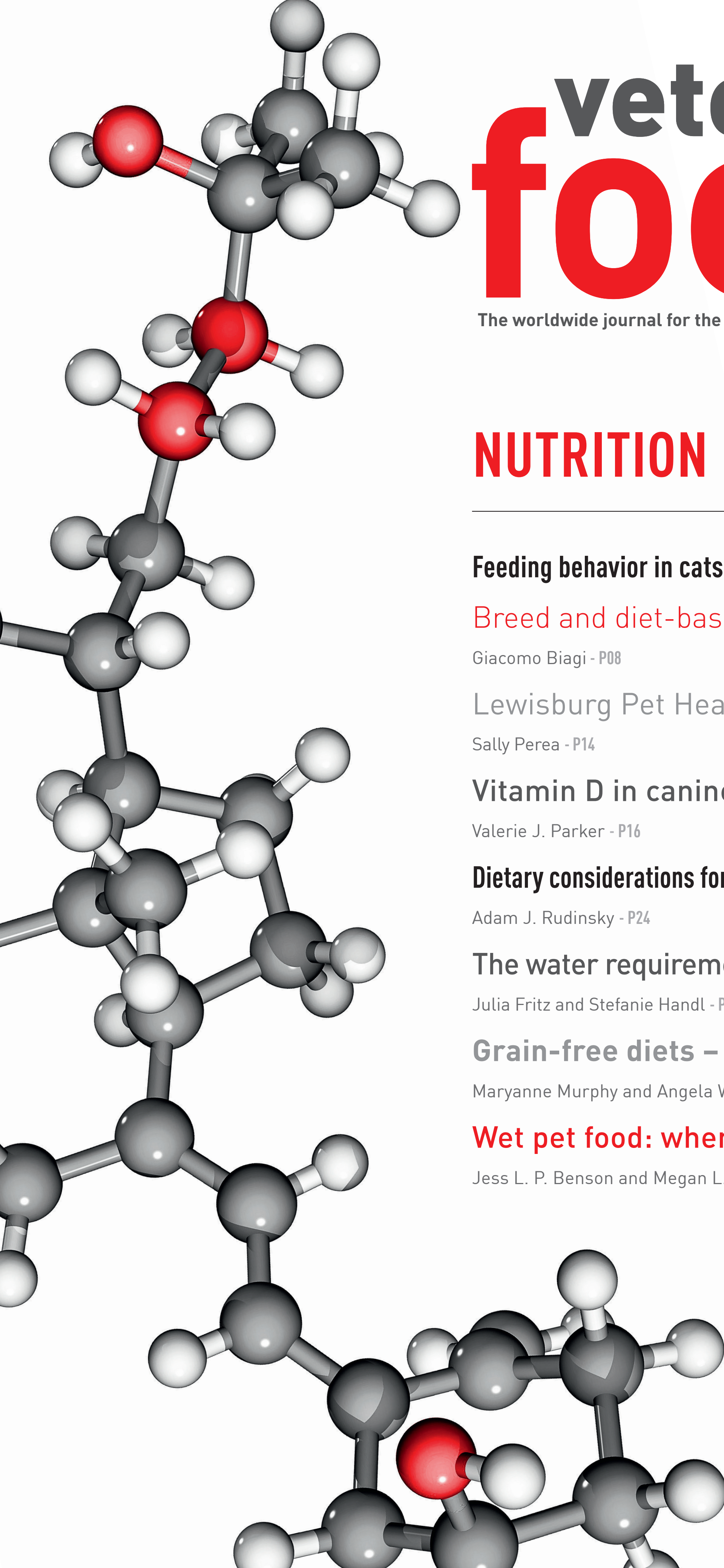

veterinary focus

#28.3

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NUTRITION MATTERS

ROYAL CANIN®

FOOD FOR THOUGHT?

"Let food be thy medicine and medicine be thy food"

These words are attributed to Hippocrates, the Greek physician regarded as the founding father of modern medicine, and while he is rightly considered one of the history's most outstanding figures, separating the facts from the fictions that surround the man and his legacy is difficult, if not impossible. This includes the above quotation, as many scholars can offer no evidence that he ever uttered these words; it is perhaps ironic that much mystery surrounds a man who advocated a disciplined and logical approach to medicine.

It is also ironic that while exact science and good research is regarded as paramount these days, fake news and popular misconceptions seem to be as widespread as ever; much which is claimed to be fact is anecdotal at best and nonsense at worst, and what starts as one person's opinion can easily become generally accepted. Reversing a fashionable theory can then be both difficult and unpopular.

Nutrition is one of these areas where fact and fiction can often intertwine, so this issue of *Veterinary Focus* seeks – as always – to present only confirmed wisdom and robust evidence. Hippocrates would presumably approve; another quote attributed to him – "science is the father of knowledge, but opinion breeds ignorance" – may or may not be his, but the sentiment is undeniably true.

Ewan McNEILL
Editor-in-chief

• Focus on *Veterinary Focus*

In the wild, cats will generally **eat throughout a 24-hour period,** with most feeding activity around dawn and dusk, but a domesticated cat is often subject to a different set of "rules" imposed by its owner, which can lead to a variety of problems.

p02

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It may seem that putting a bowl of water out for a cat is the simplest of husbandry procedures, but it appears that cats can be quite particular about where they choose to drink and what they want to drink from.

p32

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p41

Cats and dogs can often be maintained **on a grain-free diet**, but such foodstuffs are not necessarily carbohydrate-free, nor is there evidence to support the idea that they are better than diets containing grains.

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Editor-in-chief: Ewan McNeill, BVMS, Cert VR, MRCVS
Editorial secretary
- Laurent Cathalan (lcathalan@buena-media.fr)

Artwork
- Pierre Ménard

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FEEDING BEHAVIOR IN CATS

We all need to eat to survive. But for humans, eating can be much more than a simple task to be undertaken on a daily basis; our mealtimes allow us to rest and relax, and perhaps catch up with friends or family as we enjoy our food. But from a cat's point of view, eating is not quite the same, as Jon Bowen explains.

KEY POINTS

1. In the wild, cats will eat – assuming free access to food – throughout a 24-hour period, with most feeding activity around dawn and dusk.
2. Cats are strongly sensitive to the flavor of amino acids and nucleotides, and will show strong preferences or dislikes to certain tastes.
3. Cats tend to follow fairly strict routines, and if the owner has an irregular lifestyle this can create a stressful and unpredictable routine for the cat.
4. Owners tend to believe that offering food equates to caring for their cat, but they should also find other ways to show attention.

Introduction

Empathy is at the root of pet keeping; the sense of a shared emotional experience is not only the basis of the human-animal bond but also the origin of its key benefits for pet owners. A recent scientific statement from the American Heart Association noted that pet keeping was strongly associated with a range of cardiovascular health benefits, but these benefits were also linked to the quality of the bond and not merely due to the presence of a pet in the household (1).

Although research in this area is limited, evidence is accumulating that pets with behavioral problems might adversely affect their owner's lifestyle and wellbeing. For example, a study of dog owners found that both major behavior problems (such as aggression and separation anxiety) and minor problems (such as leash pulling and restlessness) can have a significant impact on lifestyle and satisfaction with pet ownership (2). The same kinds of owner-lifestyle impacts would be expected with cats that are unsociable, destructive, or show inappropriate toileting in the home.

Pets provide both an opportunity for owners to receive emotional support from a non-judgmental individual, and to express caregiving behaviors in return. Being expressions of empathy, both giving and receiving care provides similar positive emotional benefits to people, with the offering of food being a primary means of human expression of care (3). So for some people, and especially for cat owners, offering food and seeing it eaten are important aspects of expressing care, and some individuals, who are out of the house for long periods each day – either with work or for other reasons – may regard feeding as the main point of contact with their pet **(Figure 1)**.

Figure 1. Offering food to a pet is a primary means of human expression of care.

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Jon Bowen,

BVetMed, MRCVS, Dipl. AS (CABC), Royal Veterinary College, London, UK

Dr. Bowen graduated from the Royal Veterinary College in 1992 and spent several years in first opinion small animal practice. He then pursued an interest in animal behavior after completing a postgraduate diploma in behavior at Southampton University, and currently runs the behavioral medicine referral service at London's Royal Veterinary College, where he also teaches. He has authored several book chapters on behavioral topics and is a regular speaker at both national and international veterinary conferences.

This interaction works perfectly well for a pet species such as the dog, for which feeding is a social activity and meal frequency is flexible. Dogs adapt easily to having one, two or three meals a day, they show appreciation when offered food, and will usually accept restrictions on when and what they can eat. However, the hunting and feeding patterns of cats make it hard for them to adapt to, or show much appreciation for, human attempts to show care through the offering of food **(Figure 2)**. In fact, as we will see, the mismatch between the feeding motivations and behaviors of cats and people can lead to behavioral problems that damage owner lifestyle and the human-animal bond.

What is normal hunting and feeding behavior?

In the wild, and when given free access to food, cats will eat throughout a 24-hour period (4). Meal frequency can be as high as 20 times per day (5), although there does seem to be variation between cat breeds; for example, one small study in Bengal cats showed a higher average meal frequency than domestic shorthaired cats (6).

For feral cats, meal frequency depends upon the availability of food and of hunting success, and therefore upon the availability of prey. Cats will regularly visit a set of hunting sites within their territory, focusing on times when their prey is likely to be active or easily caught. Typically, this means that cats most actively hunt at dawn and dusk, although they also hunt during the night when roosting birds may be more easily caught. Having a visual system that has evolved to work best in low-light conditions, cats also have difficulty coping with bright sunlight, which is why they may be less active during sunny days. Prey size is small, and includes both vertebrates and invertebrates (7), but since each catch is essentially a small pre-packaged meal which only provides energy for a few hours of activity, satiation plays a minimal role in regulating either hunting or feeding. Having eaten, a cat needs to quickly return to hunting in order to obtain its next meal. Cats do not normally eat large meals because of their limited stomach volume.

At each hunting site, the cat searches for odors and signs of local disturbance which could indicate that prey has been recently active in the area. It will then go to a nearby spot from which it can launch an attack within the area where prey is most likely to arrive. The cat will then wait for a few tens of minutes before moving on to another site. Predatory behavior is also activated by high-pitched sounds, and quick movements of prey-sized items; if these are detected the cat will stop moving, adopt a crouched body posture to make itself less visible, localize the prey, wait for it to approach (or move towards it cautiously) and then launch an

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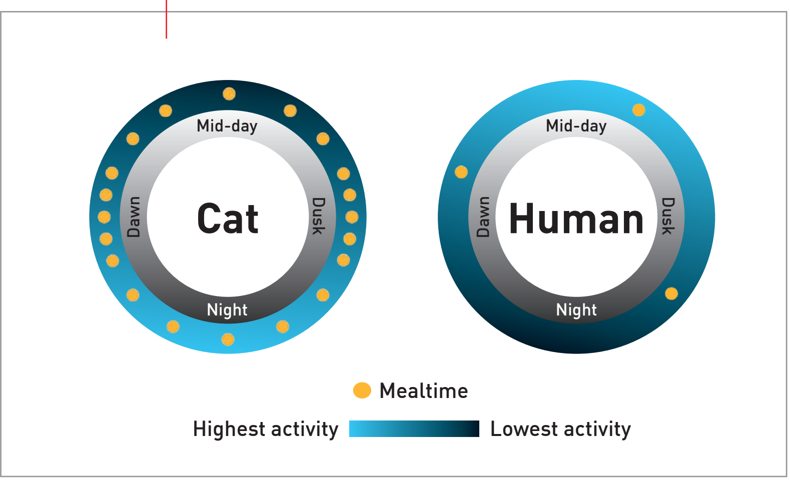
Figure 3. When hunting, a cat will adopt a crouched body posture to make itself less visible before launching an opportunistic predatory strike.

Figure 2. The activity and feeding patterns of cats and humans differ significantly, as shown in this diagram.



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opportunistic predatory strike **(Figure 3)**. When they occur, such strikes are rapid but brief, and are only over short distances of a few body lengths.

Cats have poorer visual acuity at distances of less than 15-20 cm, so during the final phase of a predatory strike the cat depends on its whiskers and tactile sensation around the mouth. Once the cat has hold of the prey, bite pressure is under the control of local reflexes, so the cat will automatically bite down harder if the prey moves in its mouth. This is one reason why cat bites can be so painful for owners, and why it is important not to use hands and feet to entice cats to play.

The predatory activity patterns of cats involve a lot of travel between hunting sites, foraging, and waiting. After catching its prey, the cat will take it back to its core territory where it can be eaten in private. For domestic cats, this may mean bringing prey home to eat, because this is a safer and more relaxing place to be; it is not that the prey is a "present" for the owner or a sign that the cat is dissatisfied with its food. It is also why some cats remove food from the bowl to eat it elsewhere; they want more privacy when they are eating. Owners should treat this as an indication that the food bowl is in the wrong place for the cat, or that it is frustrated by having to share a food bowl with other cats in the household. Free-ranging cats tend to locate their latrine, hunting and resting sites away from each other, so in the domestic home these may be too closely related, which also leads to cats not wanting to eat from the bowl they are given. Owners should therefore be encouraged to site feeding bowls and litter trays away from each other wherever possible.

Larger, more dangerous, prey may be dispatched immediately, using a kill bite that severs the cervical vertebral column. Carnassial teeth are then used to shear flesh from the carcass (4). If the cat is not hungry, and the prey is small, the cat may keep the prey alive for longer in order to practice predatory behavior with it. Cats will typically eat small mammals starting with the head and then moving onto the body and legs. They take time to chew the prey into digestible pieces and may not consume the whole animal; the aim is to refuel and then return to hunting and other behaviors. Less palatable parts of the body, such as the intestines, may not be eaten. If a cat catches a surplus of food, it may cache some of it by burying it in a patch of dry earth or leaves. This acts as a temporary food store for a few hours, and may explain why some domesticated cats perform "digging" behaviors around a food bowl after they have eaten.

"The hunting and feeding patterns of cats make it hard for them to adapt to, or show much appreciation for, human attempts to show care through the offering of food."

Jon Bowen

What tastes do cats like?

Like other carnivores, cats have major areas of taste loss (8); for example, they are insensitive to fruity-sweet and salt tastes (9). They are more strongly sensitive to the flavor of amino acids and nucleotides; they tend to reject the taste of certain amino acids (such as l-tryptophan, which humans identify as bitter tasting) and are attracted to the taste of others (such as l-glycine). Owners sometimes comment that their cats are attracted to salty items like nuts or crisps, and sweet items like cakes or biscuits, but this is probably because of subtle amino acid flavors that we are not even aware of, because our perception of salt or sugar flavors is so overwhelming. Although cats taste food in a completely different way from us, this does not mean that human and feline preferences will not sometimes overlap! For example, cats will often reject bitter-tasting foods, as it is a means of avoiding the consumption of something that is potentially toxic (10).

Initial food preferences develop as kittens observe and replicate their mother's eating habits. However, this changes when cats become independent and are exposed to the range of foods available in the environment or provided by their owners. Some individual cats are regarded by their owner as being quite fussy about what they will eat. This can be due to limited early experience of different foods and flavors, leading to neophobia. However, cats also exhibit a "monotony effect" in their food selection (4); they experience a growing aversion to familiar foods (and also prey), which may lead to a preference for novelty and dietary diversity (within the range of foods and flavors that the cat is already familiar with). This monotony effect encourages the cat to maintain a nutritional balance by eating a wide range of food/prey, and is greater in free-ranging cats than pets that have been reared on commercially prepared nutritionally complete diets (11). It probably explains the tendency for some pet cats to periodically lose interest in their regular diet, which then forces owners to try alternatives.

What dictates feline behavior?

Probably the most important aspect of feline hunting and feeding behavior, and indeed behavior in general, is that it is regulated primarily by environmental and internal factors, and not by social interaction. When a cat is within its territory, its behavioral patterns are not influenced by other cats; hunting, feeding, and self-maintenance (grooming, resting) are all solitary activities. Environmental

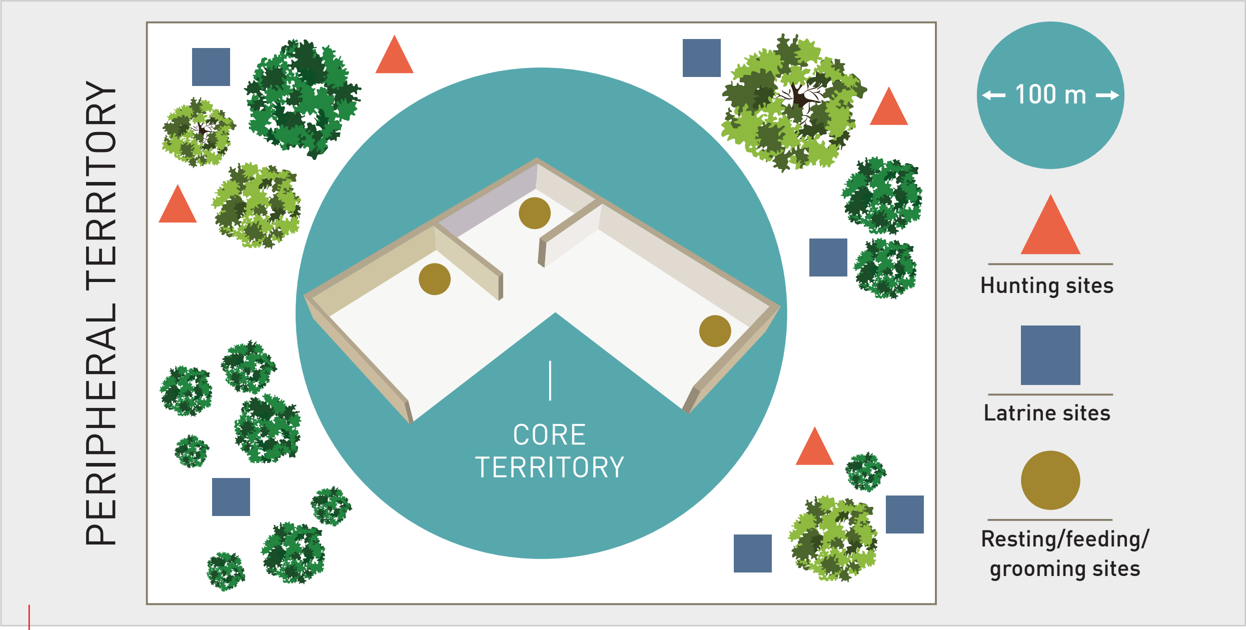

Figure 4. A diagrammatic representation of the territory of a free-ranging cat. Such cats have large territories (up to 0.5-1.3 km in length and an overall area of 300,000-1,700,000 m^2) with multiple hunting and latrine sites in the periphery, and places to eat, rest and groom in the core. For purposes of hygiene, latrines are located away from resting areas.

cues, such as light level and vegetation type, provide information that enables the cat to predict when and where prey will be available. The decision to hunt is then dependent on the cat's physical condition and the balance of competing internal motivational states (*e.g.*, the motivation to self-maintain versus finding a mate or hunting for prey).

Free-ranging cats tend to establish quite rigid personal temporal and spatial routines of hunting, feeding, territorial and self-maintenance behavior **(Figure 4)**. One reason for this is that, unlike dogs, cats do not have specific behavioral mechanisms for regulating conflict around shared resources. Instead, they use scent marks (*e.g.*, urine and claw marks) and distance maintaining signals (*e.g.*, threatening body postures, eye contact and vocalization) to keep apart from each other. Cats do voluntarily form colonies in areas where there is a surplus of shelter and food, but this still does not involve cooperation of the kind which can be seen in a group of dogs. Instead, it reflects the increased level of social tolerance that members of such groups possess; socially tolerant cats can coexist and take advantage of an area of increased prey and shelter availability, whilst socially intolerant cats would never choose to live in such groups. This combination of individualism and facultative sociability enables the feline species to inhabit a wide range of environments. A short summary of feline feeding behavior is given in **Box 1**.

How easily do cats adapt to domestic living?

This article started by considering the idea that offering food is an important aspect of caregiving for people. All sorts of social conventions surround this in humans, and usually the recipient of the food is expected to somehow show that their needs have been met. In some cultures it is polite to leave a tiny amount of food at the edge of the plate, in order to show that one's appetite has been more than satisfied. In others it is considered rude not to eat absolutely everything and then round off the meal with a loud belch. Either way, consumption is evidence of satisfaction, and dogs are usually more than happy to comply with this social norm.

Cats, on the other hand, are more concerned with food as a refueling stop between other activities. Feeding has no social significance, and cats will often take only a couple of mouthfuls before walking away from the bowl. Owners can misinterpret this as dissatisfaction, and may feel obliged to offer increasingly attractive alternatives. In itself, this may not be a major issue, but in some instances it could lead to accidental over-feeding and can be frustrating for the owner.

A more serious problem is the timing and frequency of meals. Putting out food for cats twice daily will only work if the food remains fresh and is available throughout a 24-hour period. Otherwise there will be periods when the cat has no access to food.

Box 1. A summary of feline eating behavior.

- Cats eat up to 20 small meals each day.
- They eat throughout a 24-hour period.
- Hunting and feeding are not social activities that are regulated by the presence of other cats.
- Cats follow strict individual routines of hunting, feeding and self-maintenance.

Figure 5. In many homes food bowls are placed uncomfortably close to latrine and water sites, or where there is a lot of noise and activity. This can deter cats from feeding, especially if other cats are nearby.

Figure 6. This stationary tower requires a cat to move food down through various levels using its paws before it can eat the kibble.

Meal-fed cats will try to adapt to this pattern of feeding by consuming a much larger than normal amount of fresh food at each mealtime, which may be uncomfortable for them. The situation is worse in multi-cat households in which cats share food bowls, because this leads to cats queuing for food. To understand what this must be like, imagine that instead of having your own portion of breakfast, lunch and dinner every day, you were given one single massive meal randomly once or twice a week, shared with other people who were equally hungry and desperate to get their share of the food. Feeding on-demand is equally bad because the owner will be asleep or absent at key times when cats are at their most active and need to eat (*e.g.*, at dawn and dusk).

Box 2. Tips for better eating habits.

- Cats need free access to food so that they can eat small regular amounts throughout the day and night.
- It is normal for cats to eat a small amount and then walk away from the bowl.
- Feeding a single main foodstuff, with occasional small amounts of novel food items, is probably the most natural pattern for cats, and the relative monotony may help to reduce the risk of overconsumption.
- Activity feeders help to provide mental stimulation, and should be used to prevent over-consumption in *ad-lib* fed cats.
- Owners need to find other ways to show care, such as playing hunting games and talking to their cats!

Apart from an inappropriate feeding frequency, meal and on-demand feeding tether the cat's routine to that of the owner. Given the fairly strict routines that cats follow, having an owner who gets up or arrives home at different times during the week can create a stressfully unpredictable routine for the cat.

As a demonstration of how important this can be, at least two studies have investigated the importance of routine and predictability in the lives of cats. Both found that an irregular pattern of feeding, lighting, heating, cleaning and social contact led to an increase in stress-related behaviors. One study that looked at cats exposed to an unpredictable routine reported that the animals showed elevated urinary cortisol, reduced exploratory behavior, and increased arousal and hiding patterns (12). Another study found that a similarly disrupted routine led to a 60% increase in urination outside the litter box, and a near ten-fold increase in defecation outside the litter box (13). This is an important finding, because the deliberate variations in routine the cats experienced in these studies are very similar to what the average cat has to tolerate. Apart from varying food availability, cats often experience abrupt and unavoidable owner-generated changes in lighting, heating, the presence of stimulation, and human contact.

When a cat starts defecating outside the litter tray, the owner will often look for a significant change or stressor that might be responsible; while many factors can be implicated, it may be the result of an overall lack of routine and predictability. Within this general lack of environmental predictability, feeding is probably the most critical aspect, as it is the area in which human and feline needs are the most incompatible. It is also the easiest thing to fix, and in many cases of inter-cat conflict and house-soiling the key to remedying the problem is to provide the cats with free access to food. It is also, however, important to consider the siting of the feeding area within the house **(Figure 5)**.

Owners are often concerned about offering free access to food, as they assume this will lead to obesity. In most cases this is not an issue, as long as access to food is through some kind of activity feeder that slows food consumption **(Figure 6)**, and the food is of sufficiently high-protein content. Cats appear to eat to satisfy a protein intake requirement, and as long as they consume their food slowly enough to allow them to reach satiation they tend not to over-consume. Although indoor cats are at greater risk of obesity because of a lack of activity, this is best tackled by providing a more stimulating environment, along with appropriate food control, rather than relying solely on dietary restriction.

By providing free access to food using activity feeders, we can provide a more natural feeding experience for cats that will reduce stress and frustration. However, owners may not feel comfortable with this because it removes an opportunity for caregiving. One solution that satisfies both owner and cat is to provide food through "hunting games". For example, playing a game with a fishing toy **(Figure 7)** that starts with stalking the toy as it appears and disappears behind furniture, and gradually progresses through the hunting sequence until it ends with a hidden tasty treat.

Figure 7. Owners need to find other ways to show care, such as playing hunting games with their cat.

CONCLUSION

Owners will often assume that human values apply to their cats, especially when it comes to food and feeding, and the clinician should be able to advise on a few basic rules as to what to do (and what not to do), as shown in Box 2. Getting the balance right between the needs of the cat and the owner is not too difficult once owners understand the differences between animals and humans, and an appreciation of basic feline ethology can lead to better interaction between pet and owner, ultimately resulting in a more satisfying and complete human-animal bond.

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BREED AND DIET-BASED DISEASE IN DOGS

When faced with a dog that has a severe problem it can be easy at times to overlook the significance that breed plays in susceptibility to a disease. Giacomo Biagi offers a brief overview of some common breed-related problems where diet can play a major role.

KEY POINTS

1. Certain dog breeds are predisposed to developing specific types of urolith, particularly in relation to urate, cystine and xanthine calculi.
2. Zinc deficiency should be considered when reviewing possible causes of dermatitis in dogs belonging to the Northern breed group, especially if periocular lesions are present.
3. Copper-storage disease is not exclusive to Bedlington Terriers and can affect many other breeds.
4. Some dogs, especially of the Northern breed group, can develop gastrointestinal signs due to an inherited inability to digest starch secondary to pancreatic amylase deficiency.

Introduction

Many canine diseases can result from an incomplete or imbalanced diet. Whilst the nutritional needs of dogs are well known nowadays (1) various deficiency syndromes that can result from a failure to meet these needs are also recognized. We also know that some essential nutrients can be toxic if taken in excessive quantities, for example hypervitaminosis A and D, and also some mineral trace elements such as selenium, cobalt and iodine.

However, there are also other diseases in dogs that can result from an inappropriate diet. Consider, for example, how diet can affect the appearance of urinary tract disease – and urolithiasis in particular – and problems with the digestive system, including those involving the liver and pancreas. Food allergies and intolerances can also be included in this category, with signs that mainly involve the cutaneous and gastrointestinal systems. Excessive calorie intake leads to obesity, which can be regarded as a pathological condition which predisposes dogs to a multitude of problems. Furthermore, human medicine has shown that there is a relationship between people's eating habits and the risk of developing certain tumors, although this association has yet to be studied extensively in animals.

Although there are many diet-based diseases that affect dogs, this article will discuss only those that appear solely, or much more frequently, in certain breeds and which are evidently predisposed to disease due to reasons of heredity.

Urolithiasis

The term "urolithiasis" refers to the presence of stones in the urinary tract, and whilst the condition can affect any dog there is plenty of evidence that certain breeds are more predisposed to developing specific types of uroliths.

Ammonium urate calculi

A typical example of a canine pathology that reflects a breed predisposition is ammonium urate stones in Dalmatians. In most dogs uric acid is formed by purine catabolism and converted through the action of the enzyme uricase to allantoin, which is then eliminated in the urine **(Figure 1)**. In Dalmatians, although uricase is present, hepatic transformation of uric acid to allantoin is rather inefficient, due to a genetic autosomal recessive defect, and Dalmatians eliminate much greater amounts of uric acid than other breeds in the urine. The situation is

Giacomo Biagi,

DVM, Ph.D., Department of Veterinary Medical Sciences, Alma Mater Studiorum – University of Bologna, Italy

Professor Biagi graduated with honors from Bologna in 1994 and was awarded his PhD for a thesis on "Qualitative improvement of food for humans". A researcher since 2001 and associate professor since 2010 at the University of Bologna, he heads the Facility for Animal Production and Food Safety. The author or co-author of more than 110 scientific publications, Prof. Biagi is currently President of the Italian Society of Nutrition and Animal Nutrition and a member of the FEDIAF Scientific Advisory Board.

complicated by the fact that re-absorption of uric acid at the level of the renal tubules in this breed is also less efficient. A combination of these factors results in the prevalence of urate stones (predominantly ammonium urate) being particularly high in Dalmatians, with the condition being much greater in males than in females **(Figure 2)** (2).

Ammonium urate calculi are not exclusively seen in Dalmatians, however, and there are other breeds which show a greater prevalence of this problem than the average canine population, including English Bulldogs, Miniature Schnauzers, Shih-Tzus and Yorkshire Terriers.

Other risk factors for the development of ammonium urate stones – in addition to a genetic predisposition – include the presence of a portosystemic shunt or, more commonly, any serious liver disease which compromises the conversion of uric acid to allantoin and ammonia to urea.

With respect to dietary therapy, dogs with a predisposition to developing this type of urolith should avoid diets rich in purines; these tend to be found in large quantities if a foodstuff contains high levels of ingredients such as meat and organs. Protein sources such as eggs and cheese are therefore preferred, or a commercial low-purine diet is widely available[1]. Diets that tend to acidify the urine should also be avoided, and if necessary the diet should be slightly alkalized by the addition of potassium citrate (80-150 mg/kg q24H) (3). As with any type of urinary calculus, it is important to stimulate water intake in order to obtain more dilute urine and reduce salt precipitation (4). Finally, uric acid formation may be reduced by using oral allopurinol (15 mg/kg q12H) which inhibits the activity of xanthine oxidase and therefore the conversion of hypoxanthine and xanthine to uric acid. Remember, however, that an animal treated with allopurinol will tend to form xanthine crystals in the bladder if fed a diet which contains high levels of purines.

Cystine calculi

Cystine consists of two molecules of the sulfurous amino acid cysteine. When cystine is present in urine in high concentrations it tends to form crystals because of its poor solubility. Cystine urolithiasis in dogs is quite rare, with an incidence estimated to be only 1-3% of all cases of canine

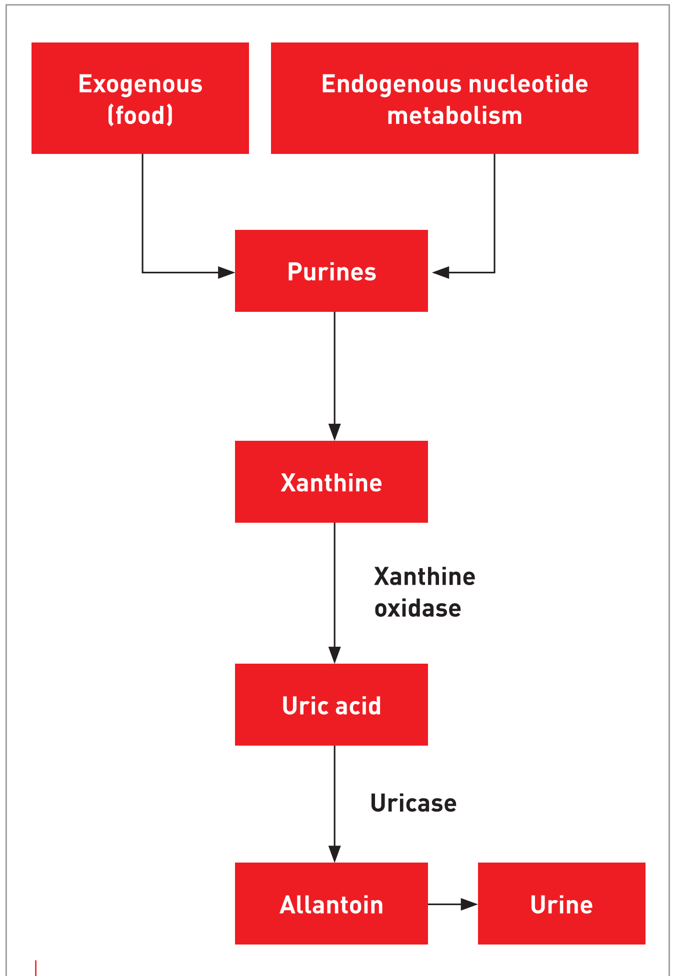

Figure 1. Purines in the body are metabolized to xanthine and then uric acid before being converted by the enzyme uricase to allantoin, which is then excreted in the urine. Dalmatians are homozygous for a genetic mutation that results in a defect of the hepatic and renal uric acid transporter, resulting in a lower conversion rate of uric acid to allantoin; this is compounded by reduced reabsorption of uric acid by the proximal renal tubules, leading to high levels of uric acid in the bladder and increased risk of urate calculi formation.

[1] Royal Canin Urinary U/C low purine

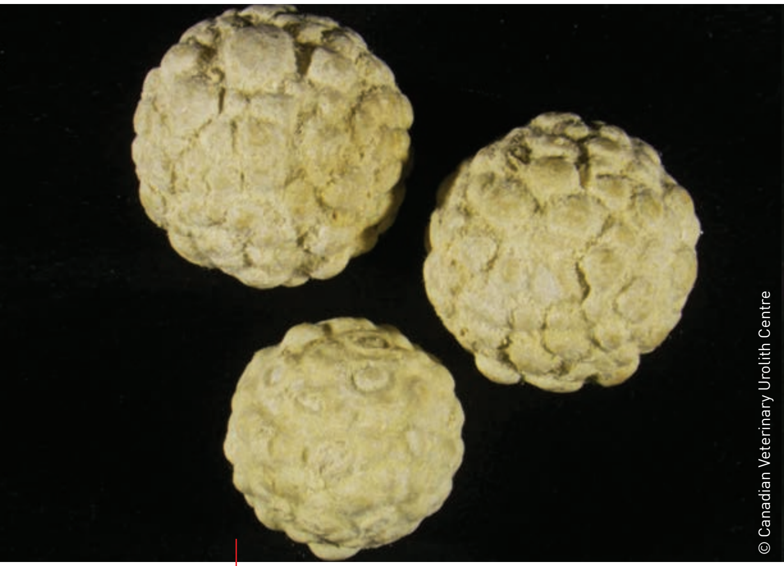

Figure 2. The typical appearance of urate stones, which are predominantly ammonium urate.

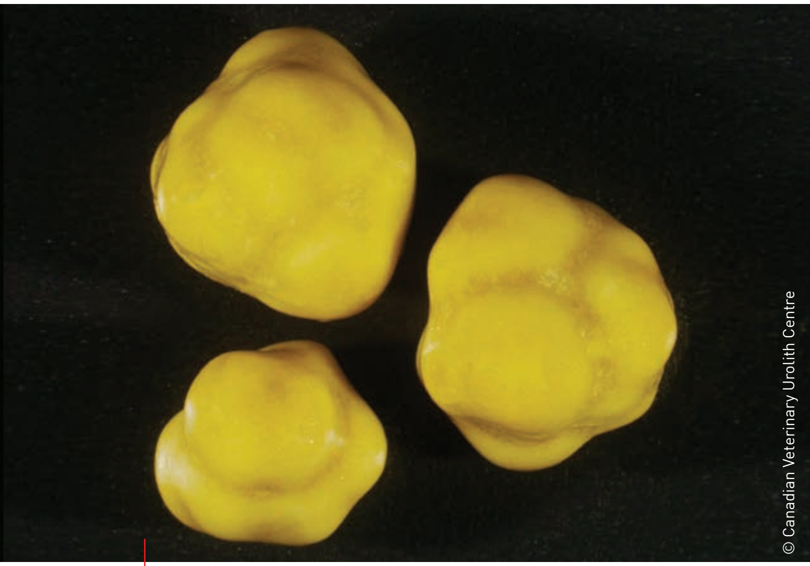

Figure 3. Cystine uroliths are estimated to be found in only 1-3% of all cases of canine uroliths.

uroliths **(Figure 3)** (5). However, forms of hereditary cystinuria have been observed in several breeds of dog, including Dachshunds, Basset Hounds, Irish Terriers and English Bulldogs, with a higher prevalence in males.

If a dog is prone to cystine urolithiasis a diet with a moderate protein content (to limit the intake of sulfurous amino acids) and which delivers an alkaline urine (if necessary by adding potassium citrate at the above dose) is recommended. Cystine has poor solubility in acidic urine but the solubility increases when the pH becomes alkaline, and cystine stones may be dissolved by dietary therapy alone through alkalinization of the urine. If dietary alteration is insufficient, drugs that further increase cystine solubility may be used, such as tiopronin (30-45 mg/kg q24H PO) or D-penicillamine (10-15 mg/kg q12H PO). When cystine stones are present it is also a good idea to increase water intake to dilute the urine. However, since a human study has shown that increasing dietary sodium intake corresponds to a higher elimination of cystine into the urine, it is advisable to avoid excessive use of table salt to induce thirst and increase the volume of urine (5).

"Many diseases with a breed disposition are partly or completely related to diet; clinicians must be vigilant to the possibility that a dog's disease is linked to what it is fed."

Giacomo Biagi

Xanthine calculi

Xanthine also originates from the catabolism of purines and is the precursor of uric acid. Since xanthine is not very soluble, when present at high concentrations in the urine it can result in the formation of crystals and sometimes uroliths. As noted above, the presence of xanthine crystals and stones in the urine **(Figure 4)** is generally a consequence of allopurinol therapy; this drug, as well as being used as a therapy for ammonium urate urolithiasis, is often used to treat leishmaniasis. However, there is also a hereditary form of xanthinuria, which is well known in humans and has also been reported in the Cavalier King Charles Spaniel (CKCS) (6). The problem seems to be rare; in the course of a recent study conducted on 35 CKCS dogs, none presented with xanthinuria (7). As with urates, if xanthine urolithiasis is detected a diet low in purines is recommended[2].

Zinc-responsive skin disorders

There are many nutrients that an animal needs included in its diet to support a healthy skin; one of the most important is zinc. Any dog fed a zinc-deficient diet will eventually develop a dermatosis, but there are two specific forms of zinc-responsive canine skin disorders. The first form typically affects puppies, especially large breeds, fed diets deficient in zinc or diets rich in substances capable of binding zinc and preventing its absorption, such as phytates, which are found in some raw plant materials. The second form is hereditary in nature and is usually seen in Northern breed dogs, such as the Alaskan Malamute and Siberian Husky, although

[2] Royal Canin Urinary U/C low purine

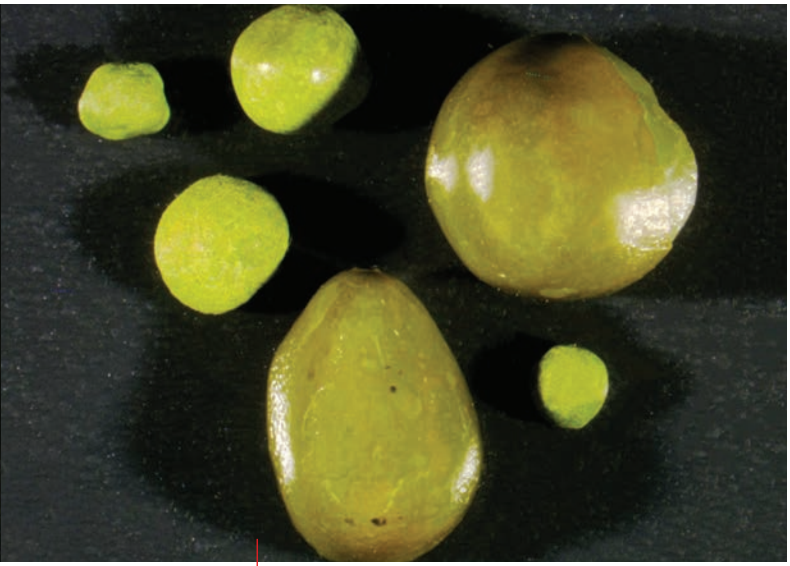

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Figure 4. Xanthine uroliths are rarely seen in dogs, although a hereditary form of xanthinuria has been reported in the Cavalier King Charles Spaniel breed.

Dobermans and Bull Terriers are also known to be affected **(Figure 5)**. Literature reports of this form of zinc-responsive dermatitis suggest that clinical signs – which can include crusting and erythema of the periorbital areas – may develop due to poor absorption of zinc in the intestine (8). This dermatosis should be treated by oral administration of a zinc salt, such as zinc methionine, zinc sulfate or zinc gluconate. The recommended dose is typically 2-3 mg/kg q24H of elemental zinc, but the clinician should be careful, as the labeling may be confusing. For example, a tablet labelled as "zinc sulfate 220 mg" actually contains 50 mg of zinc, whereas a "zinc gluconate 50 mg" tablet may contain 50 mg of actual zinc (8).

Copper-storage hepatopathy

Hereditary copper storage hepatopathy was typically associated with the Bedlington Terrier breed and has parallels with Wilson's disease in humans. In Bedlington Terriers the disease is transmitted by an autosomal recessive gene, which limits excretion of copper in the bile, causing copper to accumulate in the liver (9). The high levels of hepatic copper are toxic and promote the onset and progression of liver disease. Breeding programs have largely eliminated this problem from Bedlington Terriers, but hereditary copper-storage hepatopathies have also been observed in other breeds such as Skye Terriers, West Highland White Terriers, Dobermans, Dalmatians and Labrador Retrievers. It should also be remembered that if chronic copper-storage hepatopathy is found on biopsy, copper may have accumulated as a consequence of liver disease, rather than being the cause, as a liver disorder can reduce copper excretion into the biliary system (10).

In the presence of liver disease, if copper accumulation is detected (via analysis of a liver biopsy) it is essential that a diet with a copper concentration lower than the normal minimum requirements of the adult dog is offered. The diet should also contain high levels of zinc (at least 200 mg of zinc per kg of diet (DM)) (11), as this activates metallothionein, a protein that binds copper within the intestinal epithelial cells and inhibits its absorption. In cases where liver copper levels are particularly high, copper chelators (*e.g.*, D-penicillamine at 10-15 mg/kg q12H PO) should be added to the diet to minimize intestinal absorption. Finally, the chosen diet must be suitable for managing chronic liver disease, and the clinician should assess potential diets for protein and fat

Figure 5. Zinc-responsive dermatitis is most commonly seen in Northern breeds of dog, with clinical signs that can include crusting and erythema of the periorbital area **(a)** and muzzle **(b).**

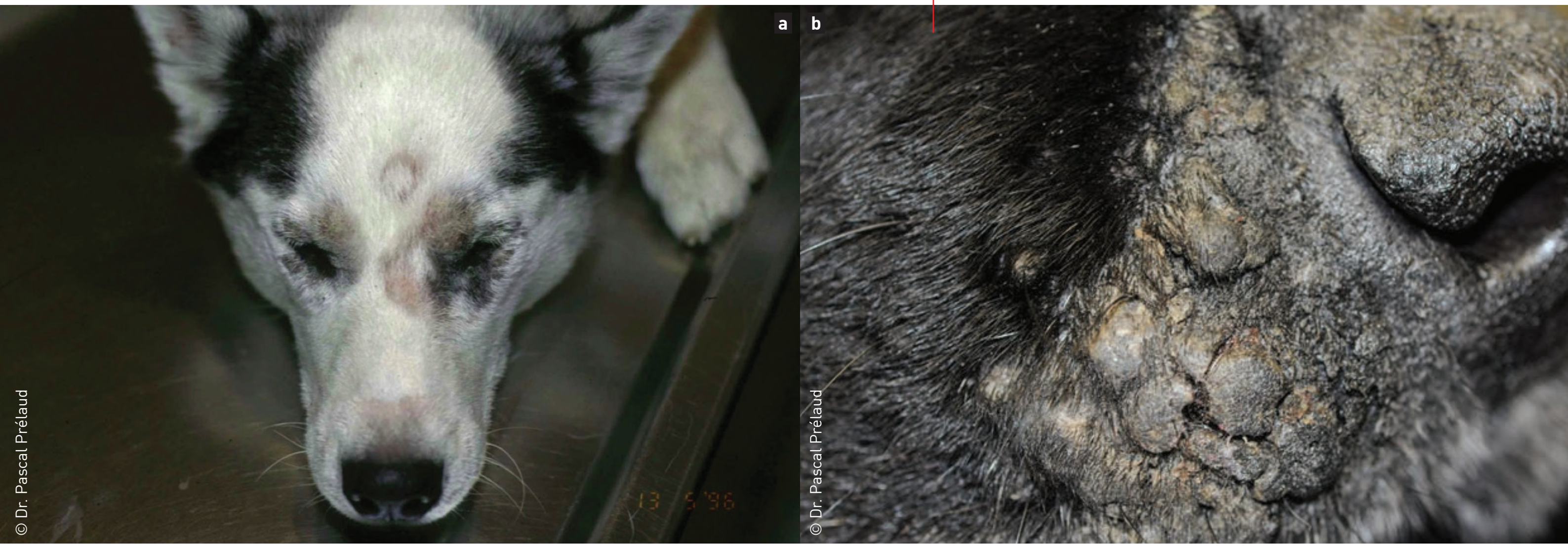

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Figure 6. Some Northern breed dogs, including the Shiba Inu, have a lower capacity to digest starch due to an inherited inability to produce amylase.

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Figure 7. The same defect in starch digestion appears to exist in several other breeds, such as the Czechoslovakian Wolfdog.

content according to the clinical picture. The use of nutraceutical ingredients that act as antioxidants and promote regeneration of hepatic tissue should also be considered, for example extract of milk thistle (especially S-adenosyl-methionine (SAME, at 20 mg/kg q24H), ursodeoxycholic acid (15 mg/kg q24H) or silymarin; the therapeutic dose has not been determined for this latter drug, but the author recommends 4-8 mg/kg q24H) (12).

Hereditary gluten intolerances

The term "gluten" refers to the wheat proteins gliadins and glutenins. Wheat gliadins are very similar to the prolamins contained in other cereals, such as barley, rye and oats. In humans, gluten ingested in the diet is responsible for celiac disease, a chronic hereditary enteropathy that affects 1% of the world's human population (13). Gluten enteropathy in Irish Setter dogs has been widely recognized (14), although selective breeding has now all but eliminated or greatly reduced this problem in many countries.

Gluten enteropathy is characterized histologically by a variable degree of atrophy of the intestinal villi, with the presence of cellular infiltrate in the lamina propria and the epithelium. The alteration of the intestinal architecture has various effects, including decreased enzyme activity of the ciliated border. Affected Irish Setters fed a gluten-containing diet typically show clinical signs of malabsorption, such as chronic diarrhea, weight loss and eventually emaciation, which can develop from around six months of age. Wheat gluten is certainly the trigger for the disease, but to date it is not clear whether barley, rye and (possibly) oats are also harmful for dogs with gluten enteropathy; all these cereals are generally detrimental in human celiac disease patients. The elimination of gluten from the diet leads to an improvement in clinical signs and resolution of the lesions in the intestinal epithelium, and for this reason it represents both the therapy and the only safe method to diagnose the pathology (13).

More recently, a possible role for gluten in the etiology of two other breed-related canine diseases has been proposed. Firstly, gluten seems to play a major role in the so-called "epileptoid cramping syndrome" seen in the Border Terrier. The condition is characterized by neurological signs, with episodes of paroxysmal dyskinesia, sometimes associated with gastrointestinal disorders (15). It has been postulated that this disease results from a hereditary gluten intolerance and at least one study has shown that feeding a gluten-free diet can cause resolution of clinical signs in affected animals (16). Secondly, the role of gluten has also been studied in

"Zinc-responsive dermatitis can be hereditary in nature and is usually seen in Northern breeds, such as the Alaskan Malamute and Siberian Husky, although other breeds can also be affected."

Giacomo Biagi

protein-losing enteropathy (PLE) and protein-losing nephropathy (PLN) in Soft-Coated Wheaten Terriers (17). The authors of this study observed that the administration of gluten to affected dogs resulted in a reduction in blood globulins, but concluded that there were also other factors involved in the pathogenesis of the diseases, and that there did not appear to be a true gluten intolerance in this breed.

Amylase deficiency and starch digestion

In the course of evolution, or (more accurately) in the process of domestication by humans, the canine species has acquired the capacity to digest starch (18). This contrasts with its progenitor, the wolf, which does not possess this ability. However, it is well recognized that this ability is not equally developed in all breeds; some dogs, especially the Northern breeds, have a lower capacity to digest starch, and affected dogs can develop intestinal disorders with signs such as malformed stools and diarrhea if fed high-starch diets. A recent report demonstrated that production of amylase, the pancreatic enzyme responsible for digesting starch, is less efficient in some Northern breed dogs, such as the Siberian Husky, Alaskan Malamute, Akita Inu and Shiba Inu **(Figure 6)** (19). Note that this condition is distinct from the more commonly seen exocrine pancreatic insufficiency. It has been suggested that starch was not an important source of energy for the Northern breeds during their evolutionary selection. The same defect in starch digestion appears to exist in several other breeds, such as the Czechoslovakian Wolfdog **(Figure 7)**, but to date there are no scientific studies to prove this. Starch-intolerant dogs should be provided with a diet that is free from starch or contains it in quantities that the animal can tolerate.

Other pathologies

There are many other conditions in dogs with a hereditary basis and that are in some way related to nutrition. Space limits a discussion of such conditions but it is briefly worth noting two of them. Firstly, hypertriglyceridemia has been reported in the Miniature Schnauzer (20) and it has been suggested that dogs with severe hypertriglyceridemia might be at increased risk for the development of pancreatitis, seizures, or both, although the relationship between these disorders and the hypertriglyceridemia has not been proven (21). A diet low in lipids and enriched with fish oil (a source of omega-3 fatty acids that can reduce serum triglyceride levels) is advised for affected animals. Secondly, a defect in the intestinal absorption of vitamin B_{12} (cyanocobalamin) has been occasionally observed in some breeds, including the Giant Schnauzer, Border Collie, and Beagle (22). Referred to as Imerslund-Gräsbeck syndrome (IGS), affected dogs may show a lack of appetite, failure to gain weight, lethargy and malaise that intensifies after eating. Clinically, anemia and excess proteinuria is observed. The treatment simply involves administration of cyanocobalamin on a long-term basis.

CONCLUSION

Knowledge of dog breeds and the diseases to which the various breeds are predisposed is of great help in daily practice and can enable the veterinarian to arrive at a correct diagnosis of these diseases more quickly. Many diseases with a breed disposition are diet-based and require action be taken with the animal's diet to better manage the problem.

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LEWISBURG PET HEALTH AND NUTRITION CENTER

KEY POINTS

The main purpose of the Lewisburg Center is to assess palatability, digestibility and RSS of Royal Canin diets and help improve them.

1

The Lewisburg center specializes in areas such as skin and coat health, mobility, immunity and aging.

2

Sally Perea,

DVM, MS, Dipl. ACVN, Lewisburg, Ohio, USA

Dr. Perea is a Diplomate of the American College of Veterinary Nutrition, having completed her clinical nutrition residency, DVM, and MS at the University of California, Davis (UCD) before serving there as an Assistant Clinical Professor. She later went on to work within industry, and is currently with Royal Canin Research and Development.

The more we know, the more we need to know… Sally Perea showcases the latest addition to Royal Canin's worldwide network of research facilities, and underlines the company's commitment to continue the mission to identify the best possible nutrition for our pets.

Delivery of high-quality nutrition to cats and dogs is a multi-step process. The procedure begins with a scientific observation, followed by the development of a research hypothesis, and ultimately to the validation of a new nutritional solution and novel product development. Evaluation of product performance is not only a cornerstone of this development process, it is crucial for ongoing product monitoring and continuous improvement.

The Pet Health and Nutrition Center (PHNC), located at Lewisburg, Ohio, was acquired by Royal Canin in 2014 to help expand the company's research capabilities with the rapidly growing North American market. The PHNC now serves as one of two pet centers within the Royal Canin network, increasing the company's capacity to respond to research needs and undertake investigation in defined areas of specialty. Both centers evaluate key

© Brandon Schneider

The rural location of the Lewisburg Center permits plenty of space for dogs to exercise freely.

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Cats are housed in large purpose-built rooms designed to offer maximum stimulation and opportunities for recreation and exercise, such as climbing frames.

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Standard Poodles **(a)** and German Shorthair Pointers **(b)** are two of the breeds at the PHNC that enjoy daily exercise and play at the large outdoor dog park.

product performance measures, such as palatability, digestibility, and urinary relative super saturation (RSS). In addition, the PHNC provides focus in specific areas such as skin and coat health, mobility, immunity, and aging. This additional level of expertise helps to enable increased nutritional precision and the development of products tailored to individual pet needs. All the research involves only healthy animals and is non-invasive in nature.

The PHNC associates also bring a valuable depth of knowledge to veterinary and nutritional research worldwide, working together with experts at the Royal Canin campus in Aimargues, France, and the WALTHAM Centre for Pet Nutrition in Melton Mowbray, UK. This expanding collaborative network helps to foster advancements in animal welfare, scientific methods, innovative thinking, and – ultimately – the delivery of high-quality nutrition for cats and dogs.

"Evaluation of product performance is key to the success of Royal Canin, both in developing new diets and for ongoing monitoring and improvement of existing products."

Sally Perea

The Ragdoll is one of the newer cat breeds introduced to the PHNC, enabling Royal Canin to continue to build knowledge on breed-specific nutritional needs.

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The Bengal is another unique cat breed, helping to diversify the breed representation at the PHNC.

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VITAMIN D IN CANINE HEALTH

Nobody ever said that vitamins are an easy subject to understand – and although they are essential for life, too much or too little of a vitamin can make a huge difference to an animal's health. Valerie Parker makes it all clear in her excellent review of Vitamin D.

KEY POINTS

1. Vitamin D metabolism is complex and is affected by numerous dietary and hormonal factors.
2. Depending on the methodology used, vitamin D metabolite concentrations can vary dramatically, and inter-laboratory results may not be comparable.
3. Dietary vitamin D intake cannot predict a dog's 25(OH)D status.
4. Various forms of vitamin D supplementation exist, but it is not clear what the best form of supplementation is for most diseases.

Vitamin D synthesis and metabolism

In many species, the biosynthesis of vitamin D begins with exposure to UV light, whereby 7-dehydrocholesterol is transformed to previtamin D_3. Factors that affect synthesis of vitamin D_3 include quantity and quality of the UV light, the animal's coat type, and skin pigmentation. Dogs differ from humans (and many other species) in that they lack the ability to synthesize vitamin D_3 in the skin, likely because of high activity of the enzyme 7-dehydrocholesterol-Δ7-reductase. For this reason, dogs require dietary supplementation with vitamin D to meet nutritional requirements. There are two dietary forms of vitamin D: cholecalciferol (vitamin D_3), which typically comes from animal food sources, and ergocalciferol (vitamin D_2), which typically comes from plant sources.

Vitamin D is supplied in commercial dog foods in the form of various ingredients (*e.g.*, organ meat or oily fish products) and supplemental cholecalciferol. Current AAFCO[1] recommendations for minimum and maximum amounts of dietary vitamin D intake are 125 IU and 750 IU per 1000 kilocalories, respectively. While the cholecalciferol concentration in most commercially available diets has minimal impact on a dog's serum 25(OH)D concentration, it can, if given in high enough quantities (up to 2700 IU/kg body weight) impact serum 25(OH)D concentrations (1). Clinicians should be aware that this dose far exceeds the National Research Council (NRC) safe upper limit of 2.6 μg (*i.e.*, 104 IU) per kg body weight (BW)$^{0.75}$.

Once ingested, vitamin D is transported to the liver via the portal system and intestinal lymphatics **(Figure 1)**. This process requires digestive enzymes, chylomicrons, bile acids, vitamin D-binding protein (VDBP), and transcalciferin. In the liver, cholecalciferol is hydroxylated by 25-hydroxylase to form 25(OH)D (also known as calcidiol or calcifediol), which binds to VDBP in the circulation. With a half-life of approximately 2 to 3 weeks, 25(OH)D is thought to be the most reliable indicator of systemic vitamin D status.

25(OH)D is then hydroxylated (by 1α-hydroxylase) to form 1,25(OH)$_2$D (also known as calcitriol), the most active naturally occurring vitamin D metabolite; this affects many target cells via a vitamin D receptor (VDR)–mediated mechanism **(Figure 1)**. Calcitriol binds to the VDR much more readily (approximately 500 times) than vitamin D_3 or 25(OH)D. This activation of 1,25(OH)$_2$D occurs predominantly in the kidneys but also in other tissues that express 1α-hydroxylase. In dogs, VDR expression has been identified in several tissues, especially the kidney, duodenum, skin, ileum, and spleen. Although the exact mechanism has not been completely elucidated, 1α-hydroxylase activity is tightly

[1] AAFCO – Association of American Feed Control Officials

Valerie J. Parker,

DVM, Dipl. ACVIM, Dipl. ACVN, The Ohio State University (OSU) Veterinary Medical Center, Columbus, USA

Dr. Parker received her DVM from Tufts University and went on to complete a small animal internship at the Animal Medical Center in New York City. She then undertook a small animal internal medicine residency at Iowa State University and a clinical nutrition residency at Tufts University. She is currently associate professor at OSU, with research interests that include vitamin D status in chronic kidney disease and its relationship to nutrition management.

regulated by serum concentrations of calcium, parathormone (PTH), 1,25(OH)$_2$D, fibroblast growth factor 23 (FGF-23), and activity of the enzyme Klotho. Within cells, 1,25(OH)$_2$D can promote or suppress gene transcription and expression. Both 25(OH)D and 1,25(OH)$_2$D are inactivated via 24-hydroxylase to form 24,25(OH)$_2$D and 1,24,25-trihydroxyvitamin D respectively, and other metabolites (*e.g.*, 25[OH]D-23,23 lactone) that are excreted in the urine and bile.

Vitamin D roles

Classically, vitamin D is known for its influence on calcium-phosphorus homeostasis via the bone-parathyroid-kidney axis. However, vitamin D has multiple other effects throughout the body, as evidenced by the wide variety of cells that express the VDR. Actions induced by VDR activation in humans include differentiation of immune cells, reductions in inflammation and proteinuria, increased insulin secretion, and improvement of hematopoiesis.

Measuring vitamin D metabolites

There are no universally accepted "normal" reference ranges for vitamin D metabolites. Part of the difficulty in interpreting laboratory results relates to the fact that multiple techniques are employed to measure the metabolites; these include liquid chromatographic methods, immunoassay techniques, chemiluminescence immunoassays, and radioimmunoassays. There can be significant inter-assay, intra-assay, and inter-laboratory variance. In an effort to assist in the development of standard reference materials and to examine differences among assay performance the National Institute of Standards and Technology (NIST) and the National Institutes of Health (NIH) Office of Dietary Supplements (ODS) established a Vitamin D Metabolites Quality Assurance Program (VitDQAP). Comparability of vitamin D metabolite measurements has improved greatly over time via development of these quality control efforts; however, the studies were performed with human samples, and the effect of a canine or feline matrix on these variables and comparability of results is unknown.[2]

Liquid chromatography assays are currently the most commonly used methods and remain the criterion-referenced standard (liquid chromatography with tandem mass spectrometric detection) for measurement. Wherever possible, it is recommended to use a laboratory that has received certification either from The Centers for Disease Control and Prevention (CDC) Vitamin D Standardization-Certification Program (VDSCP) and/or the Vitamin D External Quality Assessment Scheme (DEQAS) to increase the likelihood of accurate results.[3]

How much vitamin D is enough?

Defining 25(OH)D sufficiency, insufficiency, and deficiency is controversial. In humans, vitamin D deficiency is generally defined as < 20 ng/mL and sufficiency is generally >30 ng/mL. Optimal repletion is defined by some as > 50 or > 60 ng/mL to achieve the aforementioned pleiotropic effects on the VDR. Multiple variables (including signalment, disease, assay technique, and physiologic variation) affect the reference range and the therapeutic target range. Consensus on optimal, adequate, or deficient vitamin D status in healthy canine populations has not been determined. Wide ranges of 25(OH)D concentrations have been reported for healthy dogs, and there is no universally accepted "normal" range – and importantly, assay choice and technique differ among many of these studies. In one study of apparently healthy dogs, the circulating 25(OH)D concentrations varied markedly, from 9.5 to 249 ng/mL (2).

Vitamin D metabolite status in various diseases

Kidney disease

Vitamin D metabolites have been measured in dogs with several forms of kidney disease, including acute renal failure, chronic kidney disease (CKD), and proteinuric kidney disease. Dogs with CKD have lower 25(OH)D and 1,25(OH)$_2$D concentrations compared with concentrations in control dogs (3-5). Vitamin D metabolites are correlated with the stage of kidney disease (determined via International Renal Interest Society criteria), as indicated by the

[2] www.nist.gov/programs-projects/vitamin-d-metabolites-quality-assurance-program

[3] see www.cdc.gov/labstandards/vdscp.html and www.deqas.org/

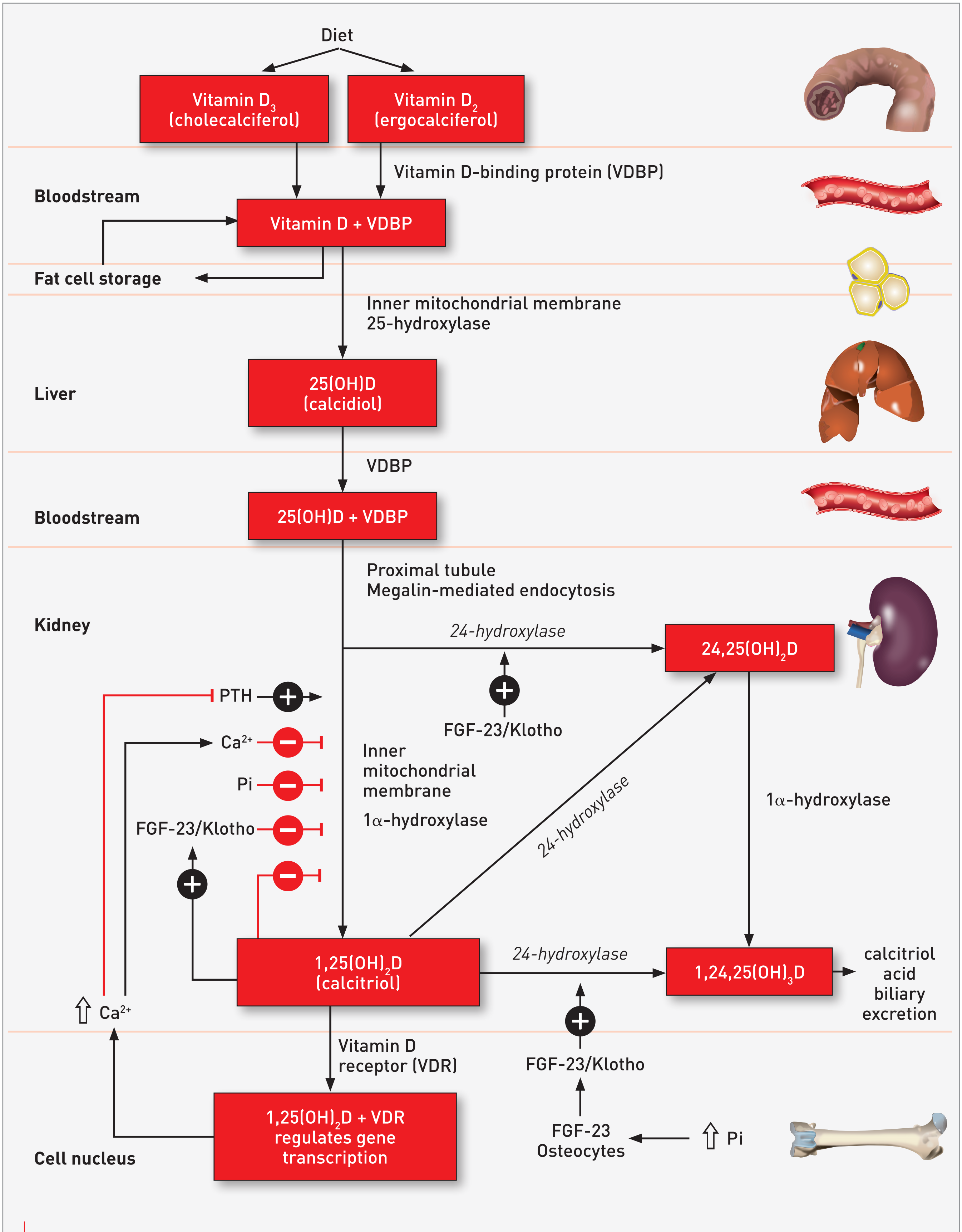

Figure 1. An overview of vitamin D metabolism, starting with dietary intake and progressing through hepatic and renal transformation. The black lines and (+) signs indicate a stimulus, and red lines and (–) signs indicate negative feedback or decreased activity. Also note the influences of phosphate (Pi), ionized calcium (Ca^{2+}), FGF-23, Klotho, and PTH.

fact that concentrations of 25(OH)D, 1,25(OH)$_2$D and 24,25(OH)$_2$D are significantly decreased in dogs with stage 3 kidney disease, compared with control dogs (3,4). However, in other studies, many dogs had 25(OH)D and 1,25(OH)$_2$D concentrations within reference limits (6,7). One possible explanation for this lack of difference could be the inclusion of dogs with earlier stages of CKD. Alternatively, significant differences in concentrations of vitamin D metabolites may not have been detected because of relatively large reference ranges or the method used to calculate reference ranges.

One of the consequences of CKD is the development of secondary hyperparathyroidism and CKD-induced mineral and bone disorders **(Figure 2)**. Plasma FGF-23 concentrations are increased in dogs with CKD, and the concentration of FGF-23 has been found to be negatively correlated with 25(OH)D, 1,25(OH)$_2$D, and 24,25(OH)$_2$D concentrations and survival in dogs with CKD (4,8). Calcitriol treatment has been recommended for several decades for dogs with CKD to reduce PTH concentrations and improve quality of life. However, prospective, controlled clinical studies are needed to determine the manner in which supplementation with various forms of vitamin D influences FGF-23 concentrations, Klotho expression, vitamin D repletion, quality of life, preservation of renal function, and survival.

Finally, dogs with acute renal failure have been reported to have significantly lower 25(OH)D and 1,25(OH)$_2$D concentrations, compared with control dogs, but most (7/10) of the dogs with acute renal failure had concentrations within reference limits (6). These findings possibly could have been attributable to acute inflammation or critical illness, or could have been spurious results. Proteinuric dogs have significantly lower 25(OH)D, 1,25(OH)$_2$D, and 24,25(OH)$_2$D concentrations than control dogs. This relationship has been definitively established in people with proteinuria, and VDR activators are frequently prescribed to reduce proteinuria in such cases.

There are several mechanisms by which vitamin D metabolism can be disrupted with kidney disease, including decreased dietary intake of vitamin D, decreased enzymatic conversion from cholecalciferol to 25(OH)D in the liver, decreased activation via 1α-hydroxylase from 25(OH)D to 1,25(OH)$_2$D, and increased inactivation of 25(OH)D and 1,25(OH)$_2$D. With proteinuria, there are additional potential mechanisms to consider, including urinary loss of VDBP (with 25(OH)D and 1,25(OH)$_2$D bound to VDBP) and decreased endocytosis of 25(OH)D into renal cells because of decreased megalin expression in the proximal renal tubules. Furthermore, inflammation may act to reduce 25(OH)D concentrations.

Neoplasia

Decreased 25(OH)D concentrations have been linked to increased risk of numerous neoplasms in humans, and 1,25(OH)$_2$D has been found to have antineoplastic activity. Concentrations of circulating vitamin D metabolites have been measured in dogs with various tumors and serum 25(OH)D concentrations are significantly lower in many

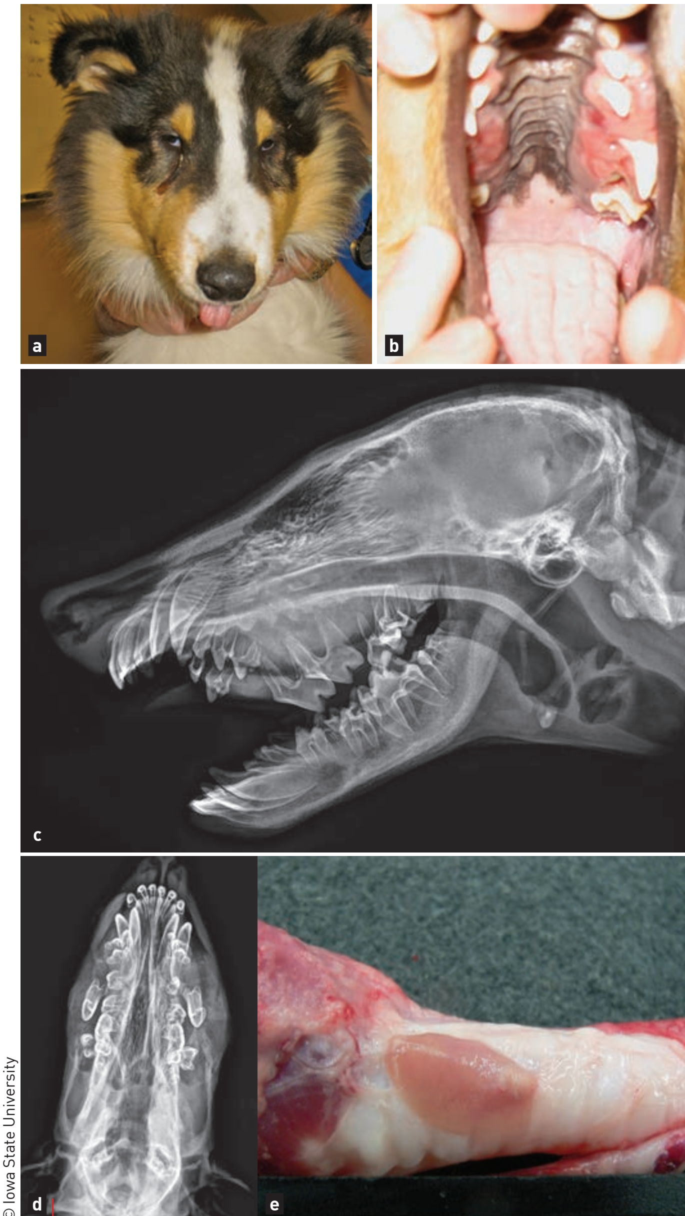

Figure 2. A 5-month-old male Collie dog that presented with a widened maxilla **(a)**. This was due to congenital renal dysplasia and subsequent renal secondary hyperparathyroidism (*i.e.*, CKD-mineral bone disease; CKD-MBD). Examination of the maxilla revealed fibrous osteodystrophy **(b)**, which was confirmed histologically. Skull radiographs **(c,d)** revealed severe loss of normal alveolar bone with the majority of the maxillary premolars and molars displaced ventrolaterally with a large amount of adjacent soft tissue swelling, giving an appearance that the teeth are “floating” in soft tissue. Postmortem examination revealed parathyroid gland hyperplasia secondary to the congenital renal dysplasia and chronic kidney disease **(e)**.

"Vitamin D homeostasis is characterized by complex interactions in the body, and the regulatory pathways can be disrupted in a variety of ways. Various diseases have been associated with lower concentrations of vitamin D metabolites, whereas others have been associated with increased concentrations."

Valerie J. Parker

neoplastic conditions, including dogs with neoplasia and hemoabdomen, cutaneous mast cell tumor, and lymphoma. It is not clear whether dogs develop hypovitaminosis D secondary to neoplasia or whether hypovitaminosis D is actually a risk factor for development of cancer. Dogs with neoplasia are often ill; this puts them at risk of developing hypovitaminosis D from a reduced appetite, which leads to reduced cholecalciferol intake, and potentially from decreased intestinal absorption of cholecalciferol. It has recently been suggested that alteration of 25(OH)D concentrations in dogs with various neoplasms is mediated by ionized calcium concentrations (9).

Serum 1,25(OH)$_2$D concentrations have been measured in populations of dogs with lymphoma, both with and without hypercalcemia, with wide differences in findings. From an antineoplastic standpoint, calcitriol can have *in vitro* activity against osteosarcoma, squamous cell carcinoma, neoplastic prostatic epithelial cells, transitional cell carcinoma, mammary gland cancer, and mast cell tumor canine cell lines. One study revealed a synergistic effect of administering calcitriol with cisplatin against various tumors (*e.g.*, osteosarcoma and chondrosarcoma) in dogs (10). Investigators of another study found that calcitriol treatment could induce remission of mast cell tumors, but the trial was discontinued because of the high rate of toxicity (*i.e.*, hypercalcemia and azotemia) observed (11).

Primary hyperparathyroidism

Although primary hyperparathyroidism is technically a neoplastic condition, it is separated here to avoid confusion with malignant conditions, because most dogs with primary hyperthyroidism have benign parathyroid gland adenomas. Compared with control dogs, five dogs with primary hyperparathyroidism had significantly lower serum 25(OH)D concentrations (7) although all values for the affected dogs were within reference limits. Serum 1,25(OH)$_2$D concentrations were significantly higher in dogs with primary hyperparathyroidism than in control dogs, and 1,25(OH)$_2$D concentrations in 4 of 5 dogs with primary hyperparathyroidism were above reference limits (7). Both findings could possibly be attributed to an upregulating effect of PTH on renal 1α-hydroxylase activity, which would increase 1,25(OH)$_2$D synthesis.

In a study of 10 dogs with primary hyperparathyroidism treated by surgical excision of parathyroid gland adenomas, all had low 25(OH)D concentrations at the time of diagnosis, compared with control dogs, whereas 1,25(OH)$_2$D concentrations were within reference limits. At the time of the post-parathyroidectomy nadir in ionized calcium concentration, 25(OH)D concentrations did not differ from results at the time of initial diagnosis, but mean 1,25(OH)$_2$D concentrations were lower (12).

A diagnosis of primary hyperparathyroidism has traditionally been made on the basis of an increased ionized calcium concentration at the time of an inappropriately high concentration of PTH. The concentration of circulating 25(OH)D is an important regulatory factor for the suppression of PTH synthesis in humans (likely following its conversion to 1,25(OH)$_2$D within the parathyroid gland). Concentrations of PTH are higher in humans with concomitant lower circulating 25(OH)D concentrations. It is currently recommended that a diagnosis of primary hyperparathyroidism in humans is made only when 25(OH)D concentrations are sufficient or after 25(OH)D has been normalized following supplementation with vitamin D. The importance of concurrent evaluation of ionized calcium, PTH, and 25(OH)D concentrations to make an accurate diagnosis of primary hyperparathyroidism has not yet been investigated in veterinary medicine.

Gastrointestinal disease

Absorption of fat-soluble vitamins depends on adequate absorption of dietary fat; malabsorptive intestinal diseases can therefore adversely affect vitamin D absorption and ultimately contribute to hypovitaminosis D. Serum 25(OH)D and 1,25(OH)$_2$D concentrations have been evaluated in dogs with inflammatory bowel disease (IBD) and protein-losing enteropathy (PLE), and both metabolites were significantly lower in the PLE group than in dogs with IBD or healthy dogs (13,14). Additionally, lower 25(OH)D concentrations were significantly correlated with duodenal inflammation and death (14-16).

It is possible that hypoalbuminemia contributes to hypovitaminosis D through loss of VDBP via diseased intestines. Alternatively, hypovitaminosis D may contribute to intestinal protein loss through the effect of vitamin D on the immune response. It is known that vitamin D receptor–knockout mice are more likely to develop induced IBD, and vitamin D-deficient diets predispose mice to colitis via dysregulated colonic antimicrobial activity and impaired homeostasis of enteric bacteria (17).

Orthopedic disease

Osteoblasts and chondrocytes express 1α-hydroxylase and VDR but it is unknown whether vitamin D plays a direct or indirect role in bone growth and mineralization. Rickets is a metabolic bone disease typically caused by dietary deficiency of vitamin D, calcium or phosphorus, or by genetic defects affecting vitamin D or phosphorus metabolism **(Figure 3)**. The most common clinical abnormality is widening of the physeal growth plates of fast-growing bones such as the radius and ulna. Histologically, hypertrophic chondrocytes accumulate, which leads to thickened, irregular growth plates. Animals fed unbalanced meat-based diets without vitamin D supplementation are more likely to develop fibrous osteodystrophy, rather than rickets, because of the development of nutritional hyperparathyroidism. For an animal with dietary-induced rickets, treatment entails transitioning the animal to a complete and balanced diet.

Two autosomal recessive disorders that cause vitamin D-dependent rickets (VDDR) in humans are recognized. Type I VDDR is caused by a defect in the gene encoding 1α-hydroxylase, which subsequently leads to inadequate activation of 25(OH)D to form $1,25(OH)_2D$. This leads to 25(OH)D concentrations within the reference range but low $1,25(OH)_2D$ concentrations. Type II VDDR is caused by a defect in the VDR gene, which leads to hypocalcemia, secondary hyperparathyroidism, and high $1,25(OH)_2D$ concentrations. A few cases of both types of VDDR have been reported in dogs (18,19). Treatment of type I VDDR entails providing supplemental $1,25(OH)_2D$ and typically has a better prognosis than type II VDDR, which requires high doses of both $1,25(OH)_2D$ and calcium. Most mutations in people result in a defective VDR that can no longer respond to even high doses of $1,25(OH)_2D$. Some children can be treated by high doses of $1,25(OH)_2D$ that overcome the defect in binding affinity for $1,25(OH)_2D$.

Cardiovascular disease

Vitamin D plays a role in the pathophysiologic processes of cardiac disease. Cardiac myocytes express VDR and a calcitriol-dependent calcium-binding protein. In humans, hypovitaminosis D is associated with increased rates of myocardial infarction and cardiovascular events. An inverse relationship between vitamin D status and hypertension has been described in people, but a meta-analysis of 46 trials revealed that vitamin D supplementation had no effect on lowering blood pressure (20). No study in dogs has documented a clear relationship between hypertension and vitamin D.

The association between vitamin D and canine cardiac disease has been investigated. In one study that involved evaluation of 31 dogs with congestive heart failure, mean serum 25(OH)D concentrations were approximately 20% less than those of healthy control dogs (21). Another study revealed that serum 25(OH)D concentrations were significantly lower in dogs with stage B2, C, or D chronic valvular disease (American College of Veterinary Internal Medicine criteria), compared with those in dogs with stage B1 chronic valvular disease (*i.e.*, no evidence of cardiac remodeling). Serum 25(OH)D concentrations were significantly correlated with left ventricular and atrial sizes (22). As with other diseases, decreased serum 25(OH)D concentrations may be linked to decreased dietary intake or

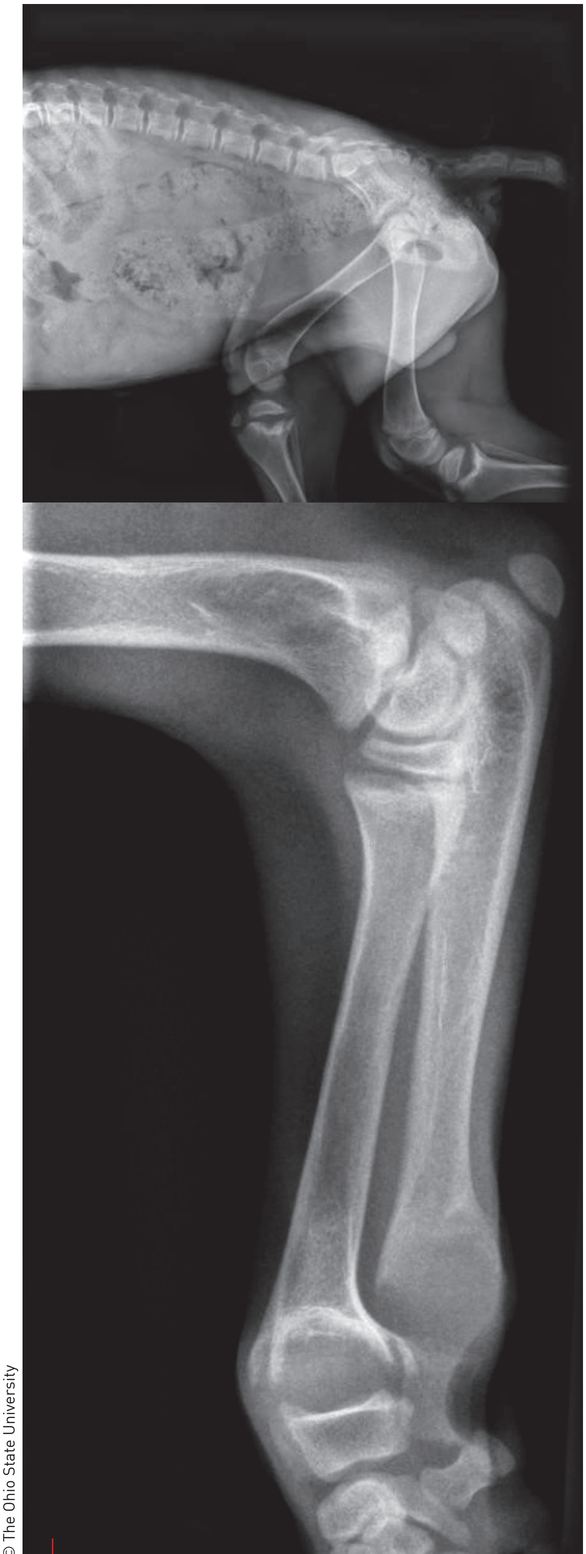

Figure 3. Right lateral pelvis and radius/ulna radiographs of a young (estimated 1-year-old) dog. The radial, ulnar and tibial physes exhibit expansile widening with cup-shaped flaring, and there is diffuse osteopenia present. These findings are consistent with rickets.

increased inflammation. To the author's knowledge, no veterinary studies have been conducted to evaluate FGF-23 or Klotho concentrations in relation to cardiovascular disease, although both FGF-23 and Klotho have been linked to cardiovascular disease (*e.g.*, atherosclerosis, vascular stiffening, and left ventricular hypertrophy) in human CKD.

Inflammatory conditions

Vitamin D has been associated with inflammation and the immune system because most leukocytes express VDR. Serum 25(OH)D is a negative acute-phase reactant and is typically inversely related to inflammatory markers (*e.g.*, C-reactive protein, CRP) in humans. Furthermore, 25(OH)D and 1,25(OH)$_2$D modulate inflammation by inhibiting production of interleukin-6 and tumor necrosis factor-α. After strenuous racing, despite having higher CRP concentrations, sled dogs were found to have higher 25(OH)D concentrations (23). No correlation between 25(OH)D and CRP concentrations in dogs with cancer has been noted (2). With regard to leukocyte counts, serum 25(OH)D concentrations are significantly negatively correlated with neutrophil count, monocyte count, and interleukin-2 and -8 concentrations in dogs with chronic enteropathy (15).

Other causes

Serum 25(OH)D concentrations have been investigated for some canine infectious diseases. Dogs with both neoplastic and non-neoplastic spirocercosis had significantly lower 25(OH)D concentrations than healthy dogs; dogs with neoplastic spirocercosis had significantly lower 25(OH)D concentrations than those with non-neoplastic spirocercosis (24). Granulomatous disease may induce hypercalcemia in dogs. This was originally thought to be mainly due to dysregulated production of calcitriol (*i.e.*, increased production of 1,25(OH)$_2$D); however, there are granulomatous diseases in both humans and dogs in which hypercalcemia has been attributed to PTH-related peptide and not to calcitriol.

Finally, dogs with acute polyradiculoneuritis have been shown to have lower 25(OH)D concentrations than dogs with idiopathic epilepsy (25). The significance of this remains unknown.

Mortality rate and death

Low serum 25(OH)D concentrations have been linked to higher mortality rates in people, and serum 25(OH)D status has been shown to be predictive of 30-day mortality rate for hospitalized critically ill dogs (26). Serum 25(OH)D concentration at time of diagnosis was a significant predictor of mortality rate for dogs with chronic enteropathy. It remains to be determined whether a low 25(OH)D concentration specifically influences the mortality rate, or if it is a consequence of increased inflammation and a greater severity of underlying disease.

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Figure 4. Dogs may develop vitamin D toxicosis after ingestion of cholecalciferol rodenticides when foraging.

Vitamin D supplementation and toxicosis

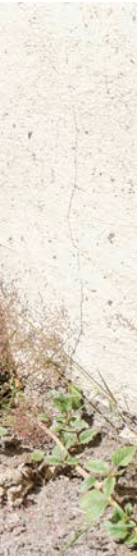
Numerous studies have identified decreased concentrations of vitamin D metabolites in dogs with various diseases; however, it has not yet been determined whether such animals should receive supplemental vitamin D or vitamin D metabolites, and if so, the manner for providing them. Potential options include vitamin D_2 (ergocalciferol), vitamin D_3 (cholecalciferol), calcidiol, calcitriol, or other VDR activators (*e.g.*, paricalcitol).

In a prospective study of canine atopic dermatitis, pruritus and lesion scores improved with cholecalciferol intake (1). There was minimal toxicity observed but extremely high doses (up to 1400 IU/kg, higher than recommended by either AAFCO or NRC) were required to affect serum 25(OH)D concentrations and clinical signs. Recently, a modified-release formulation of 25(OH)D has been approved for the treatment of humans with advanced CKD[4]. Providing supplemental 25(OH)D to dogs more rapidly and efficiently increases serum 25(OH)D concentrations than does cholecalciferol, but additional studies are necessary to elucidate appropriate dosing recommendations.

The goal of supplementation with vitamin D or 25(OH)D should be to increase serum 25(OH)D concentrations and improve outcomes specific to the disease being managed (*e.g.*, reducing pruritus or improving the survival rate or duration). The form of supplemental vitamin D administered, half-life of the product, and potential for toxic effects may differ, so caution must be exercised, and treated animals must be monitored closely.

Vitamin D toxicosis is most commonly diagnosed after the development of hypercalcemia and a

[4] Rayaldee, OPKO Healthy Inc, Miami, Fla.



subsequent risk for acute kidney injury and soft tissue mineralization. Development of hypercalcemia as a result of vitamin D toxicosis is a relatively late finding. Several factors influence the potential for vitamin D toxicosis, including lipophilicity, affinity of vitamin D metabolites for VDBP, and rates of metabolite synthesis and degradation. Vitamin D is fat soluble, a major reason why it has a long whole-body half-life of approximately 2 months. Half-lives for 25(OH)D and 1,25(OH)$_2$D are approximately 2-3 weeks and 4-6 hours, respectively.

Vitamin D toxicosis in humans that results in hypercalcemia is thought to occur when serum 25(OH)D concentrations exceed 100-150 ng/mL. In studies of various animal species (rats, cows, pigs, rabbits, dogs, and horses), plasma 25(OH)D concentrations associated with hypercalcemia exceed 150 ng/mL. The most commonly encountered forms of vitamin D toxicosis in dogs include ingestion of cholecalciferol rodenticides **(Figure 4)** and skin creams that contain calcitriol or an analogue (calcipotriol/calcipotriene). Occasionally, misformulation of commercial pet foods may contribute to vitamin D toxicosis. Iatrogenic toxicosis, typically determined by measurement of 1,25(OH)$_2$D concentrations, may occur secondary to provision of supplemental calcitriol for management of renal secondary hyperparathyroidism, primary hypoparathyroidism, PLE, or pre- or postsurgical treatment of primary hyperparathyroidism.

Note that hypercalciuria develops during the early phases of vitamin D toxicosis, before hypercalcemia develops, and can have a negative impact by increasing the risk of developing calcium-containing uroliths and renal injury. The urinary calcium-to-creatinine ratio is used to detect hypercalciuria in humans, and this concept has received attention in the investigation of dogs that form calcium-containing uroliths.

CONCLUSION

Vitamin D homeostasis is characterized by complex interactions between vitamin D metabolites, ionized calcium, phosphorus, FGF-23, and Klotho, and regulatory pathways can be disrupted in a variety of ways. Although reference limits for serum vitamin D metabolites in healthy dogs remain to be determined, many diseases have been associated with lower concentrations of vitamin D metabolites, whereas some have been associated with increased concentrations. The chicken-and-egg conundrum often applies to these diseases, and it is not definitively clear whether vitamin D deficiency is the cause or the result of these diseases. Additional studies are needed to determine whether vitamin D supplementation for dogs with certain diseases would improve patient outcomes, and the form and dosing regimen that would best provide this supplemental vitamin D.

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DIETARY CONSIDERATIONS FOR DOGS WITH CHRONIC ENTEROPATHIES

The various options now offered by specialist petfood companies for a dog with chronic gastrointestinal disease can be quite baffling, and the clinician may be tempted to reach for the nearest product that claims to be effective for enteric disease. Adam Rudinsky offers some pointers to help the clinician.

KEY POINTS

1. Dietary management can be effective in many dogs affected by idiopathic chronic enteropathies but effective therapy requires an understanding of the patient, dietary options available, and the likely disease process.
2. Diet ingredient profiles within a therapeutic class, for example low-fat diets, can be radically different, resulting in an inability to use these diets interchangeably.
3. Some diets can fit into multiple therapeutic classes and can be used to the clinician's benefit to potentially maximize the treatment response.
4. Due to contaminants and variable processing rigor, over-the-counter diets are not acceptable alternatives to veterinary diets manufactured and designed to treat gastrointestinal disorders.

Introduction

Chronic enteropathy (CE) is a poorly defined term in veterinary medicine. In its most basic definition, it is a descriptor of all gastrointestinal (GI) disorders which are chronic in nature. The designation of "chronic" disease should be made on an animal-by-animal basis through a thorough assessment of the patient's individual history and clinical signs **(Figure 1)**. Signs should be persisting in the animal for at least ten to fourteen days in duration before the classification of chronic is made. This distinction between acute and chronic GI disorders is important from both a diagnostic and therapeutic perspective; this article deals with chronic GI disorders and cannot necessarily be extrapolated to acute GI disorders and their associated dietary management. In addition, this broad definition of CE inherently includes all chronic GI disorders, including those that may result from inflammatory, autoimmune, metabolic, neoplastic and infectious etiologies.

As a practicing clinician, achieving a correct diagnosis and establishing what is causing the CE is essential to allow for targeted application of both dietary and medical therapies. A definitive diagnosis can be accomplished by assessing patient factors, utilizing a targeted diagnostic testing approach (*e.g.*, clinical pathology, fecal

Figure 1. Diarrhea is a cardinal sign of a chronic enteropathy, but the possible etiologies are numerous, and include inflammatory, autoimmune, metabolic, neoplastic and infectious causes.

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Adam J. Rudinsky,

DVM, MS, Dipl. ACVIM, College of Veterinary Medicine, The Ohio State University (OSU), Columbus, USA

Dr. Rudinsky received his DVM degree from OSU and completed a small animal rotating internship at Purdue University before returning to undertake a combined residency in internal medicine and MS degree at Ohio State. He is now on faculty as a staff internist where he provides the service with a specialized interest, clinical perspective and clinically applicable research in gastroenterology, pancreatology, and hepatology. He has received multiple teaching awards and hospital service awards.

testing, molecular diagnostics, imaging **(Figure 2)** and GI biopsy), and performing therapeutic trials as indicated on a case-by-case basis. One of the primary goals when evaluating the patient should be to eliminate the systemic, infectious and neoplastic disorders which may be largely clinically indistinguishable from food-responsive CE and require specific treatment in conjunction with, or separate from, dietary management.

Understanding diet categories for dogs with GI disease

Understanding the variety of dietary options available for treating GI disease is the first step in being able to properly implement dietary therapy in CE cases. There is no "one size fits all" approach; each dietary category is suited for specific disease syndromes and situations while potentially not advisable in others. The proper implementation of specific dietary strategies is imperative for successful use of diets as a therapeutic tool. Canine CE can often be effectively managed with diet, and may avoid some of the problems that can develop with the use of long-term antibiotics (*e.g.*, alteration of the gastrointestinal microbiome) or immunomodulatory medications (*e.g.*, altered immune status and risk of infection). The clinician should always consider three things when making a diet selection, namely: (I) diet history (II) diet strategy, and (III) diagnosis **(Figure 3)**. The following diet types (therapeutic classes) are the most commonly employed and are readily available through many petfood companies for treatment of canine GI diseases: easily digestible, limited-ingredient, hydrolyzed, low-fat, and fiber-fortified

Figure 2. Imaging modalities such as ultrasound scan can be useful when assessing a dog with a chronic enteropathy.

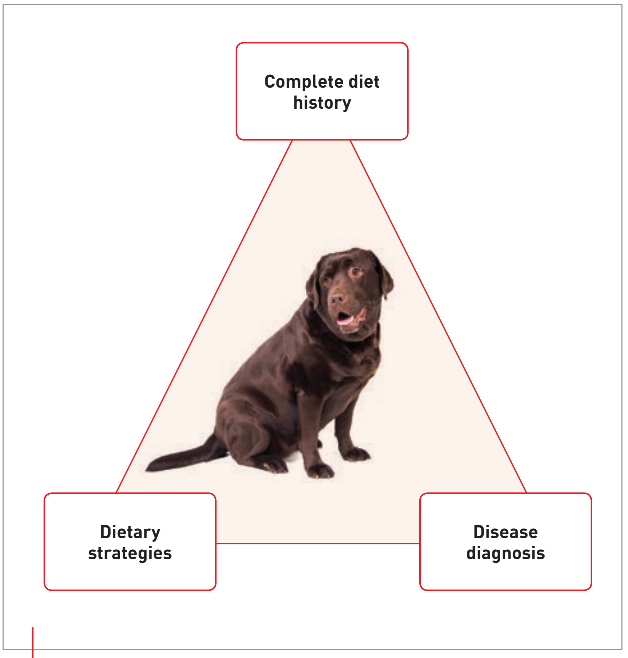

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Figure 3. The success of dietary management is dependent on the relationship between three main factors. It is imperative that the clinician evaluates: **(I)** the diet history of the patient, **(II)** the dietary strategies available to the patient, and **(III)** the disease that is to be treated. A specific dietary approach should be obtainable if these three facets are assessed for each case.

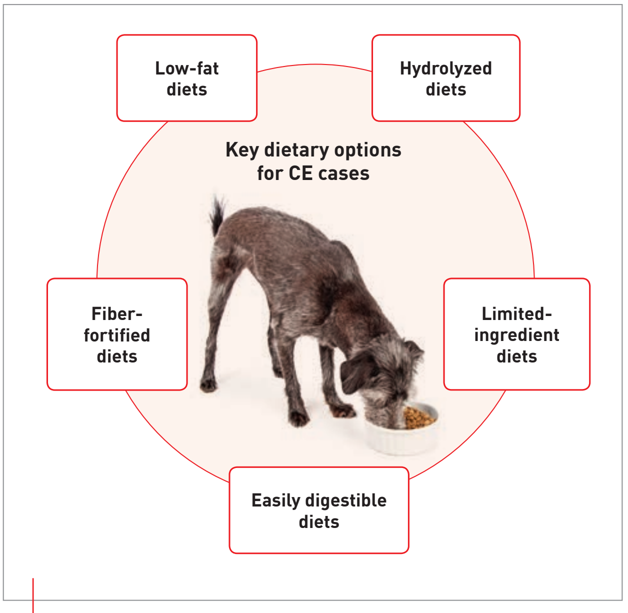

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Figure 4. Multiple dietary strategies are marketed towards patients with GI disease. The five that are most commonly utilized include: **(I)** low-fat diets, **(II)** fiber-fortified diets, **(III)** easily digestible diets, **(IV)** limited-ingredient diets, and **(V)** hydrolyzed diets. Each diet category should be utilized in the specific areas of chronic enteropathies where they are most likely to exhibit a benefit to the animal.

diets **(Figure 4)**. Identifying which category or categories a potential diet falls within is best done based on information provided by the manufacturer and the individual patient's complete dietary history. Amongst GI diets available on the market, many overlap and meet the requirements for multiple of the above categories at the same time, and such overlap can be to the clinician's benefit. It is also vital that clinicians are aware that the nutrient profiles of different diets may vary over time. In order to be certain that the prescribed diet meets the needs of the patient, up-to-date product information should be evaluated at least yearly. Lastly, diets in a given category (*e.g.*, all easily digestible diets) are not the same; they often have different nutrient profiles and can have different effects in an individual animal if used interchangeably.

Easily digested diets

Easily digestible diets form a large portion of diets marketed for GI disease and are commonly associated with their frequent use in acute GI diseases. The industry currently lacks a consensus definition on what makes a diet "highly digestible" – or indeed the most appropriate and consistent way to calculate digestibility. As a result, it is best practice to utilize veterinary diets verified by reputable petfood companies and labeled for the purpose of being highly digestible. The practitioner has to trust the diet label when considering prescribing a highly digestible diet, as many companies do not report the specific digestibility profiles of their diets in product guides. Considering the diets that do provide this information, around 90% digestibility of the major macronutrients (*i.e.,* fat, protein and carbohydrate) is common amongst this category. Multiple factors can affect the digestibility of a diet, including the ingredient source, the processing inherent to the diet, the GI physiology of the specific animal ingesting the diet, the bacterial populations in the GI tract, and chemical breakdown and anti-nutritional traits of dietary components (1). Many of these factors are separate from the diet itself and will affect how an individual diet performs in an individual animal.

Limited-ingredient and hydrolyzed diets

These two dietary classes are the next most commonly utilized categories in GI medicine and are frequently associated with their use in chronic GI disorders. Limited-ingredient diets were initially marketed for cases of food allergies manifesting with dermatologic signs (2) where they provide a balanced diet void of the ingredient to which the animal is experiencing an allergic reaction. However, in CE the prevalence of food intolerance appears to be much higher than true food allergy. While a food allergy is always an immunologic reaction, food intolerance can occur through multiple mechanisms. In animals with food intolerance, these diets may work by eliminating an offending ingredient completely or by limiting the overall dietary antigen load to the GI tract; it is unclear which of these theoretical mechanisms will work in an individual patient. Therefore, when selecting a limited-ingredient diet, it is advisable

Figure 5. It is imperative that the clinician obtains a thorough and accurate dietary history in order to select an appropriate limited-ingredient diet.

to choose one with only a single carbohydrate and a single protein source in the ingredient list, and ideally both should be novel to the patient. In order to select a limited-ingredient diet appropriately, a thorough and accurate dietary history is imperative **(Figure 5)**. It also must be emphasized to owners that many over-the-counter diets marketed for this purpose contain ingredients that are not listed on the product label and are therefore not recommended in practice (3).

Alternatively, hydrolyzed diets are processed to reduce allergenicity and antigenicity by altering protein structure (4). If hydrolysis is thorough such diets can be effective in managing allergic cases. However, the degree to which a diet is hydrolyzed can vary depending on the manufacturing process, and with some commercial diets there may still be an allergic or antigenic potential if the processing is not complete. This does emphasize the need for a comprehensive diet history to be taken in all cases. Since each commercial hydrolyzed diet contains different protein (and other macronutrient sources), the protein source should still be evaluated – as with limited-ingredient diets – if food allergy is a primary differential. Other useful components of these diets include a highly digestible profile and reduced fiber content, which may provide additional benefits or drawbacks to the individual patient; such properties are related to the processing techniques used for these diets. Concerns over palatability and side effects related to these diets, seen occasionally in humans, appear minimal or non-existent in canine studies.

Reduced fat and enriched fiber diets

The last categories of commercially marketed GI diets are those which have macronutrient quantities altered for therapeutic purposes. These diets are usually either reduced in fat content or enriched by dietary fiber. Fat content has been identified as an important component in the management of some canine GI diseases (5,6). Inadequate digestion of dietary fat can promote both secretory and osmotic diarrhea (7). In animals where there is a suspicion of fat-responsive disease, diets with a fat content within the range of veterinary therapeutic low-fat diets (1.7-2.6 g of fat per 100 kcal) are advisable. This information is easily identified in company product guides, but it is again the case that there is no recognized definition of what constitutes a "low-fat" diet or at what level of dietary fat restriction a benefit should be noted in an individual patient.

Fiber is added to diets for multiple reasons and therapeutic indications, and the fiber type and source will influence the effect that is seen in the patient. Total dietary fiber is much more informative than crude fiber, the more commonly employed descriptor (8). Crude fiber does not reveal any information about the soluble fiber in the diet, limiting its usefulness as a descriptor to guide the clinician's ability to decide whether a diet meets the intended expectations. Benefits of soluble and insoluble fiber include fermentation, production of volatile fatty acids, benefits to enterocyte health, augmentation of the microbiota, as well as alterations in gut motility and passage of GI luminal contents.

Nutritional management of common canine chronic enteropathies

Food intolerance

Inflammatory bowel disease (IBD) is a complex disease where the GI tract mounts an aberrant response to genetic, microbial, immune, and environmental factors, with the classical clinical sign of diarrhea. Such cases are often referred to as having food responsive diarrhea (FRD). Interestingly, two thirds of affected dogs will respond to nutritional management when empirical diet trials are systematically applied (9,10). The most frequently

"There is no 'one size fits all' approach to dietary therapy... the proper implementation of specific dietary strategies is imperative for successful use of diets as a therapeutic tool."

Adam J. Rudinsky

"Achieving a correct diagnosis and establishing the cause of a chronic enteropathy is essential to allow for targeted application of both dietary and medical therapies."

Adam J. Rudinsky

cited dietary strategy for these dogs include the use of either a hydrolyzed or limited-ingredient diet. Although initial case reports and expert opinion in published proceedings have supported these choices for dogs, there are only three larger studies examining the efficacy of limited-ingredient diets and three larger studies examining the impact of hydrolyzed diets (9,11-14).

The largest study involving limited-ingredient diets was a retrospective study that looked at 131 FRD dogs, of which 73 responded to a limited-ingredient diet (9). Diet selection was not controlled and was potentially influenced by clinician, owner or animal preference, but it still provides good retrospective data demonstrating a proof of concept in a large cohort of animals. The second largest study involved 65 dogs, which underwent a 10-day limited-ingredient diet trial (11) where a response rate of 60% was observed. In this study, the diet response rate was not compared to another diet type, however it was similar to the general dietary response rate reported in other studies. The final study reported a cohort of dogs that responded to a limited-ingredient diet (12). The trial was initiated to investigate the effects of a probiotic, but the noted clinical improvement was attributed to the diet and not the probiotic.

In the same previously cited retrospective study of 131 FRD dogs, hydrolyzed diets were successful in 58 cases, once again providing proof of concept in a larger population of dogs (9). A second, separate prospective study looked at 26 dogs fed either a highly digestible diet, or a hydrolyzed protein diet (13). These dogs were then followed for sustained response up to 3 years after study inclusion. In both groups, approximately 90% of dogs were controlled based on clinical signs at 3 months. Long-term, only the dogs on the hydrolyzed diet maintained remission status through the first year of the study. The dogs on the easily digestible diet saw a 28% control rate at 6 months and a 12% control rate at 12 months, indicating a more robust long-term response to the hydrolyzed diet. The final study reported a cohort of dogs that responded to a hydrolyzed diet and was investigating impact on GI histopathology (14).

In summary, the currently published data regarding dietary options indicate that limited-ingredient and hydrolyzed diets should be the primary strategies for FRD management. There may be a potential benefit to easily digestible diets, but further study will be necessary to determine this approach. The question as to which diet type is best is unknown. A recent informal poll asked whether clinicians prefer a hydrolyzed or a novel ingredient diet as their first-choice dietary strategy[1]. The results were mixed, with 60% of responders choosing hydrolyzed diets as their first strategy, and the remainder choosing limited-ingredient diets. Unfortunately, the literature is lacking comparative studies to determine if there is a benefit to one diet type over another in a controlled, comparative study in dogs. It is also possible that some FRD dogs will only respond to one diet type while being unresponsive to others. Therefore, until additional information is available, it may be beneficial to attempt multiple dietary approaches before ruling out FRD.

Food allergy

Food allergies are likely to be less common than food intolerance in dogs with chronic GI signs. However, the author is not aware of any study which has examined the relative prevalence of these two disorders. If a true food allergy is suspected, a complete and accurate diet history is vital to successful implementation of nutritional management. The selection of the diet needs to take into account whether the diet provides novel macronutrient sources and/or a hydrolyzed protein source. It is also hard to predict which ingredient is the offending agent without elimination and challenge trials. Experimentally, most macronutrients – and specifically proteins – can be antigenic, but a set group of antigens are more commonly implicated in canine disease, namely beef, dairy products, and wheat (15,16).

Studies examining food allergic dogs with primarily GI signs are scarce, as most have focused on strictly cutaneous adverse food reactions. Animals with food allergies can exhibit variable clinical signs, however in a patient exhibiting both cutaneous and GI clinical signs the clinician should have a raised suspicion of a food allergy. A clinical diagnosis can be confirmed with a positive response to an appropriate diet trial, with a relapse in clinical signs after reintroduction of the offending ingredient (16). The diet trial can be completed with either a hydrolyzed or a limited-ingredient diet, as both appear to be effective for food allergies, again despite the lack of a comparative studies (2,17-20). In cases where there is a high suspicion of food allergy, an 8 week dietary trial – similar to what is performed in dogs with a cutaneous adverse food reaction – is recommended; for dogs with suspected FRD a 2-4 week diet trial may be sufficient (21,22).

Protein-losing enteropathies/ lymphangiectasia

Dietary fat restriction is most commonly used in dogs with protein-losing enteropathies (PLE). The initial basis for this presumption was based upon

[1] personal communication – conducted by Dr. Katie Tolbert with members of the Comparative Gastroenterology Society

research demonstrating that dietary fat increases lymphatic flow. When there is increased lymphatic flow – which can be seen with various diseases, including lymphangiectasia – this can theoretically worsen protein loss and destabilize disease control (5,6). PLE is also a heterogenous group of diseases which include IBD, lymphangiectasia, infectious etiologies (*e.g.*, histoplasmosis), and GI lymphoma, among others, and the role of dietary therapy varies between these diagnoses.

Initial reports on the responsiveness of PLE cases to low-fat diets were published in case reports, case series, and proceedings. Larger case series and studies have also reported on the efficacy of feeding low-fat diets to dogs with PLE. However, these studies are limited by a lack of control groups, study design, and concurrent treatments. As a result, they are intriguing and make a strong initial argument for dietary fat restriction. However, it is once again imperative that these early findings are substantiated with more robust research on the topic. Lastly, as mentioned before, the underlying etiology in PLE cases is variable and therapies should also be directed at the definitive diagnosis. For example, if an animal is diagnosed with IBD and PLE, it would be wise to choose a diet that could also provide either a hydrolyzed nutrient source or limited-ingredient list, thus allowing the clinician to meet the needs of the PLE patient as well as the routine IBD patient from a dietary perspective.

Large bowel disease

Variable dietary strategies have been employed for cases of canine large bowel disease. Six larger studies have investigated the topic of chronic colitis in dogs (10,23-27). As with the available

Table 1. A summary of the main studies examining nutritional management of chronic enteropathies.

Dietary strategy	Indication	Notes
Hydrolyzed diet	CE*	26 dogs with CE (18 dogs on a hydrolyzed diet that responded better by CIBDAI (canine IBD activity index) scoring than 8 controls dogs on separate easily, digestible diet). Better long-term control when on the hydrolyzed diet (13).
	CE	Dietary response in 20 dogs to a hydrolyzed diet (14)
	CE	203 cases of CE (131 of which responded to dietary management), 58 of the 131 cases responded to a hydrolyzed diet (9).
Limited-ingredient diet	CE	65 dogs with CE, 39 of which responded to limited-ingredient diets (variable diets used) (11).
	CE	21 dogs diagnosed with food-responsive disease entered into prospective probiotic trial. No effect of probiotic, only diet (12).
	CE	70 dogs with CE, 39 of which responded to limited-ingredient diets (variable diets used) (10).
	CE	203 cases of CE (131 of which responded to dietary management), 73 of the 131 cases responded to a limited-ingredient diet (9).
	Colitis	Comparative study between fiber-fortified, low-fat, and limited-ingredient diets. The response rate for limited-ingredient diets was 85% (25).
Fiber-modification diet	Colitis	37 cases of chronic, idiopathic colitis treated with easily digestible diet and fiber (metamucil) supplementation (26). Complete follow-up information was available on 27 of the 37 dogs. In the subset, 26 of the 27 dogs had a good to excellent response to the addition of dietary fiber to the diet.
	Colitis	19 dogs with chronic, idiopathic colitis which initially failed on a low-fat diet trial. 12 responded to high-fiber diet and concurrent medications, which were then weaned successfully (27).
	Colitis	Comparative study between fiber-fortified, low-fat, and limited-ingredient diets. The response rate for fiber-fortified diets was 75% (25).
Highly digestible diet	CE	26 dogs with CE, 18 dogs on hydrolyzed diet that responded better by CIBDAI scoring than 8 control dogs on separate easily digestible diet. A worse long-term control was seen on the easily digestible diet compared to hydrolyzed diet (13).
	Colitis	13 dogs responded to a home-cooked (cottage cheese and rice) diet. 2 relapsed when switched to limited-ingredient diet, 9 relapsed when switched to previous diet (24).
Fat-restriction diet	PLE	11 single breed dogs (Yorkshire Terriers) which responded to dietary fat restriction without ancillary therapy (5).
	PLE**	19 of 24 dogs responded to dietary fat restriction, allowing the dosage of concurrent immunosuppressive drugs to be reduced (6).

*CE: chronic enteropathy; **PLE: protein-losing enteropathy

PLE literature, these studies are also often limited by a lack of control groups, study design, and concurrent treatments. Three of these studies in particular provide specific interesting information. In the first study the authors compared three diets (low-fat, high-fiber, or "hypoallergenic") in dogs with colitis (25). All dogs in the study were concurrently managed with anti-inflammatory medications, but there was a different response rate based on diet type. An 85% response rate was seen with the hypoallergenic diet, 75% response rate with the fiber diet, and an 18% response rate with the low-fat diet. The other two studies provided strong evidence for the role of fiber-fortified diets or fiber supplementation to traditional GI diets (easily digestible, low-fat, and/or limited-ingredient) in cases of chronic colitis (26,27). In one study, the dogs had previously failed low-fat dietary therapy (27). In summary, responses have been seen with home-cooked, easily digestible diets, limited-ingredient diets, low-fat diets, and high-fiber diets. A review of this limited evidence should be in conjunction with an analysis of the robustness of the studies reporting results, as most are uncontrolled, but they demonstrated fiber-supplemented diets and/or novel or limited-ingredient diets are best first-line options in the management of chronic colitis. As with previously cited disease, larger comparative studies are needed to determine the optimal approach in these cases, if one exists.

CONCLUSION

Canine CE can often be effectively managed with diet and this approach may avoid some of the potential problems that can be encountered with the use of long-term antibiotic or immunomodulatory medications, as many studies have demonstrated (Table 1). Diet should therefore be a focus during treatment planning for the CE patient. A variety of options exist, and patient factors and clinical signs may guide empirical dietary management choices for the clinician. Each patient should be evaluated independently, and diets chosen to best suit their needs based on the current literature. Dietary response times are well documented and there is some evidence that multiple diet trials may be advantageous in patients that fail to respond to initial empirical choices. Long-term, establishing control of canine CE with dietary modification and proper monitoring can lead to a strong, stable therapeutic response.

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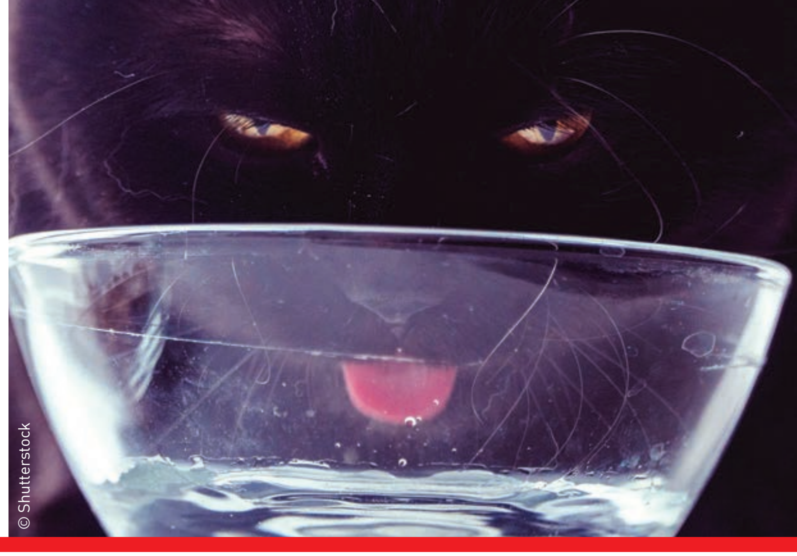

HINTS AND TIPS

FEEDING AND WATERING PET CATS

FEEDING[1]

- In the wild, cats will have up to 20 small meals each day and will eat throughout a 24-hour period, so cats need to have free access to food to allow them to eat small regular amounts throughout both day and night.
- It is normal for cats to eat a small amount of food and then walk away from the bowl.
- Feeding a single main foodstuff, with occasional small amounts of novel food items or treats (no more than 10% of the total daily intake), is probably the most natural pattern for cats, and may help reduce the risk of overconsumption.
- Feeding is not a social activity that is regulated by the presence of other cats; rather, cats will follow strict individual routines of hunting, feeding and self-maintenance.
- Activity feeders can provide mental stimulation, and may help prevent over-consumption in *ad-lib* fed cats.
- Owners can show they care by playing hunting games and talking to their cat.

[1] From: Bowen J. Feeding behavior in cats. *Vet Focus* 2018;28(3):2-7.

WATERING[2]

- Good quality tap water is sufficient for cats and is usually well accepted.
- If water is heavily chlorinated or has a strong odor, it is better to use filtered water or switch to non-carbonated mineral water. Clean rainwater can also be given.
- Offer several water points, in different rooms throughout the house if possible.
- Water bowls should be at a distance from the feeding area and preferably in other rooms.
- Small-diameter water bowls may be preferred, although individual cats can show a preference for bowls made from a particular material and/or a certain size.
- Water fountains may or may not be acceptable to cats and will depend on an individual cat's preference.
- Care must be taken that cats do not drink harmful substances. Avoid leaving receptacles with potentially toxic fluids (coffee, tea or energy drinks) within reach, prevent access to detergents in the bathroom, and take care if adding medication to an aquarium.
- For cats that have outside access, ensure that no flowerpots or watering cans contain pesticides. Antifreeze added to a garden pond in winter can be a real threat to a cat's wellbeing.
- Dairy products do not have to be avoided totally – a sip of whole milk, yogurt, or cream is unlikely to cause problems from lactose intolerance, but lactose-free milk ("cat milk") may be preferred.

[2] From: Fritz J and Handl S. The water requirements and drinking habits of cats. *Vet Focus* 2018;28(3):32-40.

THE WATER REQUIREMENTS AND DRINKING HABITS OF CATS

Water is one of the most basic molecules in the universe, and essential for life as we know it; dehydration is not compatible with health. It may therefore seem odd to have an article on water intake, but even the simplest of actions can have hidden depths, as revealed by Stefanie Handl and Julia Fritz.

KEY POINTS

1. There are very few studies on the drinking behavior and preferences of domestic cats.
2. It is well recognized that cats are predisposed to urinary tract disease, and that a lack of fluid intake can be a predisposing cause.
3. The authors' survey showed that cats apparently like to use different drinking options, and should therefore be offered several possibilities.
4. Cats seem to prefer their water to be provided in a small bowl located away for their food bowl.

Introduction

We all need to drink water to survive, but it is well recognized that certain species have evolved specific mechanisms to deal with water intake and homeostasis. The domestic cat is known to have certain physiological characteristics that can help with fluid balance; for example, cats can tolerate acute fluid losses – up to 20% of their body weight – comparatively well (1). On the other hand, they have the ability to produce highly concentrated urine (2) in order to conserve body fluid if necessary. It has been suggested that these abilities are because the domestic cat (*Felis silvestris catus*) is a descendant of the African wildcat (*Felis silvestris lybica)*, an alleged "desert dweller" **(Figure 1)**. However, the domestication of the cat most probably began 9,000-10,000 years ago, coinciding with man settling in the so-called "fertile crescent" – the area around the Euphrates and Tigris rivers, now Iraq, Syria, Lebanon, Israel, Palestine and Jordan – which was by no means a desert at that time.

It is unclear whether these characteristics actually mean that cats are predisposed to certain diseases – for example, can chronic dehydration or the production of concentrated urine lead, in time, to permanent damage of the kidneys and urinary tract? This may not be relevant for a wildcat with a relatively short life expectancy, but could certainly be important for the domestic cat, which can have a life expectancy exceeding 20 years. On the other hand, domestic cats live under very different conditions (often living indoors, with a distinct lack of exercise, and with food provided) to wildcats, and these factors may contribute to, or even cause, urinary tract disorders. Against this background, the fluid intake of the cat should certainly be given special attention, whether that is when considering general advice on how to keep and care for a cat, or in the context of dietary recommendations.

Water requirement and fluid intake

Typical recommendations are that a cat requires about 50 mL of water per kg of bodyweight daily (3) – so this translates into 200-250 mL per day for a cat weighing 4-5 kg. This water requirement can be covered by the intake of "free water" from liquids and food, or from "oxidation water" produced by metabolism. This means that burning 1 g of protein,

Julia Fritz,

Dr. med. vet., Dipl. ECVCN, Napfcheck, Munich-Planegg, Germany

Dr. Fritz graduated in 2003 from the Ludwig-Maximilian University in Munich and received her doctorate in 2007 at the local Department of Animal Nutrition and Dietetics. Here she also specialized as a veterinarian and completed her residency before she received her national diploma in 2010 and the diploma of the European College of Veterinary and Comparative Nutrition in 2011. A recognized veterinary specialist for animal nutrition and dietetics, she has run "Napfcheck", an independent private practice offering nutritional advice for companion animals since 2011.

Stefanie Handl,

Dr. med. vet., Dipl. ECVCN, Futterambulanz, Vienna, Austria

Dr. Handl studied at the University for Veterinary Medicine in Vienna and completed her doctorate in 2005 before working as a research associate at the university's Institute for Animal Nutrition. After a period doing research in the Gastrointestinal Laboratory at Texas A&M University, she gained her ECVCN diploma in 2011. In 2013 she opened "the Futterambulanz Clinic" in Vienna, a consulting practice offering nutrition and diet advice for pets.

starch or fat yields just under 0.4 g, 0.6 g and 1.1 g of water respectively (4). The natural food of cats – *i.e.,* prey such as small mammals and birds – contains about 70% moisture (5). Therefore, with 200-250 g of food ingested each day (corresponding to the average energy requirement), 70% of the animal's fluid requirement is already covered by food intake – without taking the additional "metabolic water" into account. If a cat eats wet food that has an 80% water content (again at an average requirement of 250-300 g), the fluid requirement can be fully covered. Studies conducted more than fifty years ago showed that cats could cover their fluid balance by ingestion of fresh fish or meat alone (6).

As the amount of food eaten is primarily determined by the animal's energy requirement (7), food with a low-energy density and high-moisture content consequently leads to a higher fluid intake and so to an increased amount of urine (8), as shown in **Figures 2 and 3**. With commercial dry diets, which contain a maximum of 10% moisture, cats must

Figure 1. It has been suggested that the African wildcat (*Felis silvestris lybica*) has passed on its ability to survive near-drought conditions to today's domestic cat.

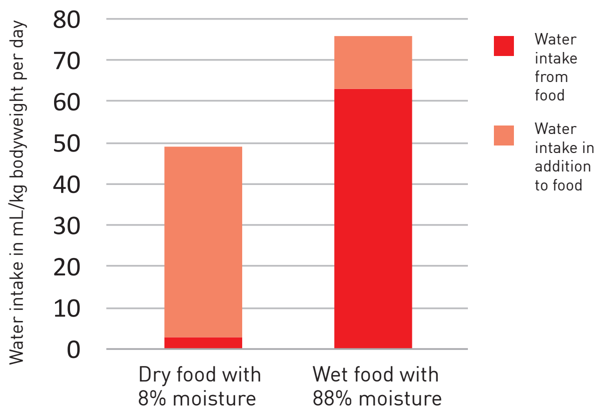

Figure 2. Fluid intake of cats fed dry and wet diets (8).

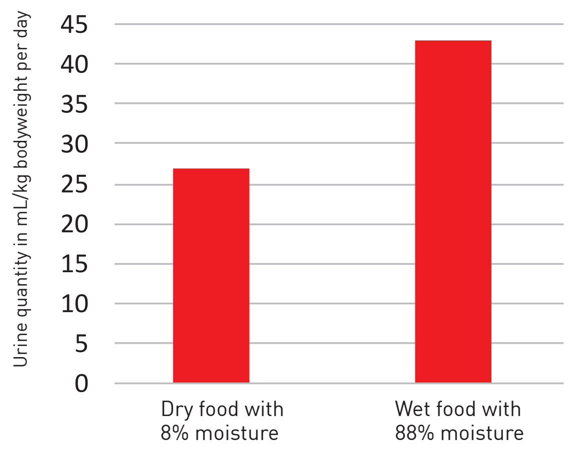

Figure 3. Urine quantity in cats fed dry and wet diets (8).

drink additional water to meet their needs. Most studies on this topic conclude that when cats are fed only dry food, they consume less water in total (9-11) and it is therefore often proposed that feeding mainly or only dry food is a risk factor for kidney and urinary tract disease, although studies to date show contradictory results.

For example, one study (12) identified dry food (either as part of the daily diet ration or fed exclusively) as a risk factor for "Feline Lower Urinary Tract Disease" but made no distinction between urolithiasis and other urinary diseases. Another study (13) concluded that the type of diet fed did not seem to be a causative factor for feline interstitial cystitis (FIC), but that obesity and stress were the main reasons. Dry food was also not shown to be a risk factor in chronic renal insufficiency (14,15). Probably the greatest influence of diet on disease is seen in urinary calculi, and here not only the moisture content, but other properties of the food (*e.g.,* the ratio of protein/fat/carbohydrates, the cation-anion balance) also play a role. In an experimental study on urolithiasis (11), researchers showed that a higher fluid content in the diet reduced the risk of calcium oxalate calculi but not struvite.

"Small-diameter water bowls are generally preferred by cats, and wherever possible an owner should provide a variety of bowls of differing materials and in different sizes."

Julia Fritz

Fluid intake and urine composition

The composition of the urine, the specific gravity and the pH value are decisive factors for the formation of urolithiasis (16). These factors are influenced by the diet fed and the fluid intake. It should not be forgotten that the volume of fluid intake does not necessarily correlate directly with the volume and concentration of urine formed. Urine concentration and composition are therefore not only dependent on the water content of the food, but also on the content of substances excreted in the urine (especially protein and minerals), which in turn affect the urine volume itself as well as the amount of minerals excreted and the urine pH (17). Study results on the influence of certain types of food or specific diets can therefore be difficult to interpret, as all these factors need to be considered.

The drinking habits of domestic cats

Despite numerous studies on the intake of water with food and risk factors for urinary tract disease, the authors are not aware of studies that specifically address the drinking habits or preferences of domestic cats. Various recommendations (*e.g.,* "cats do not want to drink near their feeding place" or "cats prefer running water from sources such as cat fountains") have their origin in popular literature or are derived from behaviors in the wild. The authors recently conducted a survey to document common practices in the provision of drinking water for cats and to identify preferences.

Methods

A questionnaire on cat data (age, breed, sex, existing diseases), living conditions (place of residence, freedom of movement, other pets in the household), feeding, range of drinking options (type, quantity, location, material) and observed drinking behavior and preferences were given to cat owners among the authors' clientele and distributed to other veterinary practices and clinics, as well as on-line platforms.

Results

Participants and demographic data

A total of 549 questionnaires were received for evaluation. Most were from Germany and Austria, with some from Switzerland. The gender split for the cats was almost exactly 50% male-female, almost all of them neutered. Two-thirds were domestic shorthair cats; the most widely represented pure breeds were Maine Coon (5%), British Shorthair (4%), Persians and Siamese (3% each).

23% were purely house cats, 40% had restricted freedom of movement (balcony, terrace, garden) and 37% had unrestricted freedom of movement. 32% of cats lived in a big city, 25% in small towns or suburbs, and 43% in a rural area. 33% were kept alone, 44% with other cats, 27% with dogs.

Feeding and health profile

Three quarters of the cats in the survey were deemed by their owners to be healthy; the remaining 25% were reported to suffer from a variety of diseases, mainly chronic renal insufficiency, osteoarthritis, allergies and acute injuries. It should be noted that the diagnosis was only from the information provided by the owners, and not necessarily corroborated by veterinary input. The type of food provided to the cats is shown in **Figures 4 and 5**. Cats that ate a lot of wet food (up to the same proportion with dry food combined) were significantly less common among affected animals. However, with regard to urinary tract disease, no obvious link between the type of diet and disease could be identified.

Water options and drinking habits

Most of the cats (> 80%) were given water in bowls, the most popular alternative being a cat fountain. However, amongst cats that had access to both options, the majority preferred the bowl. Furthermore, the size of the drinking receptacle seems to be relevant, as small bowls (<15 cm in diameter) were preferred to larger bowls. No preference was reported for the material the bowl was made of; ceramics (60%) followed by plastic (38%) were the most common materials used; less frequently metal (35%) and glass (13%) bowls were provided.

Whether cats would generally prefer the option of drinking from other than bowls or fountains could not be concluded from the data because there were too few other drinking options to make statistical evaluation possible. However, nearly 60% of the cats were observed (daily or occasionally) drinking

Figure 4. Cats in the survey were fed either commercial diets or self-prepared foodstuffs, or both.

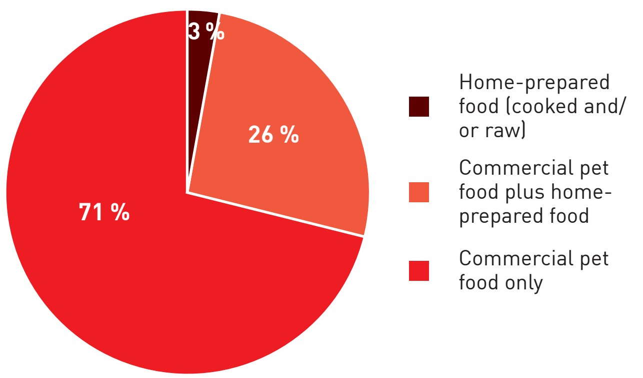

Figure 5. Cats in the survey were fed differing quantities of wet and dry food, as shown; the wet food includes commercial and self-prepared food.

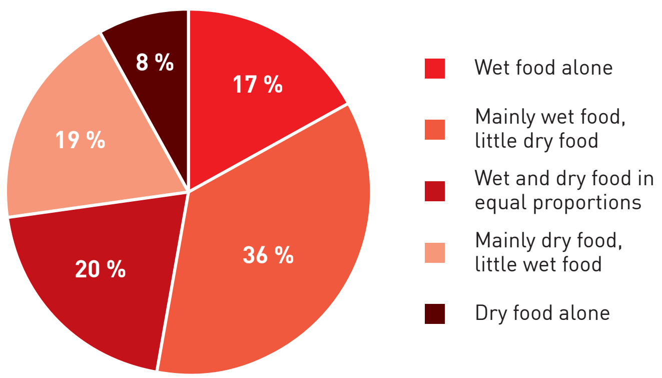

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Figure 6. Cats may be tempted to drink from outdoor receptacles such as watering cans; owners need to ensure that no toxic chemicals remain.

from other water sources, such as watering cans, flowerpots or dishes for humans **(Figure 6)**. Half of the cats with outdoor access were observed drinking from ponds, puddles or flowerpots **(Figure 7)**. Cats who had unrestricted freedom of movement significantly preferred outdoor water points rather than their bowls inside the home.

The cats mostly drank in a squatting position, although outdoor cats often also drank while standing up. Almost half (44%) not only drank, but also played with the water.

The most common water source was fresh tap water; if alternative sources were available (*i.e.*, filtered tap water, still mineral water, rainwater), the cats preferred tap water (which is of very good quality in Germany and Austria) although outdoor cats also liked to drink rainwater. 27% of pet owners also gave their cats fluids other than water to drink, most often milk or "cat milk" (lactose-free milk).

Outdoor cats used significantly more water points than purely house cats, even though more than half of the pet owners (52%) provided several sources of water. If there were several options to choose from, water points in a room other than the one where the food bowl was located were preferred. This applied to both house cats and outdoor cats. Nevertheless, in many households (41%), a water bowl was placed right next to the food bowl.

The water bowls were checked several times a week by all cat owners surveyed, and more than 90% checked the bowls "daily" or "at least once a day". Three quarters of owners also cleaned the water bowls daily. With outdoor cats, bowls were usually only washed with water, whereas for indoor only cats dishwashing detergents or dishwashers were also frequently used. Disinfectants were never used.

Summary and discussion

The primary objective of the survey was to identify the preferences of cats for the type and supply of drinking water in order to derive recommendations for practical use, and some of the results have already been presented at international conferences (18,19). When interpreting the results, it should be kept in mind that it was only possible to evaluate the information as provided by the owners, which may in turn depend on how much time they have to observe their cats, among other factors.

In general, cat owners were apparently aware of the importance of drinking water – regardless of the moisture content of the food – because they all not only checked and refilled the bowls almost daily but also frequently cleaned them. However, only half of the owners provided more than one watering point, and very often this was next to the food bowl **(Figure 8)**. To this end, this allowed confirmation that cats generally prefer water points sited away from where they eat. It is possible that this reflects original feline behavior, as feeding sites and available water sources in the open countryside are often not close to each other.

A general preference for a bowl made of a specific material did not seem apparent, but there is a preference for smaller diameter bowls when it comes to size **(Figure 9)**. This smaller size may help the cat to identify the edge of the bowl and the water surface with their whiskers.

Cat fountains are often recommended to promote fluid intake, as cats supposedly prefer running water **(Figure 10)**. This was not confirmed by the survey, but the findings are consistent with other studies that did not find a statistically significant

"Many owners will only provide one watering point for their cat, and this is very often next to the food bowl – but cats generally prefer water points sited away from where they eat."

Stefanie Handl

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Figure 7. Many cats seem to enjoy drinking rainwater from puddles. If given the option, they will prefer to drink from outdoor water points rather than their bowls inside the home.

Figure 8. Many owners will place food and water bowls together. However, it seems that cats generally prefer water points sited away from where they eat; this may reflect "original" feline behavior, as feeding sites and available water sources in the open countryside are often not close to each other.

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Figure 9. The survey identified that cats have a preference for smaller diameter water bowls.

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Figure 10. It is often suggested that a cat "fountain" will promote fluid intake, as cats supposedly prefer running water, but there is no conclusive evidence for this.

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difference in water intake between bowls and fountains, but rather large individual differences and preferences (20, 21). Interestingly, one of twelve cats in a study was stressed by a water fountain to the extent that it showed aggression, overgrooming and vomiting (20).

Cats do not only seem to be individuals when it comes to eating, but also in their drinking habits. To the authors' knowledge research has not been done on whether the behavior patterns around location, shape or quality of the water bowls or the taste of the drinking water is similar to behavior patterns linked to feeding (22), and whether a once-learned drinking preference from specific containers will last a lifetime.

It is also questionable whether the frequent use of other sources of water (such as drinking glasses, flowerpots or ponds) suggests that the water bowls provided by the owner were unacceptable to the cats, or whether it is part of natural feline behavior to have different watering points that are used "in passing". The question also remains open as to whether the frequently observed "playing with water" should be interpreted as part of drinking behavior **(Figure 11)** or whether it is triggered by boredom or an interest in something new.

In terms of feeding, the survey noted an increasing trend towards home-prepared food or the supplementation of commercial diets with meat when compared to previous reports: a 2009 survey of 243 cats found that less than 1% of the food was home-prepared and only 10% combined (23), whilst this study found more than 3% of cats were offered home-prepared (mostly raw) food and 26% cats received a combination of commercial and home-prepared diets. A diet combining both wet and dry food was by far the most popular in both studies, at 70% in the 2009 study and about 75% in this

"Cat fountains are often recommended to promote fluid intake, as cats supposedly prefer running water, but it seems that their use will depend on an individual cat's preference."

Stefanie Handl

Figure 12. Cats are invariably curious, and may opportunistically ingest potentially toxic fluids such as coffee.

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Figure 11. Cats will often "play" with water running from a tap. It is still uncertain if this should be interpreted as part of drinking behavior or whether it is triggered by boredom or an interest in something new.

Box 1. General recommendations for offering water to cats.

- Good quality tap water is sufficient for cats and is usually well accepted. However, if it is heavily chlorinated or has a strange smell, it is better to filter it or switch to non-carbonated mineral water. Clean rainwater can also be given.
- Set up several water points in different places if possible; these should be at a distance from the feeding area and preferably in other rooms.
- Use smaller (<15 cm diameter) rather than larger bowls; these should be of differing materials and in different sizes, especially in households with more than one cat, to satisfy different preferences.
- Cat fountains may or may not be acceptable and will depend on an individual cat's preference.
- As cats like to drink water from all possible sources, care must be taken that they do not come into contact with harmful substances. This can include ensuring cups with coffee, tea or energy drinks are not left within reach **(Figure 12)**, checking that no flowerpots or watering cans contain pesticides, preventing access to detergents in the bathroom, taking care with medication added to an aquarium, and caution if antifreeze products are used in garden ponds over winter **(Figure 13)**.

Additional recommendations for cats with urinary tract problems

- Regardless of dietary recommendations regarding food composition, wet food should be preferred, or at least given in combination with dry food.
- If a cat likes a certain taste, use it to encourage drinking. This can be cooking water left over from meat or broth (as long as there is no severe heart or renal insufficiency, the salt content is negligible) or cat milk.
- Providing a cat with new options, such as ice cubes or larger blocks of ice (with added "flavor" if required) can encourage it to play and explore, and may also support water intake **(Figure 14).**
- Dairy products do not have to be avoided totally – a sip of whole milk, yogurt, or cream will not cause problems due to lactose intolerance. The maximum lactose intake for cats is 2 g/kg bodyweight (24), which corresponds to 50 mL/kg bodyweight of whole milk, *i.e.,* 200-250 mL for the average cat.

Figure 13. Ethylene glycol (antifreeze) is often added to ornamental fountains or garden ponds to stop them freezing in winter. This can be problematic; cats will often drink from ponds or fountains, and can inadvertently ingest the toxic chemical.

Figure 14. Cats may find novel water sources such as ice cubes an interesting toy, and this can also encourage water intake.

study. The proportion of cats fed only dry food was significantly lower in this study (at just under 8% compared to 17% in 2009). This development could be explained by the fact that dry food alone is often presented in popular literature as "unhealthy" – mainly because of the link to reduced water intake.

In summary, the survey identified some interesting facts regarding cats and their drinking habits, and some general recommendations can be given to pet owners, as shown in **Box 1**.

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CONCLUSION

Owners will often seek reassurances and advice from their veterinarian about their cat's water intake. Cats can obtain a large percentage of their fluid requirements through food if they are given a diet with a high-water content (either commercial wet food or home-prepared meat), but if cats eat mainly (or only) dry food, their overall fluid intake will be lower. Owners should be encouraged to consider that their cat may have preferences or dislikes when it comes to drinking water, and should also be aware that a cat's natural curiosity may lead it to source water that is potentially unsafe.

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GRAIN-FREE DIETS – GOOD OR BAD?

Fashions and fads come and go in all walks of life, and for cat and dog nutrition the latest idea is that they should be fed a diet free from all grains. What does this mean in practice, and is there any basis behind the idea? Maryanne Murphy and Angela Rollins offer some background.

Maryanne Murphy,

DVM, PhD, Dipl. ACVN, University of Tennessee, College of Veterinary Medicine, Knoxville, USA

Dr. Murphy received her DVM from Iowa State University and PhD from the University of Tennessee (UT). She completed a clinical nutrition residency at UT and worked as a clinical nutritionist in private practice before transitioning back to academia in 2016. Her professional interests include obesity prevention and management, and veterinary nutrition education.

Angela Witzel Rollins,

DVM, PhD, Dipl. ACVN, University of Tennessee, College of Veterinary Medicine, Knoxville, USA

Dr. Rollins is a Diplomate and former President of the American College of Veterinary Nutrition. She is currently a Clinical Associate Professor of Nutrition at the University of Tennessee Veterinary Medical Center, where she also attained her DVM, PhD, and residency training.

KEY POINTS

1. Owners may say they want to feed a "grain-free" diet when in fact they are specifically looking to remove gluten or certain individual grains from their pet's diet.
2. Dogs and cats have distinct (but different) preferences for foods with a specific percentage of protein, fat and carbohydrate.
3. When conducting a food trial, challenge with specific ingredients is necessary to identify actual reactivity to dietary allergens; failure to do so may unnecessarily limit potential diet options.
4. While cats and dogs may be well maintained on a grain-free diet, such foodstuffs are not necessarily carbohydrate-free, nor are there data suggesting these diets are more optimal than those that contain grains.

Introduction

The general term "grain" refers to dry seeds harvested from flowering plants containing either one seed leaf (monocotyledon or monocots) or two seed leaves (dicotyledon or dicots); these can be further classified as cereals, minor cereals (grasses), or pseudocereals (non-grasses) **(Figure 1)**. Examples of dietary grains and their classifications are shown in **Box 1**. Gluten, a protein mixture of glutenins and gliadins, is specifically found only in wheat, barley, rye and triticale; oats in themselves are gluten-free, but may be contaminated with wheat during harvesting or processing[1]. Gluten can also be found in some processed sauces, medications and supplements, and processed meats (1).

All of this terminology and background information is important to keep in mind when considering grain-free diets for companion animals, because pet owners may voice a desire to feed a "grain-free" diet when in fact they are specifically looking

[1] Corn gluten meal (CGM) is a byproduct of corn (maize) processing that is used in some countries as an animal feed, but the phrase is misleading; corn contains neither gliadin nor glutenin.

Figure 1. The word "grain" is a general term that encompasses a large number of different cereals, minor cereals (grasses), or pseudocereals (non-grasses).

Figure 2. It is important that both the clinician and the owner agree on what they define as "grain-free" when discussing ingredients in a foodstuff to avoid confusion.

to remove gluten or individual grains without actually considering the entire list of grains to be inappropriate. Especially with respect to dogs, many owners appear to be most concerned with removing cereals (*i.e.*, corn/maize, rice, wheat) from the diet. Individual owners may, however, consider some or all of the minor cereals to be acceptable, and many actually prefer to include pseudocereals in their pet's diet. Ensuring the veterinary team and the owner are both referring to the same individual food items when using the term "grain-free" will abate any future confusion and increase the likelihood of recommending dietary ingredients with which the owner is comfortable **(Figure 2)**.

Grain-free diets for cats and dogs have recently increased in popularity, representing 29% of the United States "pet specialty" market sales in 2015 (2) and 19% of dog food and 15% of cat food purchases in 2016 (3). Many reasons for this feeding trend are espoused, including a desire to feed a more biologically "ancestral" diet, to avoid unnecessary blood glucose fluctuations caused by diets with high-carbohydrate levels, to improve overall diet digestibility and quality, and to avoid food allergies. This article reviews what is known about grain consumption in both cats and dogs related to these points.

Box 1. Examples of dietary grains, based on classification.

Cereals	Minor cereals	Pseudocereals
Corn/maize	Barley	Amaranth
Rice	Job's tears	Buckwheat
Wheat*	Millet	Chia
	Oats	Kaniwa
	Rye	Quinoa
	Sorghum/milo	
	Teff	
	Triticale (rye/wheat hybrid)	

* Varieties or preparations of wheat include bulgur, common wheat, durum wheat, Einkorn, emmer/farro, freekeh, Khorasan, semolina, and spelt.

Biological ancestral diets

A biological ancestral diet refers to the type of diet that would be eaten by the intended species if it were to live in the wild. For pet dogs, this generally results in a desire to feed the same diet as a wolf, while domestic cats are compared to their wildcat lineage. In winter months, gray wolves preferentially kill and consume large ungulates every 2-3 days, although they often encounter fluctuating food availability (4). After killing their prey, a pack of wolves immediately consumes internal organs, followed by large skeletal muscles. Over the next 48 hours they consume bone, tendon, cartilage and hide, leaving the rumen and unbreakable bones behind. In summer months, their diet becomes more varied, and includes rodents, birds, invertebrates and plant material. The typical macronutrient intake of wolves is 54% metabolizable energy (ME) protein, 45% ME fat and 1% ME carbohydrate (4), while

"Research indicates genes with key roles in starch metabolism were targets of selection during dog domestication, but selection for docility was the major force that first altered the domestic cat genome."

Maryanne Murphy

domestic dogs have a preference for dry or canned diets containing 30% ME protein, 63% ME fat and 7% ME carbohydrate **(Box 2)** (5).

Wildcats have been shown to have a preference for rabbit prey, secondarily consume rodents, and round out the remainder of their diet with insectivores, reptiles, birds and arthropods, based on availability. The main dietary components of a free-ranging feral cat are reported as 78% mammalian, 16% birds, 3.7% reptiles and amphibians, and 1.2% invertebrates, with prey availability also dictating consumption preferences (6). The daily macronutrient intake of feral cats is 52% ME protein, 46% ME fat and 2% ME carbohydrate **(Box 2)** (6). When domestic cats were offered a variety of dry and canned diets, their preferred macronutrient distribution was 52% ME protein, 36% ME fat and 12% ME carbohydrate **(Box 2)** (7). Grain-free dry diets for cats contain less carbohydrate compared to grain-containing diets (22.4 ± 5.6%ME vs 30.1 ± 7.7%ME; calculated using 3.5 Kcal/g energy factor; P <0.001) (8). Similar data are not yet available for dog diets.

In addition to feeding a diet that mimics the macronutrient profile typically selected by the species, proponents of grain-free diets argue domestic cats and dogs need this type of diet due to their carnivorous nature. Wolves are classified as generalist carnivores, based on their ability to feed on a diverse array of foods, but typical consumption of prey. Their canine and incisor teeth are used to subdue prey, slash the hide and muscle, and grasp and hold prey while the carnassial pair of teeth (upper fourth premolar and lower first molar) have two shearing edges to trap and cut food in a self-sharpening motion. The back of the lower carnassial tooth and the upper first molar acts as a crushing or grinding surface. The dentition of dogs is very similar, and while some consider them to be carnivores, they have been classified as omnivores by the National Research Council (9). In support of this classification is whole-genome resequencing data reporting that three genes with key roles in starch digestion (*AMY2B*, *MGAM* and *SGLT1*) were targets of selection during dog domestication (10). After domestication, positive selection continued to affect *AMY2B* copy number in dog breeds based on their level of habitual starch consumption (11).

Cats, however, are obligate carnivores as they are required to obtain several essential nutrients from a diet based on animal tissue (6). In one study, evaluation of domestic cats (*Felis catus*) revealed genes involved with neural processes (such as behavior and contextual clues related to reward) differ from the wildcat (*Felis silvestris silvestris* and *Felis silvestris lybica*) genome; this suggests selection for docility was the major force that first altered the domestic cat genome (12). The authors suggest the modest genetic effect of feline domestication seen in their results are due to a recent divergence from an ongoing mingling with wildcats, a relatively short human cohabitation time, and a lack of clear morphological and behavioral differences from wildcats. In short, there is currently no genetic evidence supporting a divergence in diet-related characteristics between domestic cats and wildcats, although there are slight macronutrient preference differences between domestic and free-ranging feral cats as noted above.

Box 2. A comparison of macronutrient intake (% metabolizable energy, ME).

	Wolves	Domestic dogs	Free-ranging feral cats	Domestic cats
Protein	54	30	52	52
Fat	45	63	46	36
Carbohydrate	1	7	2	12

Carbohydrates, blood glucose and diet digestibility

Another common reason some owners prefer feeding a grain-free diet is to limit carbohydrate intake and secondary fluctuations in blood glucose. Although dogs lack salivary α-amylase, which initiates the process of cleaving carbohydrates into oligosaccharides, they have similar carbohydrate digestive and metabolic enzymes found in omnivorous species such as humans. Cats, on the other hand, have numerous differences in their ability to digest, absorb, and metabolize starches and sugars. Details of these metabolic adaptations are beyond the scope of this discussion, but have been recently reviewed (13).

Despite having reduced numbers and types of carbohydrate enzymes, cats are still able to effectively digest and utilize carbohydrates. A study evaluating six different carbohydrate sources found cats had starch digestibility values similar to rats and dogs (14). While cats are capable of digesting carbohydrates, there is still much debate and controversy regarding the long-term effects of high-carbohydrate diets on the development of obesity and diabetes mellitus in this species. There is currently no evidence that dietary carbohydrate content directly impacts on the risk or development of obesity in cats. On the contrary, studies have found cats fed a high-fat or high-protein versus a high-carbohydrate diet gain more fat mass and consume more calories (15). However, some studies do suggest a lower carbohydrate diet better regulates blood glucose concentrations in diabetic cats (16) and can reduce post-prandial insulin and glucose concentrations in healthy cats (15). Whether or not long-term feeding of high-carbohydrate diets contributes to the development of diabetes in cats remains unclear.

When contemplating the effects of carbohydrates on blood sugar, some consideration should also be made regarding the types of carbohydrates in a diet. In both dogs and cats, carbohydrate sources with higher concentrations of fiber (digestive-resistant starch) and protein tend to have lower glycemic responses (14,17). For example, corn and brewer's rice elicit a higher glucose and insulin response in cats than ingredients like peas and lentils (14), so diets with similar carbohydrate contents could have differing metabolic effects.

Food allergies

Owners may choose grain-free diets for their pets in an effort to avoid food allergies. The term "food allergy" may be defined as an adverse immune response toward food proteins, or an intolerance associated with a hypersensitive immune response, which is repeatable with a dietary challenge (18). Food allergies can be immediate (IgE-mediated), delayed (non-IgE-mediated), or a combination of the two (18). In people, food allergens are water-soluble glycoproteins ranging from 10-70 kD molecular weight and are divided into either class 1 primary sensitizers and/or class 2 sensitizers that are cross-reactive (18). There is a risk for cross-reactivity among food items within a single food family; for example, in humans there is a 75% risk of cross-reactivity among species of shellfish, but legumes have only a 5% risk, whilst grains have a 25% risk (18). Cross-reactivity categories have not yet been verified in cats and dogs, although there does not appear to be cross-reactivity between beef and dairy or soy and wheat in dogs, but there may be reactivity between chicken and eggs (19). For this reason, dietary challenge with specific ingredients should be undertaken to identify actual reactivity, and removing all ingredients within a single food family without such a challenge may be unnecessarily limiting potential diet options.

In contrast to food allergy, a general food intolerance involves a non-immunologic response to a food that is also repeatable with a dietary challenge (18). A classic example is lactose intolerance, where a deficiency of the enzyme lactase results in an inability to adequately digest foods that contain lactose, with subsequent gastrointestinal signs. It is important to realize that distinguishing between a true allergy versus a dietary intolerance is challenging in companion animals, and it may be preferable to use the term "adverse food reaction (AFR)".

In dogs, the most common food ingredients reported in association with an AFR are beef, dairy, poultry, wheat and egg **(Figure 3)**, while the most common ingredients in cats are beef, dairy, fish, lamb, poultry and wheat **(Figure 4)**. As highlighted in one paper (24) it is important to note these data do not reflect the true prevalence of specific food allergies in the population of cats and dogs, since the animals were not challenged with all possible food allergens, and details of challenge protocols used are often unclear. What can be gleaned from these data, however, is that most food allergens in cats and dogs are related to the animal-derived component, rather than the plant-derived component of the diet. In addition, the likelihood of allergy development increases with exposure, so it is possible the most common allergens will change over time if the general companion animal diet is adjusted to avoid the currently implicated ingredients.

One study compared the individual ingredient composition of grain-containing and grain-free dry cat diets available in the United States (8). The most common animal-sourced ingredients in grain-containing diets are largely poultry, followed by fish and egg. Grain-free diets are more likely to contain equal proportions of poultry and fish, with egg rounding out the rest of the majority of animal-sourced ingredients **(Figure 5)**. For plant-sourced ingredients, the grain-containing diets were more likely to contain rice, flax, cranberry, oat, carrot,

Figure 3. Reported ingredients associated with adverse food reaction (AFR) in dogs, based on 373 reported food ingredients associated with AFR following a dietary challenge. Published reports that contained data for at least 5 dogs were included, whilst studies that selected for a specific food-based reaction (*e.g.*, dogs with a suspected chicken-based reaction) were excluded (20-25).

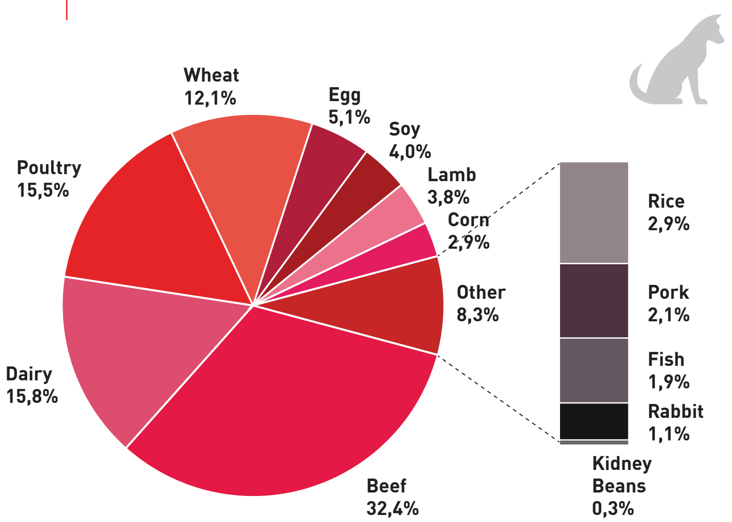
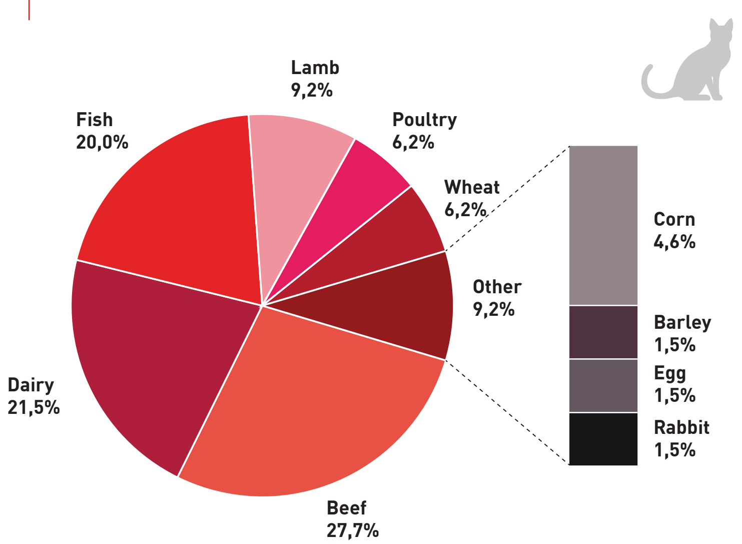


Figure 4. Reported ingredients associated with adverse food reaction (AFR) in cats based on 65 reported food ingredients associated with AFR following a dietary challenge. Published reports that contained data for at least 5 cats that were not selected for a specific food-based reaction were included, whilst studies that selected for a specific food-based reaction (*e.g.,* cats with a suspected chicken-based reaction) were excluded (24,25).



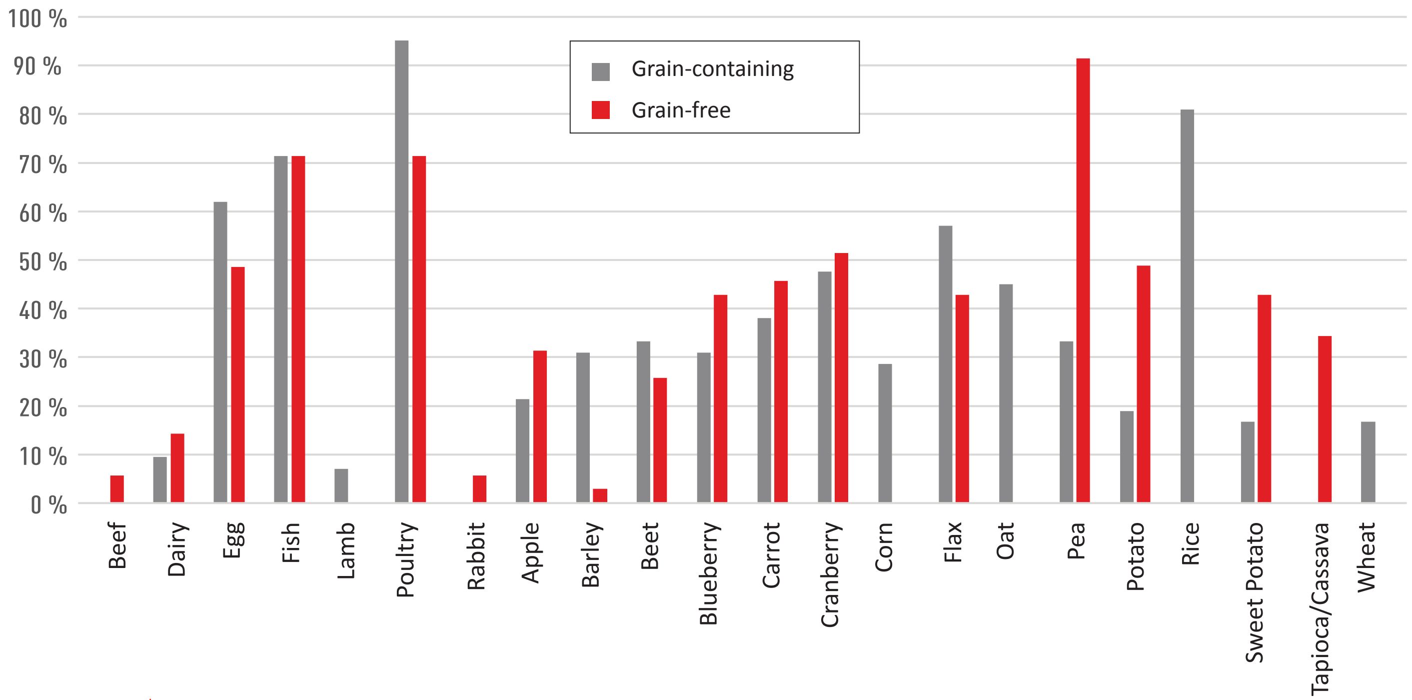


Figure 5. Distribution of the most common animal- and plant-based ingredients in grain-containing and grain-free dry cat diets sold in the United States (8). Data were compiled from 42 grain-containing and 35 grain-free dry cat diets. All of the reported ingredients associated with adverse food reaction (AFR) in cats (shown in **Figure 4**) are also included. Other ingredients representing < 30% of either diet type (unless included for comparison) are not shown.

beet, pea, barley, and blueberry, while the grain-free diets generally contained pea, cranberry, potato, carrot, blueberry, flax, sweet potato, tapioca/cassava, and apple **(Figure 5)**. Based on this information, both types of diet are less likely to contain some of the most common food allergens in cats, including beef, dairy, lamb, wheat, or corn **(Figure 5)**, but are likely to contain fish and poultry, respectively the third and fifth most common ingredients associated with feline AFR. Essentially, this means the allergenic potential of a diet is not really altered simply by feeding a grain-free diet.

In addition to removing dietary grains for general food allergies, some owners pursue this type of diet to specifically exclude gluten. 1% of the world's human population is affected by celiac disease, a multisystem immune disorder that is triggered by ingestion of gluten (1). A syndrome referred to as non-celiac gluten sensitivity, in which people without celiac disease or a wheat allergy describe an improvement in symptoms after maintaining a gluten-free diet, has been reported, although whether this is actually a separate and unique condition has yet to be established (1). Some owners that follow a gluten-free diet themselves may choose to remove gluten in their pet's diet in order to reduce their own risk of reactivity. In dogs, gluten-sensitive enteropathy has been reported in Irish Setters (26) (but it has been largely eliminated in this breed) and gluten-responsive epileptoid cramping syndrome has been described in Border Terriers (27). For affected animals, switching to a gluten-free diet, which does not necessarily need to be completely grain-free, will likely be helpful. Gluten-specific conditions have not been described in cats.

Grain free diets and DCM

Very recently, the development of dilated cardiomyopathy (DCM) in dogs eating a high proportion of ingredients consistent with grain-free diets (peas, potatoes, lentils, other legume seeds) has been reported (28). While there are known breed predispositions to canine DCM, the U.S. Food and Drug Administration has received reports from

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Angela Witzel Rollins

atypical breeds fed on grain-free diets. Half of these cases had low blood taurine concentrations, and taurine deficiency is a known cause of DCM. Dogs are able to synthesize taurine and do not typically have a dietary requirement for the amino acid, but some individuals or breeds may have conditionally essential requirements. It may be that the ingredients in these diets interfere with the bioavailability of taurine or another nutrient(s) yet to be evaluated. At this point, it is difficult to draw any conclusions regarding an association of grain-free diets with the development of DCM, as the number of cases reported is a very small fraction of dogs fed these types of diets, and more investigation is needed.

So are grain-free diets good or bad?

Cats and dogs are both capable of digesting and metabolizing carbohydrates, including grains. As a general rule, placing both species on this type of diet is not inherently problematic, although there are no specific data suggesting it is truly a more optimal feeding plan. While dry grain-free diets for cats may contain less total carbohydrates compared to grain-containing diets, neither diet type is completely carbohydrate-free and may not reflect the macronutrient profile domestic cats and dogs tend to prefer. Importantly, a diet that is low in total carbohydrates must inherently be higher in protein and fat, which may be an inappropriate profile for animals with some medical conditions, including chronic kidney disease and those requiring dietary fat reduction. Simply switching to a grain-free diet may also not improve clinical signs in animals that are actually suffering from an AFR, since these reactions are more likely to be due to animal-sourced ingredients, and two of the most commonly associated ingredients in feline petfoods are likely to be included in dry grain-free diets. If a cat or dog does have an AFR to a specific individual grain, cross-reactivity to all grains has not been demonstrated in these species – and is likely in only 25% of affected people.

CONCLUSION

The bottom line is that if a domestic cat or dog is thriving on a well-formulated grain-free diet, this type of feeding plan may be continued, although it may be prudent to bear in mind the comments on DCM above. However, if an animal is switched to a grain-free diet in an attempt to feed a more biological ancestral diet, avoid unnecessary blood glucose fluctuations, improve overall diet digestibility and/or avoid food allergies, it may not actually be the grain cessation that is responsible for any beneficial effects.

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WET PET FOOD: WHEN IS IT INDICATED?

Jess L. P. Benson,

DVM, Virginia Maryland College of Veterinary Medicine, Blacksburg, Virginia, USA

Dr. Benson received her DVM from Virginia Maryland College of Veterinary Medicine (VMCVM) in 2018. She has a particular interest in nutrition for all species, and is currently pursuing an internship at Carolina Equine Hospital in North Carolina.

Megan L. Shepherd,

DVM, PhD, Dipl. ACVN, Virginia Maryland College of Veterinary Medicine, Blacksburg, Virginia, USA

Dr. Shepherd received her DVM from VMCVM in 2006 and spent two years in general equine practice before returning to VMCVM, where she completed her PhD in 2012 and a residency in comparative nutrition in 2013. She is currently Clinical Assistant Professor at VMCVM, where she runs the Nutrition Service and teaches nutrition.

KEY POINTS

Wet pet foods may offer some advantages over semi-moist and dry pet foods in certain situations.

1

Consider feeding wet pet food after evaluating the pet's health, diet history and the owner's resources, and always purchase pet food from reputable manufacturers.

2

Semi-dry and kibble-based diets have gained in popularity in recent years, but wet pet foods have some unique features and may offer distinct advantages in certain situations. Megan Shepherd and Jess Benson take a brief look at some of the facts behind these diets and discuss why they may be the food of choice for some cats and dogs.

Introduction

Most pets are fed a commercially produced pet food. Few pets consume commercially produced wet pet food (wet food) as their primary food (1), although cats appear to consume more wet food than dogs (2). Owners will often seek veterinary advice as to the best food to offer their pet, and this brief article reviews some of the salient points for wet foods.

Some important facts

Wet food (*i.e.*, moist, canned) contains 60-80% moisture, which is in contrast to semi-moist food, at around 25-35% moisture, and kibble (*i.e.*, dry food), which is around 10% moisture (3). Wet foods include gelling ingredients, such as soluble fibers (4), starch, wheat gluten and spray-dried animal plasma (5), for texture. The gelling agents do not appear to impact macronutrient digestibility (5,6). However, micronutrients such as selenium (7), sodium and potassium (8) appear to be less bioavailable in wet food, possibly due to the gelling agents (5). Furthermore, thiamine is a heat-labile essential nutrient reported to be deficient in some pâté-style wet foods, and in wet food produced by some small petfood companies (9). Additionally, wet food should contain a higher taurine content (as compared to dry food) to balance the enhanced bile acid excretion and subsequent microbial degradation of taurine seen with wet vs. dry food (10).

What are the advantages of wet foods?

Wet food is often reported to be more palatable than dry foods (11,12). This may partly be because wet foods are typically higher in protein when compared to dry foods (13), which cats in particular find palatable (14). Furthermore,

Figure 1. Wet food may offer certain advantages over dry or semi-moist foods, and can be more palatable, as it is usually more aromatic and is available in a variety of textures.

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Figure 2. The strongest indication for wet food may be the patient with urinary disease, where urine dilution is required.

wet food is often higher in fat, which generally enhances palatability **(Figure 1)**. Wet food may also be more aromatic and is available in different forms (textures), such as pâté or morsels and gravy (15). While some pets may show a preference to wet food, some pets express a strong desire for dry food rather than wet food (16).

The high-moisture content of wet food may reduce the total calories consumed at a meal (17), and may also decrease the risk of obesity in cats (18). However, pets have successfully lost weight on dry food with enhanced insoluble fiber. Cost (price per calorie) and the perishable nature of wet food may reduce the incidence of overfeeding, as compared to dry food. However, wet food has a higher fat content than dry food and thus a higher calorie content on a dry matter basis.

Wet food increases total daily water intake (19,20) despite negatively influencing drinking water intake (21). The strongest indication for wet food is for the patient with urinary disease in general, where urine dilution is required **(Figure 2)**. Feeding a wet diet can be indicated for management of feline idiopathic cystitis (FIC) (22). Urine specific gravity (USG) and the relative supersaturation (RSS) of calcium oxalate is reduced when cats (19) and at-risk dog breeds (20) are fed a diet with 73% moisture, as compared to a diet with 7% moisture. Feeding dry food can be one of many other dietary risk factors for calcium oxalate urolithiasis in dogs (23).

Wet foods are generally lower in digestible carbohydrates and thus may be a good option for the patient with diabetes. Furthermore, the perishable nature of wet food promotes meal feeding (as opposed to *ad-lib* feeding), which is likely ideal for the diabetic patient. Wet foods may also be helpful for patients with oral pain due to the softer texture. However, wet foods do not serve a role in preventing dental disease due to the lack of gingival stimulation, as provided by dental-specific dry food and/or brushing.

CONCLUSION

There are many factors to be considered when selecting an appropriate diet for a pet. In some situations, wet food may be helpful. Wet food is more expensive (price/kcal) and more perishable than dry food. Therefore, a pet's health and diet history, as well as the caregiver's resources should be considered when selecting a diet. Importantly, whatever diet is endorsed, the clinician should emphasize that all pet foods should be sourced from reputable manufacturers that employ scientists trained in pet nutrition, food science and engineering, to ensure the food is both nutritious and safe.

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  Dan Thompson, UK
- **Performance of cat-friendly clinics**
  Pere Mercader, Spain
- **How I approach... the kitten with a heart murmur**
  Meg Sleeper and Camden Rouben, USA
- **Feline infectious peritonitis**
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