoptosis. A similar protective effect against apoptosis has been demonstrated in neutrophils, in which glutamine also appears to positively regulate the expression of the NADPH oxidase. The immunosuppressive effect of asparaginase has been shown to be due to its ability to hydrolyse glutamine, rather than to the reduction of asparagines *(Kitoh et al, 1992)*. In addition, states associated with low plasma glutamine concentrations are also associated with suppression of both innate and adaptive immunity.

Plasma glutamine is almost entirely derived from skeletal muscle, since dietary glutamine is either utilized by the intestine or the liver, and plasma glutamine only rises very slightly following a meal. During inflammatory responses, muscle catabolism increases in response to low plasma insulin, or muscle insulin resistance induced by cortisol and catabolic cytokines *(Kotler, 2000)*. This provides a source of glutamine both for hepatic gluconeogenesis, but also directly to leukocytes. Thus feeding in systemic inflammatory disease states with glutamine free amino acid sources would be expected to inhibit muscle glutamine release, suppress plasma glutamine concentrations, and thus lead to relative immunosuppression. Conversely, glutamine supplementation enhances macrophage phagocytic activity, helps maintain circulating T lymphocyte numbers, and normalizes lymphocyte function in models of severe sepsis. Predictably, glutamine supplementation of TPN solutions has been shown to reduce morbidity in some septic human patients *(Fuentes-Orozco et al, 2004)*.

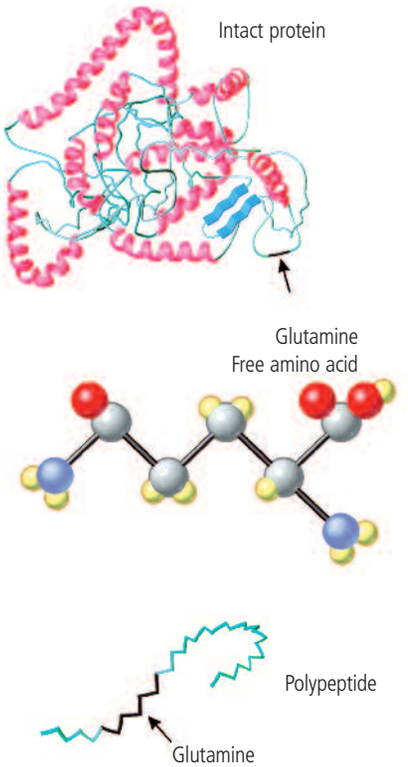
When glutamine is supplemented orally, the form of glutamine that is administered is important. Glutamine utilization is significantly more efficient when glutamine is consumed as part of a polypeptide than when it is consumed as a free amino acid *(Boza et al, 2000)*.

GLUTAMINE ABSORPTION

Absorption and utilization of amino acids differs when they are fed as free amino acids or as part of intact polypeptides. A mixture of small peptides is of greater nutritive value than a mixture of free amino acids with a similar composition for both growth and recovery from malnutrition. When starved rats are re-fed, body weight gain is greater, and the plasma concentration of total amino acids -especially glutamine- is significantly higher in rats fed a whey protein hydrolysate-based diet compared with those fed an amino acid-based diet *(Boza et al, 2000).*

In addition, energy conversion efficiency, protein efficiency ratio, and nitrogen retention are significantly higher in hydrolysate-fed rats. In humans, the glutamine concentration in the duodenal mucosa increases with the enteral supplementation of glutamine-rich proteins compared with a free glutamine solution, despite there being no difference in plasma glutamine concentrations *(Preiser et al, 2003).* Potential explanations for these findings include poor solubility of certain free amino acids in the intestinal lumen, rapid absorption of free amino acids leading to an increase in hepatic oxidation, altered intestinal oxidation, and increased catabolism by intestinal flora of free amino acids over polypeptides.

Glutamine can be fed as a free amino acid supplement, as part of a polypeptide in a hydrolysed protein diet, or as part of an intact protein in a conventional food protein source. The combination of glutamine availability, digestibility, and reduced antigenicity may make moderately hydrolysed protein diets ideal for enteral feeding in severe inflammatory disease states.



► Cell division

Other than essential amino acids and sufficient substrate for fuel, several vitamins are required for leukocyte function and replication **(Table 3)**. During an immune response, this is particularly important for lymphocytes.

Deficiencies in any of the essential nutrients listed in **Table 2** will limit cell proliferation, and hence alter cell mediated and humoral immune responses.

Glutamine warrants special mention again, since its availability is often reduced in severe illness, and low plasma concentrations are correlated with morbidity in humans and experimental studies. The major use of glutamine by replicating lymphocytes is not simply as a fuel, but also for nucleotide synthesis **(Figure 8)**, whereby low glutamine concentrations inhibit, and increased concentrations stimulate lymphocyte proliferation following stimulation. In addition, this effect of glutamine on replicating lymphocytes is enhanced by the amino acid arginine.

FIGURE 8 - GLUTAMINE AND CELLULAR REPLICATION

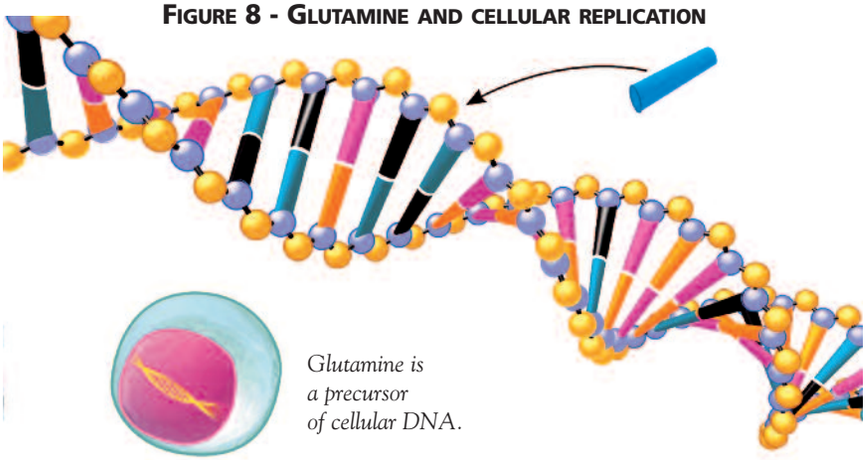
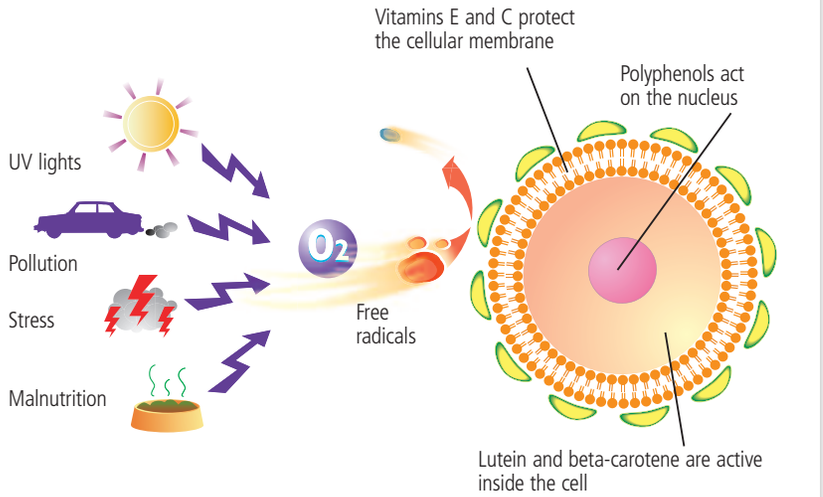


TABLE 3 - KEY NUTRIENTS FOR LEUKOCYTE REPLICATION

Vitamins	Other compounds
Biotin	Choline
Folic acid	Inositol
B_{12}	Para-amino benzoic acid
Pyridoxine	Glutamine
Riboflavin	
Thiamine	
Pantothenic acid	
Niacin	

FIGURE 9 - ANTIOXIDANTS: MODE OF ACTION



► Antioxidants

Generally speaking, dietary antioxidants fulfill two roles in immune responses. Firstly they protect leukocytes against endogenously derived free radical damage, and secondly they protect the host against bystander damage from the same free radicals **(Figure 9).** The requirement for increased intracellular antioxidant capacity in neutrophils and macrophages has been discussed above. This requirement is met by taurine, glutathione, ascorbate, and tocopherol. Glutathione plays a pivotal role as an antioxidant both through direct interaction with free radicals, but also as a substrate for the regeneration of ascorbate. Glutamine availability can limit glutathione production, and supplementation of glutamine can increase superoxide production by neutrophils.

In addition, several other dietary antioxidants have been shown to have an effect on immunity. Notable amongst them, are the carotenoids **(Figure 9)**. Both β-carotene and lutein are incorporated into lymphocytes and neutrophils of both cats and dogs, especially mitochondrial membranes, where they probably function to protect the lipid membranes from endogenous free-radical damage *(Chew & Park, 2004)*.

Extracellular (plasma) antioxidants are also important for limiting damage to whole tissues and the vascular endothelium during an immune response. Taurine, ascorbate, tocopherol, glutathione, and carotenoids, all contribute to whole organ defense against free radicals produced by activated phagocytes.

4-Effects of malnutrition on immunity

► Starvation

Starvation leads to atrophy of lymphoid organs, decreased numbers and function of circulating leukocytes, and physical and functional defects in the epithelial barriers **(Table 3)**. The net result is an increase in susceptibility to infection from both endogenous sources such as skin and intestinal commensals, and exogenous sources such as nosocomially derived organisms.

In dogs, starvation results in decreased circulating lymphocyte numbers, decreased lymphocyte proliferation in response to stimulation, and impaired ability to generate antigen-specific T-lymphocyte and B-lymphocyte responses to exogenously administered antigens. Neutrophil chemotaxis, and hepatic production of acute phase proteins is reduced *(Dionigi et al, 1977)*. Deficiencies of specific nutrients can produce various defects including vitamin E deficiency, which in dogs has been shown to reduce lymphocyte proliferation, an effect that is only partially restored by supplementation with other antioxidants *(Langweiler et al, 1983)*. Although the effects of malnutrition on immunity have not been specifically evaluated in cats, it is unlikely to be significantly different from other species. Serum albumin concentration correlates strongly with body condition score in cats presenting to veterinary hospitals, and it is likely that immune-indices are likewise decreased *(Chandler & Gunn-Moore, 2004)*.

► Leptin

Leptin receptors are expressed on many leukocytes including lymphocytes, monocytes, and neutrophils. Leptin has many influences on adaptive immunity, such as inducing a switch towards Th1-biased responses by increasing IFN-γ and TNF-α secretion, and by suppressing Th2-lymphocyte responses. Leptin promotes the generation, maturation and survival of thymic T cells, and it increases the proliferation of, and IL-2 secretion by, naive T cells. Thus during starvation or prolonged periods of weight loss, suppressed leptin secretion probably contributes to the immunosuppressive state, which can be corrected with either leptin administration or recovery of body fat mass *(Meyers et al, 2005)*.

► Obesity

No studies have yet evaluated immune function in obese cats; It is expected that obesity in cats will result in similar alterations in immunocompetence as have been recognized in obese humans, and many studies of experimental obesity in rodents.

In species studied to date, reductions in lymphocyte responses to stimulation are seen in obesity and the normalization of these responses have been reported following weight reduction. Reduced NK cell function, altered CD8: CD4 lymphocyte ratios, and reduced respiratory burst activity by neutrophils have been described in obese humans and rodents.

Perhaps paradoxically, obesity in humans and experimental models is increasingly recognized as a state associated with chronic inflammation. Obesity is characterized by increased circulating inflammatory cytokine concentrations and increased acute phase protein production *(Tilg & Moschen, 2006)*. The inflammatory cytokines are produced from activated macrophages within the excessive adipose tissue, but also from excessively full adipocytes themselves. The subclinical low-grade inflammation contributes to peripheral insulin resistance in humans, and may do so in obese cats as well.

5 - Effects of immune responses on nutritional status

Immune responses to infection, neoplasia, or as the result of immune-mediated disease, can affect the nutritional status of the patient **(Table 4)**.

► Anorexia

An almost universal finding in significant inflammatory disease states is a disturbance in food intake that ranges from a suppressed appetite to complete anorexia. This loss of appetite is considered part of the acute phase response. Inflammatory cytokines are important mediators of the suppression of food intake, particularly IL-1, IL-6, and TNF-α *(Langhans, 2000)*. The site of action of cytokines can be on central nuclei (hypothalamus) or on peripheral nerves that then produce ascending signals through sensory afferent pathways to central feeding centers.

The fact that anorexia of infection is an almost universal effect in all mammalian species, suggests that it might have a benefit. In support of this notion is the observation that force feeding of anorexic septic mice increases mortality, and in those that survive, the time

TABLE 4 - THE EFFECTS OF IMMUNE RESPONSES ON NUTRITIONAL STATUS

	Mechanisms	Sequelae or examples
Depressed food intake	IL-1, IL-6, TNF-α: CNS and peripheral effects	Weight loss, loss of lean body mass, loss of fat mass, nutrient deficiency
Impaired nutrient absorption	Villous atrophy, enteritis	Decreased fat soluble vitamin absorption, vitamin B_{12} deficiency
Increased loss	Enteritis, increased glomerula permeability	Hypoproteinemia, vitamin A deficiency
Increased requirements	Fever, leukocyte replication, tissue repair	Increased glutamine, tocopherol, folic acid, vitamin A, energy requirements?
Altered metabolism and systemic transport		Insulin resistance and hyperglycemia, hyperlipidemia, decreased serum glutamine

Table 5 - Serum analytes that change during an acute phase response (acute phase reactants)

Positive acute phase reactants in mammals	Negative acute phase reactants in mammals
TNF-α, IL-1, IL-6,	*Retinol binding protein*
Cortisol	Albumin
C-reactive protein, Serum amyloid A, fibrinogen, haptoglobulin, ceruloplasmin	Transferrin
Cu	Fe, Zn, Ca

to survival is increased *(Murray & Murray, 1979)*. This deleterious effect of over-nutrition in sepsis and other systemic inflammatory responses has been confirmed in other species, including humans (see below).

These findings suggest that in seriously ill septic patients, consideration should be given to the risks of overfeeding, as well as what might constitute an ideal dietary composition. Thus although it is not suggested that starvation is preferable to supportive nutrition in severe infection, it is important that one considers how the evolved response of anorexia and the associated metabolic derangements might be instructive in formulating ideal diets for sepsis.

► The acute phase response

The acute phase response (APR) is a prominent systemic reaction of the organism to local or systemic disturbances in its homeostasis caused by infection, trauma or surgery, neoplasia, or immune mediated diseases. Cytokines activate receptors on different target cells leading to a systemic reaction resulting in activation of the hypothalamic-pituitary-adrenal axis, reduction of growth hormone secretion and a number of physical changes clinically characterized by fever, anorexia, negative nitrogen balance and catabolism of muscle cells *(Gruys et al, 2005)*. Other effects on endocrine and nutritional parameters include a decrease in HDL and LDL, increased ACTH and glucocorticoids, decreased serum levels of calcium, zinc, iron, vitamin A and of α-tocopherol, and a change in concentration of several plasma proteins **(Table 5)** *(Gruys et al, 2005)*.

The acute-phase response to injury or infection is associated with alteration in dynamics of many trace elements, particularly iron, zinc and copper. The fall in serum iron and zinc, and rise in serum copper, is brought about by changes in the concentration of specific tissue proteins controlled by cytokines, especially IL-1, TNF-α, and IL-6. These are generally believed to be beneficial aspects of the early acute phase response.

In addition to the decrease of serum zinc, iron and albumin, a decrease of transferrin, cortisol-binding globulin, transthyretin (TTR) and retinol-binding protein have been described. The resulting disturbance in vitamin A metabolism that occurs in chronic infestation and inflammatory states worsens the vitamin A deficiency that is seen in children and pregnant mothers in developing countries from malnutrition *(Stephensen, 2001)*. Vitamin A deficiency has a well-known negative feedback effect on immunity, producing one of the best described immunosuppressive effects of malnutrition.

► Cachexia

Starvation (simple energy deprivation) is accompanied by metabolic adaptations to ensure essential nutrients are available for vital organs. Starvation results in decreased insulin secretion and a moderate increase in cortisol, leading to muscle catabolism and lipolysis. Lipolysis liberates fatty acids which are picked up by the liver, packaged into lipoproteins (VLDL), and exported back out into the circulation along with ketone bodies for utilization as fuel by the majority of cells in the body. Amino acids released from muscle are used by the liver for the synthesis of essential proteins (e.g. clotting proteins), and by the kidney and liver to synthesize glucose for those tissues dependant upon it (e.g. leukocytes, erythrocytes). As tissues (e.g. the brain) adapt to utilizing ketones in preference to glucose, the release of amino acids from muscle slows, and lean body mass is preserved. All of the metabolic adaptations can be reversed with feeding.

Severe inflammatory responses also induce a collection of metabolic derangements that result in accelerated lipolysis and muscle catabolism, producing wasting that is not explained solely by a decrease in food intake **(Table 6)**. The defining difference between starvation and cachex-

ia, is that in cachexia, forced feeding will not reverse the derangements, will not preserve the loss in lean body mass, and results only in fat accumulation. Cachexia has been shown to occur in association with sepsis, non-septic inflammatory disease, neoplasia, and cardiac failure. Cachexia accounts for 30-80% of cancer-related deaths in humans (diaphragmatic failure, edema, immune compromise) *(Kotler 2000)*.

Inflammatory cytokines, particularly IL-6, TNF-α, and IL-1, are largely responsible for the derangements, and produce both local effects at the site of inflammation, but also endocrine effects (IL-6).

For instance, in severe infection, circulating TNF-α is an important inducer of accelerated lipolysis, and by up-regulating the ubiquitin-proteosome system, is largely responsible for the disproportionate muscle catabolism associated with cachexia *(Camps et al, 2006)*. In addition to generalized muscle catabolism, the metabolism of individual amino acids can be deranged. In FIV infected cats, similar to human HIV-AIDS patients, the IFN-γ produced in response to the infection stimulates accelerated tryptophan catabolism and a decrease in serum tryptophan concentrations *(Kenny et al, 2007)*. The exact consequences of this metabolic response are uncertain so far, although it does raise the possibility that supplementation with tryptophan metabolites such as niacin or melatonin might have some therapeutic benefit in FIV-infected cats.

TABLE 6 - METABOLIC DIFFERENCES BETWEEN SIMPLE STARVATION AND CACHEXIA

Parameter	Starvation	Inflammation/Cachexia
Body weight	–	⇩ or no change
Body fat	⇩⇩⇩	⇩⇩
RER	⇩⇩⇩	⇧ or no change
MER	⇩⇩⇩	⇩
Protein synthesis	⇩⇩⇩	⇧ ou ⇩
Protein degradation	⇩⇩	⇧⇧⇧
Serum insulin	⇩⇩	⇧⇧⇧
Serum cortisol	No change	⇧⇧⇧
Serum glucose	No change	⇧⇧⇧
Serum lipids	⇧ VLDL, ⇧ fatty acids ⇧⇧⇧ ketones	⇧⇧ VLDL, ⇧⇧ fatty acids ⇩ ketones

In inflammatory diseases, there is an exaggerated secretion of insulin in response to feeding, but most cells in the body (especially the liver) are resistant to the effects. This resistance prevents utilization of precious glucose and preserves blood glucose for essential tissues (brain, erythrocytes, leukocytes). There is a massive increase in cortisol which induces a large breakdown of fat and muscle, increasing the delivery of free fatty acids and amino acids to the liver, and greatly increasing muscle and visceral protein breakdown. Since the liver is resistant to insulin, feeding does little to prevent it from continuing to produce glucose, and hyperglycemia results *(Andersen et al, 2004)*.

► Risks of over feeding and hyperglycemia

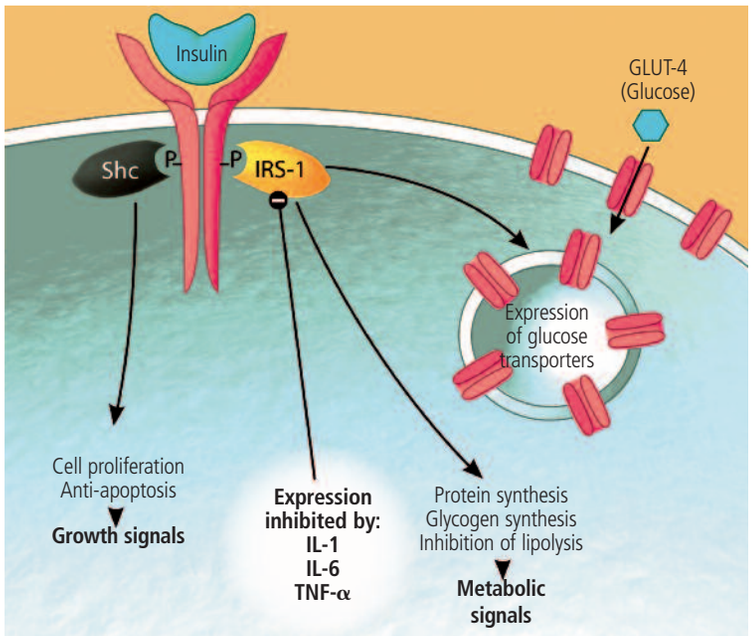
> Hyperglycemia – more than a number?

Therefore, any serious acute illness can result in:
- hyperglycemia
- insulin resistance
- increased hepatic glucose production.

This has been termed the "Diabetes of injury". Previously this insulin resistance and hyperglycemia was thought to be an adaptive response promoting glucose uptake by essential tissues and prevention of uptake by muscle. Thus moderate hyperglycemia has been tolerated by veterinary and medical clinicians.

In 2001, a study of 1548 human intensive care patients was instigated to determine if there was any benefit to tightly controlling blood glucose in severe illness *(van den Berghe et al, 2001)*. Blood glucose was controlled with intensive insulin therapy to less than 6 mmol/L (110 mg/dL). Amazingly there was a 43% reduction in mortality in all patients, and even in "long stay"

Figure 10 - Metabolic effects of insulin on the cells



In systemic inflammatory states, cytokines reduce the expression of the insulin-receptor substrate (IRS-1), which prevents glucose transporter (GLUT-4) expression and produces peripheral insulin resistance. However, other signaling pathways that promote cellular proliferation and inhibit apoptosis still occur. The persistant hyperinsulinemia in response to the hyperglycemia leads to exaggerated signaling down growth pathways and cellular dysfunction.

patients, mortality was reduced by 10.6%. In addition there was:
- shortened hospitalization
- reduced nosocomial infections
- reduced acute renal failure
- reduced anemia
- fewer cases of liver failure
- less multiple organ dysfunction
- reduced muscle weakness.

Although no similar studies have been performed in feline patients, a "stress-hyperglycemia" is a very common finding in seriously ill cats. In critically ill dogs, hyperglycemia is also common, and hyperglycemia at presentation is associated with increased duration of hospitalization, and the occurrence of sepsis was more frequent in hyperglycemia dogs than normoglycemic dogs *(Torre et al, 2007)*. Finally, canine patients not surviving hospitalization had a higher median glucose concentration compared with those surviving to discharge *(Torre et al, 2007)*.

> Is glucose toxic?

Hyperglycemia is not normally toxic in the short term. Normally, cells are relatively protected from hyperglycemia by down-regulation of glucose transporters. However, although the insulin secreted in inflammatory states does not result in reducing blood glucose, it does lead to other signaling effects within cells (**Figure 10**). Thus hyperglycemia stimulates continued insulin release which signals to many cell types to undergo metabolic changes associated with the post-prandial state, that are inappropriate in a diseased state. These alterations have been confirmed in canine sepsis.

In addition, although there is a relative insulin resistance, some glucose is forced into some cells leading to cellular glucose overload in neurons, endothelium, alveoli, vascular smooth muscle, and renal tubule cells.

This combination of exaggerated insulin signaling and glucose overload leads to:
- acute renal failure
- accelerated removal of erythrocytes and anemia
- polyneuropathy, brain edema, depression, seizures
- immunosuppression, decreased phagocytosis and killing
- increased sepsis
- increased vascular permeability, decreased responsiveness, activation, coagulation, disseminated intravascular coagulation.

> Recommendations for feeding in severe inflammatory diseases

Clearly feeding excessive carbohydrate will exacerbate hyperglycemia and increase morbidity, whilst feeding excessive fat exacerbates hepatic load and leads to fatty liver development and liver dysfunction. The recommendations for feeding in severe inflammatory diseases are presented in **Table 7**.

Table 7 - Recommendations for feeding in severe inflammatory diseases

- Feed no more than RER until there is a demonstration of weight loss.
> BUT – ensure that the RER is being fed.
- Monitor for hyperglycemia and hyperlipidemia.
> If either are identified, reduce intake but keep feeding the gut
- Feed a high protein, high fat diet
> BUT consider the possibility of fat malabsorption
- Start with 25% RER for first 24 hours,
> then 50%, then 75%, then 100%.
- Weigh daily.

6 - Immune response to dietary antigens (oral tolerance)

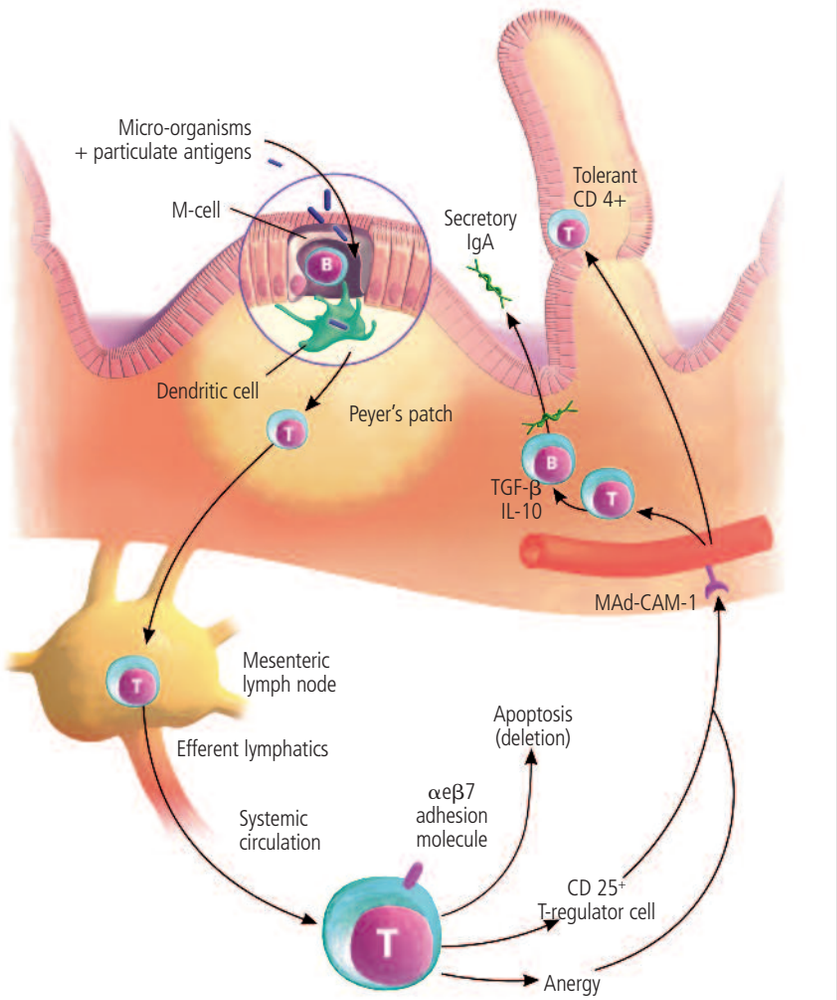
► Immunological basis for oral tolerance

Foreign dietary antigens interact with the intestinal immune system in such a way as to prevent unnecessary and detrimental immune reactions to them. In so doing, systemic immunity is rendered effectively unresponsive if the same antigen reaches the systemic circulation. This absence of reactivity to orally administered antigens is termed oral tolerance. Oral tolerance is generated in an antigen-specific and active manner that involves the induction of an atypical immune response.

Peyer's patches are the primary inductive area of the intestinal immune system. The specialized M-cells within the epithelium overlying the lymphoid follicles sample, unspecifically or by receptor-mediated uptake, particulate and insoluble antigens, and whole microorganisms *(Brandtzaeg, 2001)*. Antigens and organisms are then transported to leukocytes that reside within basal membrane invaginations, namely B-cells, macrophages, and dendritic cells. In the normal intestine these antigen presenting cells (APCs) lack co-stimulatory molecules such as CD80 and CD86. Antigens processed by these "un-activated" APCs are then presented to naïve B and T cells within the follicle, which then proliferate poorly. This occurs within a local microenvironment that differs from other sites in the body and results in induction of hyporesponsive, Th3 or Th2 biased T cells *(Kellermann & McEvoy, 2001)*. Activated cells then leave via lymphatics and pass via the mesenteric lymph nodes into the systemic circulation. They will then exit at mucosal sites via engagement of cell adhesion molecules (CAMs) specifically expressed by the high-endothelial venules of mucosal tissues. Thus activated or memory B and T lymphocytes enter the lamina propria to await a secondary encounter with their specific antigen **(Figure 11)**.

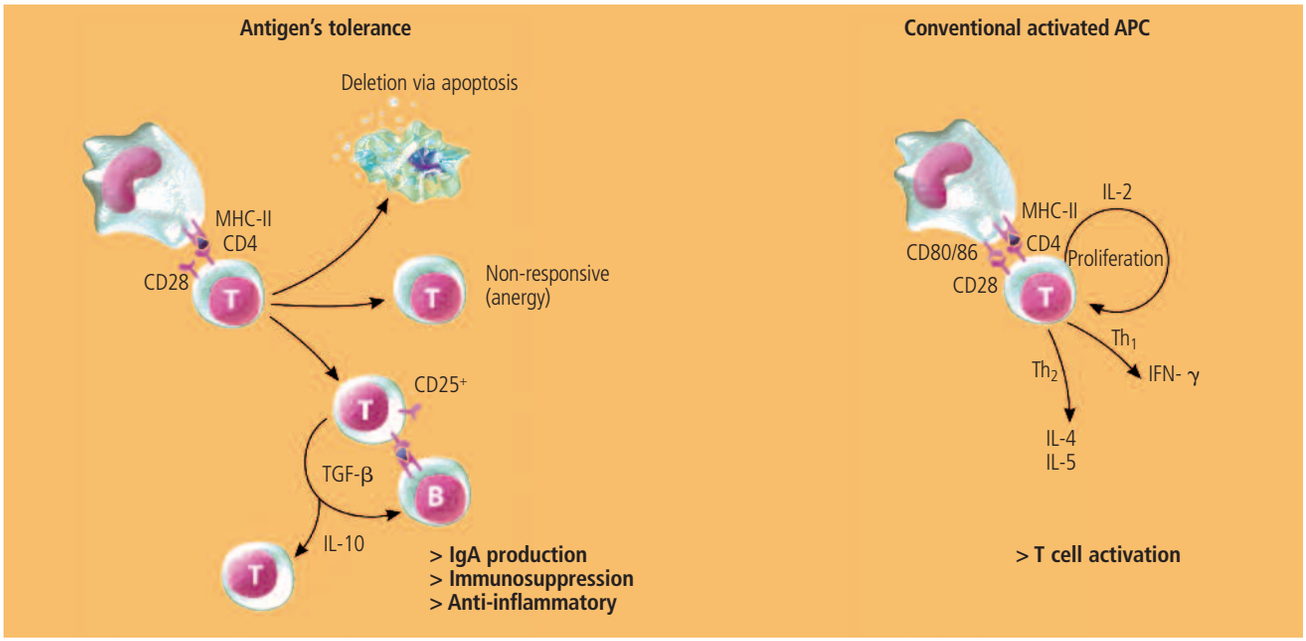
The activated cells may secrete cytokines, but full differentiation into effector T cells or plasma cells may not occur without secondary exposure. For both cell types to be re-exposed to antigen, intact antigens must reach the lamina propria. Intestinal epithelial cells are responsible for the absorption of antigen, release to professional APCs, and limited antigen presentation to cells within the mucosa on MHC class II. In the normal intes-

FIGURE 11 - ACTIVATION AND RE-HOMING OF INTESTINAL LYMPHOCYTES



The Peyer's patches are the primary inductive sites of immune responses to intestinal luminal antigens. Dendritic cells in the Peyer's patch or mesenteric lymph nodes do not normally express co-stimulary molecules (e.g.CD 80 and CD 86) and induce either apoptosis, anergy, or a regulatory function in the T cell. Lymphocytes activated within the mucosa express a unique adhesion molecule (αeβ7) which binds to MadCAM-1 expressed by venules within mucosal tissues. Thus lymphocytes activated within mucosal tissues circulate, then exit as effector cells within mucosal tissues.

Figure 12 - The general basis for immunological tolerance to luminal antigens



A: In the intestine, dendritic cells do not widely express co-stimulatory molecules such as CD 80 and CD 86. Antigen presentation leads to tolerance to the antigen through deletion, anergy, or induction of regulatory or suppressor effects in the T lymphocyte.
B: Conventional antigen presentation occurs with co-stimulatory molecule expression and results in T-lymphocyte activation as either Th1 or Th2.

tine, these secondary APCs will, like the primary presenters, lack co-stimulatory molecule expression and further add to the toleragenic environment. The effector T cell clones resident in the normal intestine secrete a bias towards Th2 and Th3 cytokines, in particular IL-10 and TGF-β, thus directing B-cell isotype switching to produce IgA-secreting plasma cells, whilst inhibiting the development of Th1 lymphocytes and IgG production.

It is important that the immune system reserves the ability to rapidly respond to pathogens. This ability to recognize pathogenicity is based on the engagement of PAMP receptors such as TLRs, producing "danger signals".

Predictably, expression of TLR-2 and TLR-4 is low to non-existent in the mucosal cells of the normal human intestine, but they can be rapidly expressed in response to inflammatory cytokines *(Abreu et al, 2001)*. The absence of these "danger signals" results in relatively inefficient antigen processing by intestinal APCs, markedly reduced or absent TNF-α/IL-1/IL-12 production, and the absence of CD80/86 co-stimulatory molecule expression. T cells activated by such an APC, will divide less with most clones undergoing early deletion by apoptosis, whilst the surviving memory cells will tend to secrete IL-10, TGF-β, or no cytokines *(Jenkins et al, 2001)*. This combination of apoptosis, functional defects in surviving clones, and T cells secreting the anti-inflammatory and IgA-supporting cytokines, is the general basis for immunological tolerance to luminal antigens **(Figure 12)**.

Thus oral tolerance is composed of a delicate balance between induction of IgA, T cell deletion, anergy, and immunosuppression; and the retention of antigen-specific lymphocytes capable of responding to invasive pathogens though antibody isotype switching to IgM, IgE, or IgG, and the production of inflammatory cytokines such as IFN-γ, IL-12, and IL-6.

► Loss of tolerance to dietary antigens

Loss of tolerance to dietary antigens will produce a conventional but detrimental immune response against the dietary antigen. Such an inappropriate response may produce inflammation locally, or at another anatomical site. The response will be characterized by one or a combination of:

- Local cell mediated inflammation: the resulting chronic stimulus may lead to lymphocytic intestinal infiltrates characteristic of inflammatory bowel disease.
- Local antibody production of isotypes other than IgA: the production of IgE will lead to mast cell priming and intestinal hypersensitivity, i.e. food allergy with gastrointestinal signs (vomiting and/or diarrhea).
- Systemic antibody production: circulating IgE will lead to priming of mast cells at sites distal to the intestine such as dermal hypersensitivity, i.e. food allergy with pruritus as the clinical sign.

The initiating events that lead to loss of oral tolerance, or prevent it from developing have not been described in cats, and remain poorly understood in any species. Suggested mechanisms include:

- *increased mucosal permeability:* e.g. following mucosal injury, or the neonatal intestine
- *co-administration of a mucosal adjuvant:* that activates and changes the phenotype of intestinal dendritic cells e.g. bacterial enterotoxins
- *parasitism:* intestinal parasitism in cats leads to an exaggerated systemic humoral response that includes increased production of IgE *(Gilbert & Halliwell 2005)*.

Currently, there is speculation as to the importance of infections that stimulate a Th-1-biased immune response in preventing Type-1 hypersensitivity reactions in people. This has been termed the "hygiene hypothesis", which states that a lack of maturation of the infant immune system from a Th-2 to a Th-1 type of immune response may be caused by less microbial stimulation in Western societies *(Romagnani, 2004)*. It is proposed that bacterial and viral infections during early life promotes a net shift of the maturing immune system towards Th-1 biased responses, and reduce potentially allergenic Th-2 biased responses. The assumed reduction in the overall microbial burden is supposed to allow the natural Th-2 bias of neonates to persist and allow an increase in allergy.

The special role of parasites in modulating allergic responses to food and other allergens has been debated for half a century. Several older reports suggested that, similar to cats, parasitized humans are more likely to suffer from allergic diseases *(Warrell et al, 1975; Carswell et al, 1977; Kayhan et al, 1978)*. In contrast to that is the higher incidence of allergic disease in Western populations, and the growing incidence of allergic disease in developing nations. Elevations of anti-inflammatory cytokines, such as interleukin-10, that occur during long-term helminth infections have been shown to be inversely correlated with allergy. It has recently been suggested that the host's response to the parasite determines their predisposition to develop allergic diseases, and that the induction of a robust anti-inflammatory regulatory response (e.g. IL-10) induced by persistent immune challenge offers a unifying explanation for the observed inverse association of many infections with allergic disorders *(Yazdanbakhsh et al, 2002)*. In cats, the role parasitism and other infections that would fall within the hygiene hypothesis have yet to be defined in determining the development of food hypersensitivity. Since the immunological mechanism for the majority of food sensitivities may not be IgE-mediated, the story may be even more complicated.

► Food immunogenicity

Adverse reactions to food are surprisingly common in cats: they have been reported to be present in up to 29% of all cases of chronic gastrointestinal disease in cats *(Guilford et al, 2001)*.

In addition, inflammatory bowel disease is the single most common cause of chronic gastrointestinal disease in cats, and novel antigen and hydrolysed protein diets are commonly reported to

be effective in its management *(Guilford & Matz, 2003; Nelson et al, 1984)*. However, although the involvement of immunological mechanisms in a proportion of these adverse reactions is suspected, it is unproven. Indeed, the normal immunological response to ingested dietary antigens in cats has only recently been partially described *(Cave & Marks, 2004)*. Surprisingly, cats develop robust serum IgG and IgA responses to dietary proteins when fed as either aqueous suspensions or as part of canned diets.

The relatively short intestinal tract of the cat suggests that they may be poorly suited to poorly digestible diets *(Morris, 2002)*. It is well established that the commercial canning process decreases protein digestibility and that this has biologically significant effects in cats *(Kim et al, 1996)*.

In rodents and rabbits, intact particulate and insoluble antigens are preferentially absorbed across the intestine through M-cells overlying the Peyer's patches *(Frey et al, 1996)*. Classically, such antigens tend to invoke active immunity appropriate for microorganisms. In contrast, soluble antigens have been found to be associated with oral tolerance *(Wikingsson & Sjoholm, 2002)*. It has also been shown that oral tolerance can be abrogated when soluble proteins are fed in oil-in-water emulsions, resulting in robust systemic humoral responses *(Kaneko et al, 2000)*. This effect may also have relevance to the pet-food industry where interactions between dietary proteins and lipids in canned or extruded diets during the cooking and the manufacturing process could feasibly result in novel interactions not present in their native states.

In stark contrast to rodents is the intestinal response in chickens, where particulate antigens induce tolerance, whilst soluble antigens provoke active immunity *(Klipper et al, 2001)*. If the physical nature of the proteins within the natural diet of a species dictates how the intestinal immune system has evolved, this might have special relevance to species that are commonly fed diets different from their ancestors.

Commercial pet foods are subjected to significant heating during the manufacturing process. The effect of heat treatment on proteins is mostly to change the 3-dimensional conformation of the protein. Although this may disrupt some antigens, it may equally uncover previously hidden antigenic determinants, or create new ones. Other reactions occurring at high temperatures include the Maillard reactions, which involve the reactions between certain amino acids and reducing sugars to produce less digestible compounds called melanoidins, which give a characteristic brown color. Melanoidins tend to be less digestible, less soluble, and certain melanoidins have been shown to be more "allergenic" than the original uncooked protein *(Maleki et al, 2000; 2003)*.

The effect of heating during the canning process on the immunogenicity of dietary proteins has been evaluated in cats *(Cave & Marks 2004)*. Using soy and casein proteins, the canning process resulted in the creation of new antigens not present in the uncooked product. In addition, a product of heated casein induced a salivary IgA response that was not induced by the raw product. Thus commercial food processing can qualitatively and quantitatively alter the immunogenicity of food proteins. Although the significance of this finding is uncertain at present, it emphasizes the need for feeding highly digestible proteins sources, or perhaps even hydrolysed proteins, when enteritis is present.

As obligate carnivores, felids have evolved on a highly digestible diet.

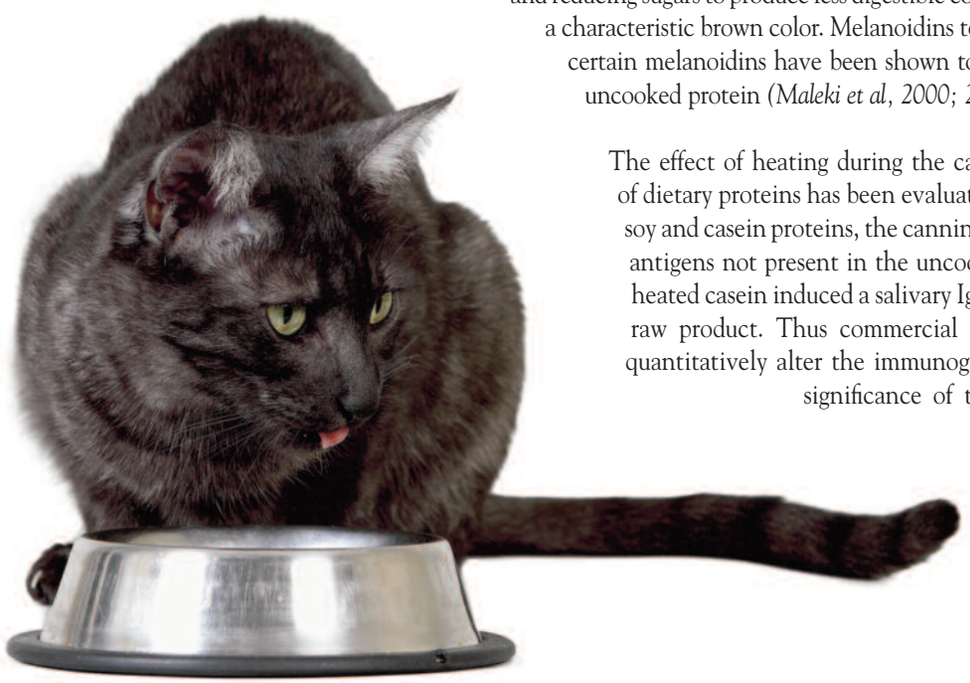
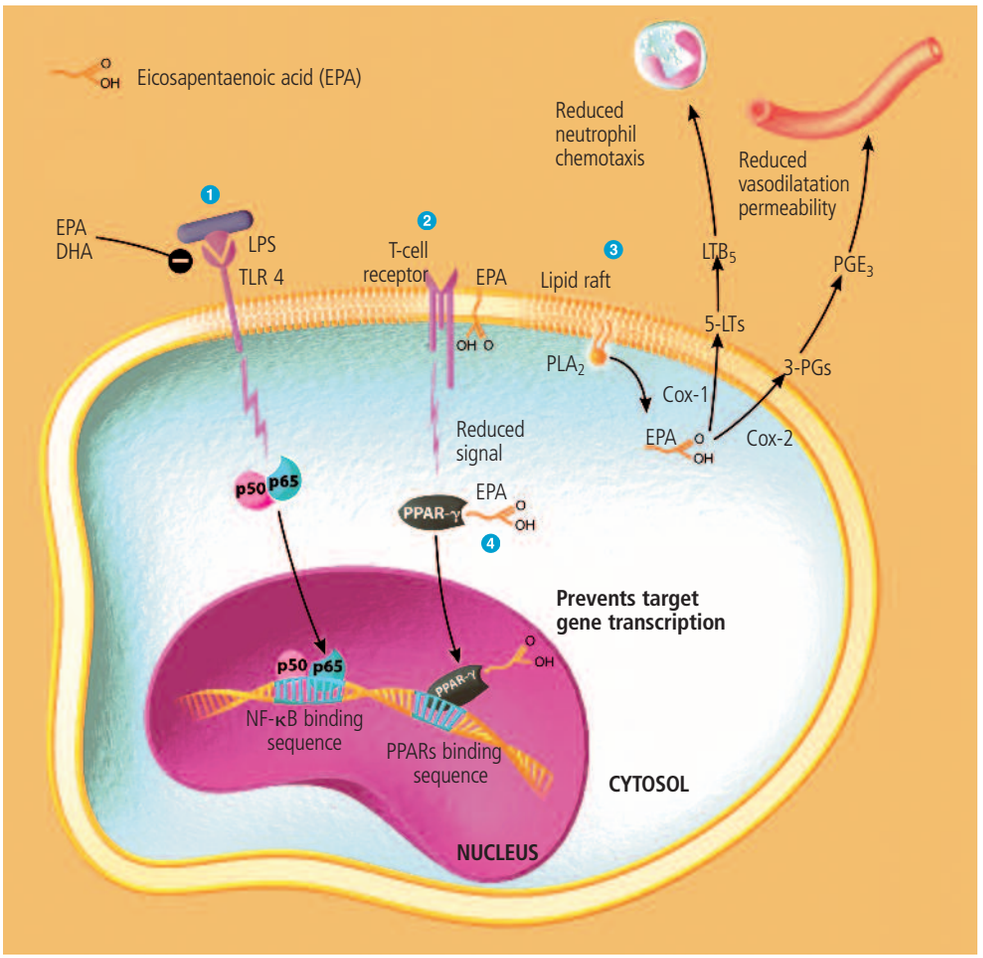


Figure 13 - Mechanisms for the modulation of immunity by dietary polyunsaturated fatty acids



Polyunsaturated fatty acids can modulate immune responses through several mechanisms.

1. *The n-3 PUFA EPA and DHA can directly inhibit signaling through TLR4 by LPS.*
2. *The 20 carbon PUFAs EPA and AA give rise to eicosanoids with differing biological actions.*
3. *Alterations in the physical properties of cell membrane lipid rafts leads to decreased signaling through the T-cell receptor.*
4. *EPA binds to the cytosolic protein PPAR-γ, which then diffuses to the nucleus where it binds to specific sequences and can inhibit gene transcription induced by NF-κB activation (e.g. following TLR signaling).*

7 - Nutritional modulation of immunity

► Polyunsaturated fatty acids

Dietary polyunsaturated fatty acids (PUFA) can modulate immune responses through several mechanisms **(Figure 13)**.

> Eicosanoid production

The dietary content of polyunsaturated fatty acids determines the proportions of the 20 carbon n-6 fatty acids arachidonic acid (ARA), dihomo-γ-linolenic acid (DGLA), and the n-3 fatty acid eicosapentaenoic acid (EPA) within the phospholipids cell membranes of leukocytes and other cell types. When ARA is used as the substrate, 2-series prostaglandins and thromboxane (e.g. PGE_2, and TXA_2), and 4-series leukotrienes (e.g. LTB_4) are produced. Those derived from EPA are the 3-series prostaglandins and thromboxane (e.g. PGE_3, and TXA_3), and the 5-series leukotrienes (e.g. LTB_5; **Figure 6**). EPA and ARA are competitive substrates for cycloxogenase (COX) and lipoxogenase (LOX). EPA is a less efficient substrate for COX, resulting in reduced prostaglandin production. In contrast, EPA is the preferred substrate for LOX, and when both ARA and EPA are available, the production of 5-series leukotrienes predominate.

Feeding diets that are enriched in the n-3 PUFA EPA can reduce ARA-derived eicosanoids by up to 75%. The conversion of the 18-carbon alpha linolenic acid (α-LA) into EPA does not occur

to any significant degree in cats. Therefore the effect of enriching a diet in α-LA will likely have little effect on immunity in cats.

The EPA-derived thromboxane TXA_3 is a much less potent platelet aggregate and vasoconstrictor than TXA_2. In contrast, the efficacy of the prostacyclins PGI_2 and PGI_3 in inducing vasodilation and inhibiting platelet aggregation are equal. Thus diets enriched in n-3 PUFA will reduce thrombosis and improve microcirculation at sites of endothelial activation.

The EPA-derived leukotriene LTB_5 is a much less potent vasoconstrictor and neutrophil chemotaxin than the ARA-derived LTB_4. Similarly, PGE_3 is less biologically active than PGE_2, and is less effective in inducing fever, increasing vascular permeability, and vasodilation. However, PGE_2 and PGE_3 are similarly effective in decreasing Th1 cytokine production and shifting the Th1 - Th2 balance in favor of a Th2 response in human lymphocytes *(Dooper et al, 2002)*.

Dietary EPA will therefore result in the production of eicosanoids that range from antagonistic to equipotent to those derived from ARA, and the overall effect of PUFA on immunity is not explained simply by the reduced efficacy of EPA-derived eicosanoids.

At present then, the effects and mechanisms of modulation of eicosanoids by dietary lipid is complex, and is very poorly described in cats, although there is some value to the generalization that diets enriched in n-3 PUFA will have an anti-inflammatory effect relative to diets enriched in n-6 PUFA. It is also not even known how significant alterations in eicosanoid production are in the modulation of immunity by n-3 PUFA, and it may be that other mechanisms are as, or even more important.

> Gene transcription

PUFA can directly affect gene transcription by interacting with nuclear receptors. The peroxisome proliferators-activated receptors (PPARs) are a family of cytosolic proteins that, once bound to an appropriate ligand, diffuse into the nucleus and either promote or inhibit gene transcription. PPARs are expressed by macrophages, T cells, B cells, dendritic cells, endothelial cells and other cell types *(Glass & Ogawa, 2006)*. Both EPA and DHA are ligands for PPAR-α, PPAR-γ, and PPAR-δ *(Kliewer et al, 1997)*. PPAR-α agonists have been shown to inhibit TNF-α, IL-6 and IL-1 production as well as inhibiting iNOS, matrix metalloprotease-9 and scavenger receptor expression by activated macrophages *(Kostadinova et al, 2005)*. In T-lymphocytes, PPAR-·α agonists inhibit IL-2 production and hence indirectly depress lymphocyte proliferation *(Glass & Ogawa, 2006)*.

Long chain n-3 PUFAs reduce expression of COX-2, 5-LOX and 5-LOX activating protein in chondrocytes. Thus, PUFAs alter eicosanoid synthesis at the level of gene expression, as well as by providing the substrates from which they are produced.

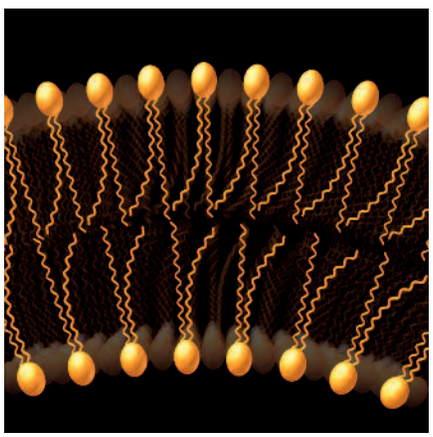
> Membrane structure (Figure 14)

Incorporation of EPA in place of ARA in phospholipid membranes alters the physical and structural properties of the cell membranes in lymphocytes. In particular, the assembly of lipid rafts, within which most cell surface receptors are localized, is altered. In T-lymphocytes in vitro, this has the effect of decreasing signal transduction through the T cell receptor and thus depresses T-lymphocyte activation *(Geyeregger et al, 2005)*.

> Inhibition of LPS-signaling

Animals fed diets enriched in EPA and/or DHA produce decreased amounts of inflammatory cytokines, and experience less morbidity and mortality following challenge with gram negative sepsis or lipopolysaccharide. In addition, lipid emulsions administered to human patients with systemic sepsis results in reduced systemic inflammatory responses as a result of suppressing production of TNF-α, IL-1, IL-6, and IL-8 by LPS-stimulated macrophages *(Mayer et al, 2003)*.

FIGURE 14 - MEMBRANE STRUCTURE



The basic biological membrane structure is always the same: it is a twin-lipid layer composed of two assembled rafts. The total thickness is 6-10 nm.

DHA and EPA, inhibit TLR4 agonist (LPS)-induced up-regulation of the costimulatory molecules, MHC class II, COX-2 induction, and cytokine production through suppression of NF-κB activation. In contrast, COX-2 expression by TLR2 or TLR4 agonists was increased by the saturated fatty acid, lauric acid *(Lee et al, 2004; Weatherill et al, 2005)*.

> Dietary PUFA content, supplementation, and ratios

The complexity of eicosanoid production and effects is added to by the complexity of dietary fatty acid interactions and metabolism. The prediction of an effect of a given diet has to take into account all of the following:

- total fat content of the diet
- relative proportions of 18-carbon n-3 and n-6 fatty acids (ALA, GLA, and LA)
- relative proportions of 20 carbon n-3 and n-6 fatty acids (ARA, DGLA, and EPA)
- absolute amounts of all individual n-3 and n-6 fatty acids
- previous dietary history of the animal
- duration of exposure to the diet in question.

The reduction of the description of the fat content of a diet to a simple ratio of n-3 to n-6 fatty acids provides very limited and potentially misleading information.

In addition, it can be seen that supplementation of a diet with a source of n-3 fatty acids (e.g. marine fish oil) will have greatly varying effects depending on the nature of the basal diet and patient. Most commercial diets are highly concentrated in linoleic acid, and the addition of a small amount of n-3 fatty acids will achieve little.

> Recommendations

There is insufficient evidence to make firm recommendations for disease modulation in cats using dietary PUFA. Using a dietary fat content of approximately 70 g/kg DMB, Saker et al found that a total n-6 to n-3 ratio of 1.3:1 (using corn oil, animal fat, and menhaden fish oil) reduced platelet aggregation *(Saker et al, 1998)*. Such a value provides a very rough estimate to the proportions required for modulating eicosanoid production, although the concentrations of EPA and ARA were not specifically assayed. In addition, the dietary concentrations required for the other effects of n-3 PUFA are unknown.

► Genistein

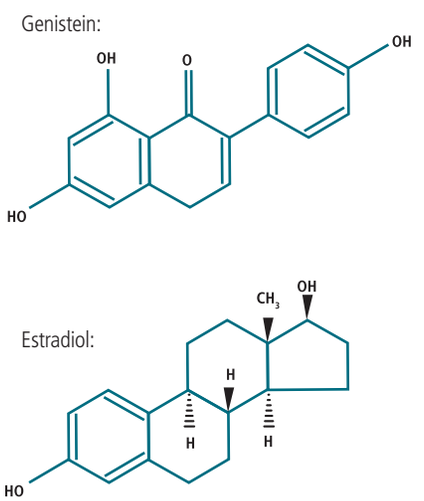
Genistein is an isoflavone compound principally found in plants of the family Leguminosae including soy, clover, and alfalfa *(Dixon & Ferreira, 2002)*. Genistein is structurally similar to 17 , β-estradiol, as depicted in **Figure 15**.

Genistein has been confirmed as a phytoestrogen *in vivo* through its ability to increase uterine weight, mammary gland development, and stimulation of prolactin secretion in ovariectomized rats and function as an estrogen in some estrogen-dependant cell lines *(Santell et al, 1997; Morito et al, 2001)*. However, due to the complexity of estrogen signaling in different tissues, in differing cells, perhaps even at varying times, genistein can have estrogenic activity, no activity, or anti-estrogenic activity *(Diel et al, 2001)*.

> Tyrosine kinase and topoisomerase II inhibition

In addition to genistein's estrogenic activity is its ability to inhibit tyrosine kinases by competitively binding to their ATP-binding site and forming non-productive enzyme-substrate complexes *(Akiyama et al, 1987)*. Inhibition of tyrosine kinases in turn inhibits numerous leukocyte signaling cascades involved in lymphocyte activation and proliferation, neutrophil activation and superoxide production, bacterial phagocytosis by macrophages, antibody responses, and delayed-type hypersensitivity responses *(Trevillyan et al, 1990; Atluru et al, 1991; Atluru & Atluru, 1991; Atluru & Gudapaty, 1993;*

FIGURE 15 - THE STRUCTURAL DIAGRAMS OF GENISTEIN AND 17 β-ESTRADIOL



Yellayi et al, 2002; 2003). Genistein has also been found to inhibit DNA topoisomerase II, resulting in double strand breaks in DNA, and has been linked to efficacy as a cancer chemotherapeutic, and as a disrupter of lymphocyte proliferation *(Markovits et al, 1989; Salti et al, 2000)*.

> Genistein in cat food

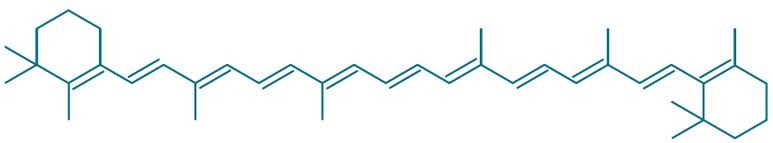
Soy-based ingredients are common in commercial diets fed to cats; the soy plant provides a source of protein, fiber, and polyunsaturated oil. As a result, several commercial diets contain genistein concentrations that could be sufficient to affect immune responses in cats. The isoflavone content of several cat foods has been assayed and concentrations have been found that would result in a cat ingesting up to 8.13 mg/kg body weight *(Court & Freeman, 2002; Bell et al, 2006)*.

Recently, it has been shown that once daily oral genistein treatment decreases circulating CD8+ cells, increases neutrophil respiratory burst, and decreases delayed-type hypersensitivity responses. Unexpected effects of genistein suggest that extrapolation from one species to other species may not be appropriate in regards to the effects of genistein on immunity.

► Carotenoids

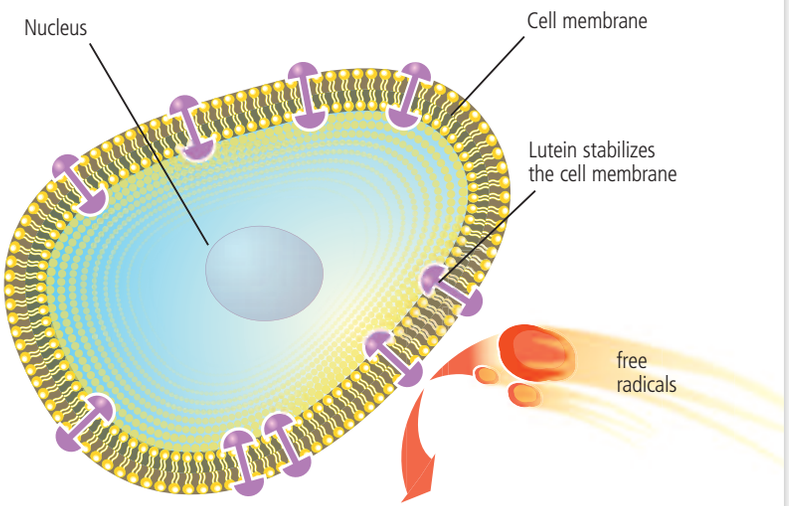
Cats are capable of absorbing dietary carotenoids, including β-carotene and lutein **(Figure 16)**. Significant amounts of both compounds are incorporated into organelle membranes, especially in the mitochondria or lymphocytes *(Chew et al, 2000; Chew & Park, 2004)*. It has been suggested that their efficiency in absorbing and stabilizing free radicals **(Figure 17)** and their ability to localize in the mitochondria combine to make them very effective antioxidants in protecting cells against endogenously derived oxidants. Their localization to organelle membranes makes them particularly effective in protecting mitochondrial proteins, lipid membranes, and DNA. In addition, since NF-κB can be activated in leukocytes in response to oxidative stress, antioxidants that concentrate in leukocytes might be expected to reduce NF-κB activation. One might question whether such effects would produce anti-inflammatory or even immunosuppressive effects, or whether simple cellular preservation through the antioxidant effect might enhance immunity.

FIGURE 16 - THE STRUCTURE OF LUTEIN



β-carotene

FIGURE 17 - LUTEIN EFFECTOR SITES



In most studies performed to date, the supplementation of a diet with carotenoids with or without vitamin A activity (e.g. β-carotene vs. lutein) has produced enhanced responses in several different immunological assays *(Chew & Park 2004)*.

The incorporation of lutein into the diet of cats has been shown to significantly affect immune responses *(Kim et al, 2000)*. The DTH response to an intradermally administered vaccine was increased, as was the in vitro lymphocyte proliferation following activation. Finally, the total IgG response after vaccination was increased by lutein treatment *(Kim et al, 2000)*. Overall then, carotenoids seem to enhance immunity independent of their vitamin-A activity. Whether this effect is solely, or even partially due to their ability to function as antioxidants is unsolved.

► Arginine

Arginine is an essential amino acid for cats because of their inability to synthesize sufficient

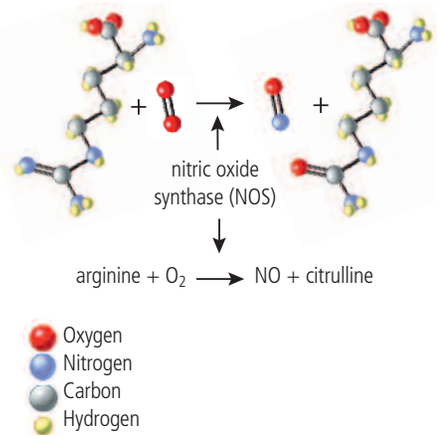
quantities in the fasting state. However, beyond its role as an essential intermediate in the ornithine cycle, dietary arginine has long been known to enhance certain aspects of immunity.

L-Arginine is oxidized to L-citrulline + •NO by nitric oxide synthetase **(Figure 18)**. The inducible form within leukocytes (iNOS) produces much greater amounts of •NO than the constitutive endothelial (eNOS) or neuronal (nNOS) forms. The production of •NO after induction of iNOS in an activated phagocyte is limited mostly by the availability of free arginine. Therefore any increase in available arginine will increase the •NO produced by any given inflammatory stimulus *(Eiserich et al, 1998)*.

Nitric oxide is a free radical. However, compared with other free radical species, in physiological conditions the molecule is relatively stable, reacting only with oxygen and its radical derivatives, transition metals, and other radicals. This low reactivity, combined with its lipophilicity, allows the molecule to diffuse away from its place of synthesis, and function as a signaling molecule on an intracellular, intercellular, and perhaps even systemic level.

Nitric oxide is required for normal intestinal epithelial maturation. It may be the principle inhibitory neurotransmitter in intestinal motility, and is essential for the maintenance of normal mucosal blood flow. In addition, •NO inhibits the expression of cellular adhesion molecules limiting unnecessary leukocyte entry, especially into the mucosal tissues. Nitric oxide inhibits T-cell proliferation, decreases NF-κB activation, and induces a Th-2 bias to local responses. However, in contrast to the paradigm that •NO inhibits the key pro-inflammatory transcription factor NF-κB, some studies have suggested that iNOS inhibition can increase pro-inflammatory cytokine production.

FIGURE 18 - ORIGIN OF NITRIC OXIDE



The reaction is catalyzed by the enzyme, nitric oxide synthase (NOS). There are three forms of NOS:
- *endothelial NOS (eNOS): eNOS is required for maintenance of normal vascular tone and as a physiologic messenger*
- *neuronal NOS (nNOS): eNOS and nNOS are constitutive forms and are always produced in low levels*
- *inducible NOS (iNOS): iNOS is inducible by a variety of inflammatory mediators including the cytokines, tumor necrosis factor (TNF), and interleukin-1 (IL-1), and free radicals.*

As mentioned, •NO is relatively unreactive with non-radical molecules. However, reaction with superoxide (O_2•$^-$) to form peroxynitrite ($ONOO^-$) is diffusion limited. Peroxynitrite is not a free radical, though it is a powerful oxidant, and has been shown to elicit a wide array of toxic effects ranging from lipid peroxidation, protein oxidation and nitration leading to inactivation of enzymes and ion channels, DNA damage, and inhibition of mitochondrial respiration *(Virag et al, 2003)*. The cellular effect of $ONOO^-$ oxidation is concentration dependant; for instance very low concentrations will be handled by protein and lipid turnover and DNA repair, higher concentrations induce apoptosis, whereas very high concentrations induce necrosis. Since both •NO and O_2•$^-$ are produced in sites of inflammation, it is reasonable to propose that $ONOO^-$ might be involved in the pathogenesis of many cases.

In light of differences in the radius of effect of both O_2•$^-$ and NO, co-localization of both molecules within the same cell would be expected to lead to disease. In this context, the finding that iNOS is capable of generating O_2•$^-$ in conditions when L-arginine is unavailable is significant. This has been demonstrated in macrophages, where limiting L-arginine availability resulted in the simultaneous production of functionally significant amounts of O_2•$^-$ and NO, and the immediate intracellular formation of $ONOO^-$ *(Xia & Zweier 1997)*.

The large number of conflicting studies evaluating the role of •NO in inflammatory disease, has resulted in a polarization of view points between those that argue •NO is protective, and those that argue it contributes to the pathogenesis. This is unfortunate since both views are probably correct. The fate of any individual molecule of •NO is determined by multiple variables that determine its role in pathogenesis including:
- site of production

Figure 19 - Interest of L-lysine supplementation in herpes virus infection

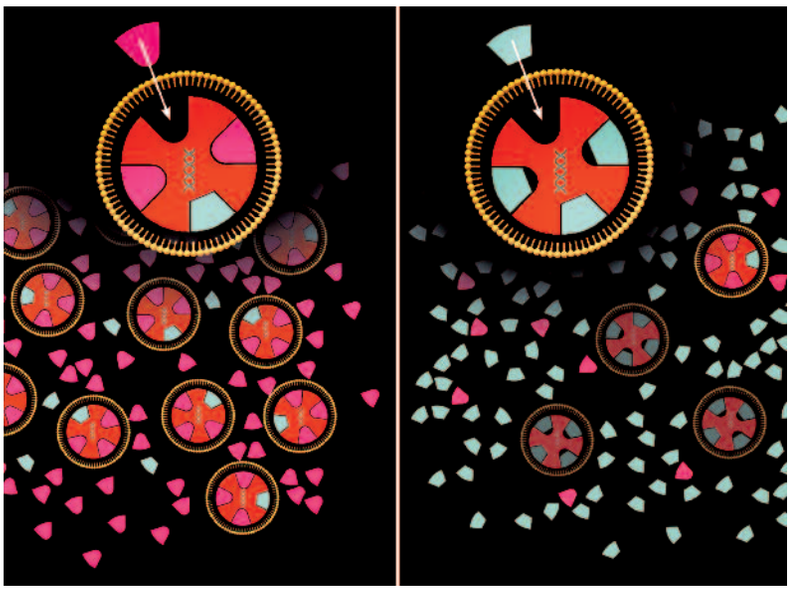
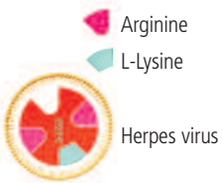


Figure 19A - Normal replication of the feline herpes virus when arginine is present.

Figure 19B - Inhibition of viral replication when L-lysine competes with arginine to enter the cells.



Beyond a certain breakpoint, the addition of L-lysine tends to inhibit herpes virus replication in vivo *and* in vitro.

- timing within the local disease process that the molecule is produced
- amount of •NO produced
- redox status of the immediate environment
- chronicity of the disease.

Overall it appears that supplemental arginine, either parenterally or orally administered, enhances the depressed immune response of individuals suffering from trauma, surgery, malnutrition, or infection. This action is presumably through its ability to augment the production of •NO by iNOS in activated neutrophils and macrophages.

However, in cases of severe sepsis (i.e. infection accompanied by a systemic inflammatory response), augmentation of •NO production might be detrimental because of its effect as a negative cardiac ino- and chronotrope, its ability to inhibit coagulation and its potent venous and arterial dilator effects *(Suchner et al, 2002)*.

Most commercial enteral nutritional formulas suitable for feeding to cats contain 1.5 to 2 times the minimum requirement of arginine for growth. However, supplementation of diets for intensive care nutrition has frequently been recommended, and is widely used in human medicine for enhancement of the immune system in critical care. Although clinical improvements in some studies have been reported, critically ill patients with SIRS, sepsis, or organ failure may actually deteriorate as the result of arginine supplementation *(Stechmiller et al, 2004)*. Thus there may be cases where supplementation with arginine, beyond that provided by a conventional protein source may be beneficial, whilst in other cases it may be detrimental.

► Lysine

As indicated in **Figure 2**, the diet ingested by the host can directly affect the pathogen. The interaction between lysine and herpes viruses is an example of such an interaction, rather than an interaction between diet and immunity **(Figure 19)**.

The genome of the feline herpes virus (FHV-1) is similar to the genomes of other alpha-herpes viruses, and several different viral proteins have been described *(Mijnes et al, 1996)*. All of the 20 common amino acids are utilized, including L-lysine *(Pellett et al, 1985)*. However, when herpes viruses are grown in cell cultures in vitro, there is no requirement for lysine to be added to the culture media, thus what little lysine is required for viral replication is derived from the labile pool of free intracellular amino acids *(Maggs et al, 2000)*. In contrast, the omission of arginine or histidine from the culture media profoundly inhibits viral replication more so that other amino acid omissions *(Tankersley, 1964)*. The addition of lysine to the culture media actually inhibits viral replication, but the breakpoint at which replication is inhibited has not be clearly defined. Tankersley (1964) demonstrated that normal replication occurs at 70 µg/mL, but profound inhibition occurs at 180 µg/mL. It is worth noting that, when cats are fed a diet containing the adequate intake of lysine recommended by the NRC for gestating queens (i.e 1.1% in a 4000 kcal/kg diet), plasma concentrations of lysine are 14 ± 2.2 µg/mL *(Fascetti et al, 2004)*.

It has been proposed that lysine may antagonize arginine availability in vitro by competing for arginine entry into cells **(Figure 19)** and in vivo by both competition, and by the induction of renal and hepatic arginase. However, Fascetti et al, have demonstrated that even very large dietary concentrations of lysine do not alter plasma arginine concentrations in cats within a two week period *(Fascetti et al, 2004)*.

- When 500 mg of L-lysine monochloride was given twice daily to cats as a bolus, starting 6 hours prior to inoculation with FHV-1, a mean plasma concentration of 97 µg/mL was achieved. Clinical signs associated with acute FHV-1 infection were reduced, but there was no reduction in viral shedding *(Stiles et al, 2002)*.
- A once daily bolus of 400 mg given to latently infected cats produced mean peak plasma concentrations of 65 µg/mL and reduced viral shedding, but had no significant effect on clinical signs *(Maggs et al, 2003)*.
- Finally, when a diet containing 5.1% lysine (as fed, in a 4000 kcal/kg diet) was fed to cats, a mean plasma concentration of 44 µg/mL was achieved. This diet was fed to groups of spontaneously latently infected cats, having recently experienced an epizootic upper respiratory disease, no effect was seen on clinical signs or herpes viral shedding *(Maggs et al, 2006)*. In fact, one group (the male cats) fed the lysine supplemented diet experienced worse clinical signs than any other, supplemented or not, and increased viral shedding. This observation was probably more due to stress or another pathogen *(Mycoplasma felis, Bordetella bronchiseptica)* than an effect of the diet, but did influence the results of the study.

Thus the efficacy of treatment with L-lysine on feline herpes viral infection remains to be challenged in cats with enzootic upper respiratory disease. To date, lysine supplementation has not show any toxic effects. Experimentally, the cat's dietary consumption is lower with a 13% lysine-diet (as fed, in a 4000 kcal/kg diet) but this level largely exceeds practical cat food formulation *(Fascetti et al, 2004)*.

8 - Effect of route of nutrition

In addition to the composition and amount of diet fed, the route of feeding (enteral or parenteral) affects innate and adaptive aspects of immunity *(Kudsk, 2002)*. A lack of enteral stimulation leads to decreased intestinal and respiratory tract IgA production and established IgA-mediated antiviral and antibacterial immunity *(Renegar et al, 2001a)*. Increased mucosal permeability and bacterial translocation of luminal bacteria to the mesenteric lymph nodes, liver, and spleen are seen with parenteral nutrition *(Kudsk, 2003a)*. In healthy cats, parenteral nutrition (PN) administered for 2 weeks resulted in small intestinal villous atrophy and fusion, and increased numbers of inflammatory cells *(Lippert et al, 1989)*. These changes are reversed when enteral feeding is reinstated.

A lack of luminal nutrients results in an increased expression of proinflammatory adhesion molecules, especially ICAM-1. A lack of enteral feeding leads to infiltration of lymphocytes into the lamina propria and is associated with trapping of lymphocytes there, which is rapidly reversed with feeding *(Ikeda et al, 2003)*. In addition, neutrophils accumulate and are activated within the vasculature of the intestine during fasting *(Kudsk, 2002; 2003b)*.

The increased number of primed neutrophils adhering to the microvasculature throughout the intestinal tract are able to contribute to oxidative and enzymatic tissue damage following activation. Fasting or PN significantly increases ICAM-1 expression within the intestine and liver 3 hours after reperfusion compared with enteral feeding. Fasting or PN results in decreases in IL-4 and IL-10 that correlate with decreases in IgA and increases in ICAM-1. Lack of enteral feeding impairs the coordinated system of sensitization, distribution, and interaction of T and B cells important in the production of IgA, in the maintenance of normal gut cytokines, and in the regulation of endothelial inflammation. Thus the lack of luminal nutrients has been described as a "first hit", and increases the inflammatory response to a secondary insult in the GIT, but also the lungs, liver, and potentially other organs as well.

Perhaps the effect of enteral nutrition on intestinal integrity is best demonstrated in cases where there is a severe mucosal insult. In canine parvoviral enteritis, the early instigation of enteral nutrition decreases the time to normalization of demeanor, appetite, vomiting, and diarrhea *(Mohr et al, 2003)*. In a model of methotrexate induced enteritis in cats, feeding a complex diet was superior to fasting or feeding a purified diet in normalizing clinical signs, maintaining intestinal integrity, and minimizing bacterial translocation *(Marks et al, 1997; 1999)*.

Intestinal immunity can have a profound negative or positive influence in the development of the systemic inflammatory response to severe trauma, surgery, or infection. In human trauma patients, enteral feeding decreases the incidence of pneumonia compared with total parenteral nutrition or starvation. Enteral nutrition increases secretory IgA production at all mucosal sites and lack of enteral stimulation significantly impairs the generation of IgA-mediated mucosal immunity, including immunity against upper respiratory tract vial infections, hastening elimination of virus *(Renegar et al, 2001b; Johnson et al, 2003)*. This has importance to feline medicine, where recovery from calici or herpes viral upper respiratory infection may be delayed in the absence of adequate enteral nutrition.

Intestinal integrity is compromised in the absence of enteral nutrients, and is accompanied by an increased rate of bacterial translocation, and increased risk of sepsis. These changes are seen with either complete fasting, or with parenteral nutrition. Thus oral fasting primes an animal for an exaggerated response to any subsequent or concurrent inflammatory insult and increases the bacterial challenge from enterically derived organisms. On the other hand, provision of enteral nutrition is one of the most important mechanisms by which systemic inflammatory responses can be reduced, and septicemia can be avoided. Compared to parenteral nutrition, enteral nutrition is beneficial in human critical patients. Patients without pre-existing septic shock who received enteral nutrition had fewer episodes of severe sepsis or septic shock, and the length of stay in ICU was shorter compared with those given PN *(Radrizzani et al, 2006)*. This effect is so significant that it has lead some authors to recommend that parenteral nutrition be abandoned in cases of critical illness when enteral nutrition can be administered, even at an initial low caloric content.

Conclusion

The interaction between nutrition and immunity is complex, bi-directional, and incompletely understood. Nutrition can modify immunity by enhancing, suppressing, or changing the nature of an immune response. Immunity can be affected by diet in utero, and at the time of mounting a response. Nutrients of importance in this regard include glutamine, arginine, PUFA, carotenoids, and genistein. Nutrients can act as fuel, precursors for mediators, antioxidants, modifiers of gene transcription, and inhibitors of cellular functions. Defects in almost any essential nutrient can impair immunity, but also nutrient excess in obesity. Whether either suppression or enhancement is good or bad depends upon the specific disease state, and the individual patient.

Immune responses alter nutritional status through changes in usage, impaired uptake, increased loss, and altered metabolism. Sustained severe immune responses result in cachexia that cannot be reversed with feeding alone. The metabolic changes associated with systemic inflammatory responses leads to insulin resistance and hyperglycemia, and forced feeding can increase morbidity and mortality. Tight glucose control appears to be more important than meeting the resting energy requirements of critically ill patients. For optimal mucosal and systemic immunity, enteral nutrition is preferred to parenteral nutrition.

Diseases in which immunosuppression may be beneficial include chronic inflammatory diseases such as IBD, osteoarthritis, and immune-mediated diseases. It is less clear in which states enhancement of immunity is beneficial. Until more information is available, nutritional support should focus primarily on preventing nutritional deficiencies whilst avoiding overfeeding, rather than on immunomodulation.

Frequently asked questions concerning nutrition and immunity

Q	A
What is "immunonutrition"?	**Any aspect of nutrition that modulates the activity of the immune system in any way could be termed immunonutrition.** However, the term has been most commonly used to describe nutritional interventions that attempt to improve the clinical outcome in critically ill patients through modulation of immunity. There is an optimal diet for every animal in every disease state, and the optimal diets for different animals may differ widely, or be the same for very different diseases. The ambiguity of the term may well have contributed to the overly simplistic thinking about the role of diet in severe inflammatory diseases that has resulted in one-diet-for-all approaches (e.g. PN solutions supplemented with glutamine, arginine, and n-3 PUFA for all septic patients).
What does it mean to "boost immunity"?	For any given immune response, if that response is amplified, exaggerated, or made more efficient, it can be said to be "boosted". However, boosting immunity is not always of benefit to the animal. The normalization of cellular immune responses in malnourished animals with adequate nutrition can be said to be boosting the immune response from deficient to normal. However, in severe sepsis where widespread activation of macrophages and neutrophils contributes significantly to vital organ and vascular damage, increasing the activity of those cells can increase morbidity and mortality. The clearest example of that is with the supplementation of arginine to critically ill humans. At its most extreme, suppression of immunity may be of benefit to the animal if immune-mediated disease is present. **The most common reason for supplementing a diet with n-3 PUFA is to reduce inflammation.** Finally, it may be that boosting immunity is of neither benefit nor detriment.
Can feeding adversely affect immunity?	Feeding incomplete or imbalanced diets always has the potential to cause immune dysfunction. In addition, feeding in excess of the resting energy requirements of an animal in a systemic inflammatory response syndrome may lead to hyperglycemia and immune-dysfunction.
What is the ideal diet for severe sepsis?	The answer to this question is unknown and there is potential for harmful intervention. For hospitalized patients, the major goals of nutritional intervention are to meet the known requirements, and avoid over-nutrition and dehydration. In cases of severe sepsis, simply meeting the resting energy requirements with a complete and balanced diet via the enteral route when possible are reasonable goals. Whilst it has not been established what the ideal macronutrient proportions might be for severe sepsis, it is known that all three macronutrients (carbohydrate, protein, and fat) can be detrimental if fed in excess. For cats, carbohydrate might be especially poorly tolerated in severe sepsis, and low carbohydrate (< 20% of energy) high fat diets, fed to not exceed the resting energy requirements, may be ideal.

Q	A
How could anorexia in sepsis be beneficial?	A potential explanation is that **anorexia leads to muscle catabolism and the liberation of essential amino acids and glutamine for optimal leukocyte function**. In addition, the increased tissue catabolism increases immunosurveilance through increased presentation of self peptides on MHC-I molecules. Thus, feeding with an imbalanced formulation may impair leukocyte responses and decrease the efficiency of pathogen clearance. **However, when the infectious agent is being directly treated, and when supportive care is provided, nutritional intervention supersedes any slight benefit from anorexia.** Feeding a highly digestible, moderate to low carbohydrate diet, with adequate glutamine and arginine, supplemented with higher concentrations than required for maintenance of antioxidants (especially ascorbate and tocopherol), and avoidance of over-feeding, the outcome will be greatly improved.
How much fish oil should I supplement to produce immunosuppression in a cat?	As discussed above, there are too few studies on which to make any confident recommendations. In addition, **the required amount will depend on the type and severity of the disease, and the fat content of the cat's diet**. However it is likely that sufficient n-3 PUFA will need to be fed to produce a ratio of at most 1.3:1 (n-6:n-3). Consider this example: A typical adult maintenance dry cat food contains the following main ingredients: chicken, chicken by-product meal, corn grits, corn meal, chicken fat, dried egg product, fish meal, beat pulp. The total n-6 content of the diet is 2.6%, whilst the total n-3 content is 0.23%. The diet has an energy density of 4 kcal/g (16.8 kJ/g), and a 4 kg cat, with a daily intake of 200 kcal (842 kJ) will consume a total of 50 g of food, which contains 1.3 g n-6 PUFA, and 0.115 g n-3 PUFA, or a ratio of 11.3 (n-6:n-3). To reduce this ratio to less than 1.3, an additional 0.9 g n-3 PUFA needs to be added. Salmon oil contains approximately 34% n-3 PUFA, with the rest as saturated, monounsaturated, and a small amount of n-6 PUFA. Therefore, 2.6 g (2.9 mL) of salmon oil is needed to be added to the diet to reduce the ratio to 1.3. That supplement provides an additional 22 kcal (92 kJ), or 11% more than the required intake. As stated above, it has not been determined what the most important variable for modulation of immunity is, though **the single most important ratio in the cat may be the ratio of ARA: EPA**. In the absence of evidence, the above calculation serves as an illustration of a starting point, where less than that amount is unlikely to have a significant effect.

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