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REVIEW

Stones in cats and dogs: What can be learnt from them?

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KEYWORDS

Uroliths;
Canine;
Feline;
Ureterolith;
Cystolith

ABBREVIATION

RSS, relative supersaturation

Abstract ***Objective:*** To review the clinical features of stone disease in dogs and cats for a non-veterinary audience.

Methods: Relevant peer-reviewed scientific reports were reviewed.

Results: Lower urinary tract stones are more common in dogs and cats than they are in humans. In addition to struvite stones, calcium oxalate, urate and cystine stones are all commonly found in the bladder and the urethra. The genetic basis for stone disease in some breeds of dog has been elucidated. The small size of cats creates technical challenges when managing ureterolithiasis.

Conclusions: Naturally occurring stone disease in companion animals is a valuable area for further study. The structure of the canine genome might facilitate the identification of novel disease loci in breeds of dog predisposed to stone formation.

Introduction

> '*Between animal and human medicine there is no dividing line–nor should there be. The object is different but the experience obtained constitutes the basis of all medicine*'.
> Rudolf Virchow (1821–1902)

The study of disease in animals has contributed a great deal to human medicine. The role that laboratory animals play in the development of the current understanding of normal physiology, disease states and potential therapies is well known. The importance of studying infectious disease in farm-animals and wildlife is also clear, as it is estimated that three-quarters of all emerging diseases are zoonoses or vector-borne diseases. However, by comparison, the study of naturally occurring disease in companion animals is relatively neglected. This is despite the fact that historically comparative medicine has led to numerous advances in medical science. Particular benefits from the study of companion animals include the following:

- Dogs and cats usually share the same environment as their owners.
- Common lifestyle problems in humans (obesity, lack of exercise) are also prevalent in pets.

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- Dogs and cats are larger than the commonly studied-laboratory animals, potentially allowing the collection of larger volumes of blood/urine or other biological material (subject to ethical approval and owner consent).
- The shorter life-span of these animals facilitates the collection of tissues at death.
- The canine genome contains breed-related 'bottle-necks' that facilitate the identification of causative mutations due to the increased linkage disequilibrium.
- Diseases in companion animals can be heterogeneous in their presentation, progression and response to treatment, because of differences in their genetics or environment. In this way disease in dogs and cats might be a better model of what is likely to occur in humans than a laboratory population of genetically similar animals sharing the same environment.

With these ideas in mind this review is broadly divided into two parts: in the first an overview is given of stone disease in dogs and cats, emphasising important similarities and differences from stone disease in humans. In the second part some potential key benefits to the study of stone disease in dogs and cats will be emphasised.

Overview of stone disease in dogs and cats

Stone location and comparative anatomy

Although nephroliths and ureteroliths are an important and increasingly common problem in companion animals, particularly cats, most stones (>97%) that are submitted for analysis have been removed from the lower urinary tract [1]. One reason for this is that almost all veterinary practitioners (without additional specialist training or qualifications) will be comfortable doing a cystotomy and/or urethrostomy, but relatively few will consider doing surgery on the upper urinary tract. Although noninvasive techniques such as ESWL, ureteric stenting and laser lithotripsy are available in a few specialist referral centres these are not widely available and are cost-prohibitive for many pet owners [2,3]. There are also technical difficulties when using these techniques in dogs and cats (see below). As a result, many nephroliths, especially if they are discovered incidentally, will be treated with 'benign neglect' and never removed. Nonetheless, even considering this, it seems that lower urinary tract stones are relatively much more common in dogs and cats than they are in humans. The reason for this might simply be because of the quadruped stance of dogs and cats. The most dependent part of the bladder is ventral, which might favour the retention of crystal aggregates or very small stones and their subsequent growth into clinically evident uroliths (Fig. 1a,b). Compared to humans, it might be less likely that small stones that either form in, or pass into, the bladder are urinated out before becoming large enough to result in a clinical problem. Although about a half of all bladder stones in dogs will be infection-related

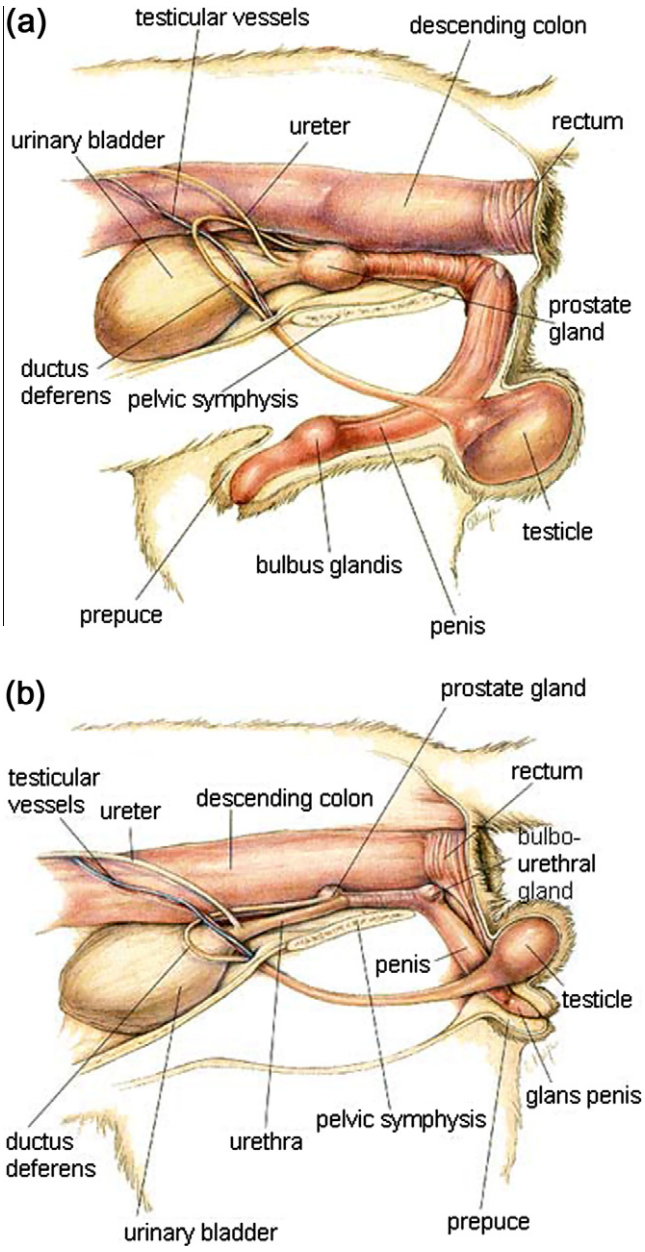

Figure 1 Schematic representation of (a) the canine urinary tract, and (b) the feline urinary tract. Reprinted with permission by the copyright owner, Hill's Pet Nutrition, Inc.

struvite, sterile struvite (cats), calcium oxalate (dogs and cats), urate (dogs and cats) and cystine (dogs) stones are all also commonly found in the lower urinary tract.

Ureteric colic is rarely recognised in dogs and cats. Nephroliths and ureteroliths are most often documented for one of three reasons: (1) Abdominal imaging (radiographs, ultrasonography or CT) is used for another reason and the stones are discovered incidentally; (2) a patient is presented with chronic kidney disease and renal imaging is used to investigate the cause; or (3) a patient is presented with acute renal failure due to ureteric

obstruction of a single functioning kidney. In the last scenario, an unrecognised episode of ureteric obstruction is presumed to have occurred in the other kidney some time previously, and these patients (typically cats) will often be clinically recognised as having the so-called 'big-kidney, little-kidney' syndrome; they can be extremely azotaemic and hyperkalaemic at presentation, and the challenges of dealing with these patients are immense. This is especially true in cats, where the luminal diameter of the normal, unobstructed ureter is only 0.4 mm.

Dogs and cats with bladder stones might present due to lower urinary tract signs (pollakiuria, haematuria, stranguria) or due to the development of urethral obstruction (usually only in males). The urethra of the male cat tapers distally and is particularly narrow within the penis (Fig. 1b), so urethral obstruction due to urolithiasis is possible; however, functional urethral obstruction due to urethral spasm or obstruction with a urethral plug (matrix with embedded struvite crystals) is relatively more common in this species [4]. The male dog has an os penis, a bone within the penis that has a groove along its length in which the urethra sits. This means that the urethra narrows abruptly where it enters the os penis and uroliths frequently become lodged at this site (Fig. 2). The location of the dog's penis on the ventral abdominal wall results in the urethra being very long, which can be a limitation when using instrumentation developed for use in humans where the urethra is comparatively shorter and wider.

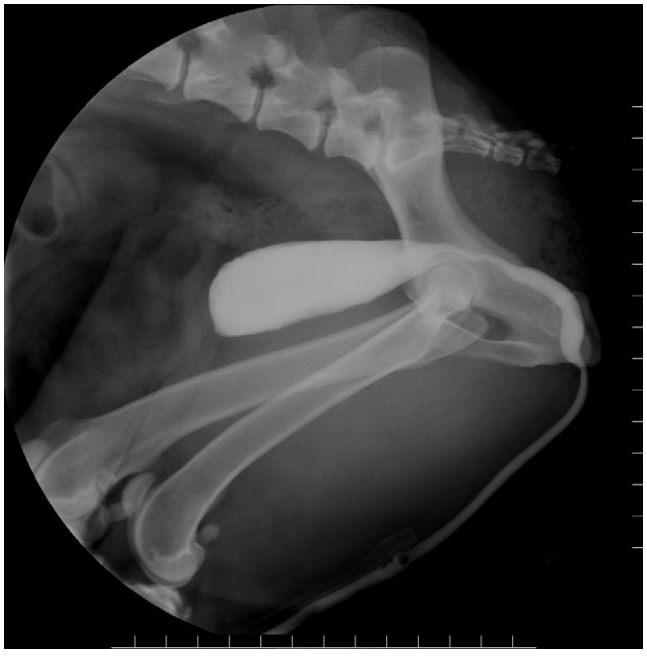

Figure 2 Lateral abdominal radiograph of a male entire Rottweiler dog. The positive-contrast urethrocystogram shows a radiolucent filling defect at the base of the os penis due to the presence of a cystine stone.

Specific stone types

The relative frequency of different stone types in the dog and cat is shown in Table 1. These data were published by the Minnesota Urolith Centre, which receives stones submitted from veterinarians practising in nearly all areas of the world, but with most of the samples submitted from North America [1]. There are other major stone centres in Canada and California, and they have published broadly similar data, with some differences resulting from the way that the samples are categorised [5,6]. There are some inherent limitations to these data; for samples to be submitted they cannot have been removed by dissolution, and upper urinary tract stones can be relatively under-represented due to the difficulty in removing these. There might also be a tendency for veterinarians not to submit stones for analysis when they are confident that they can predict the composition. Nonetheless, the sample size and the expertise of these laboratories make the data very valuable for evaluating the risk-factors for urolithiasis, particularly in regard to the animal's signalment (age, sex and breed), which is data that are usually collected at the time of stone submission. In many of the laboratories the stones are analysed free of charge to the client, being funded instead by the major pet-food companies. This is not altruistic, as once the stones are analysed then recommendations will be made for a prescribed diet, based on the mineral composition of the urolith.

Struvite

Struvite stones are common in dogs and cats, representing nearly half of all the stones that are submitted for

Table 1 Mineral composition of canine and feline uroliths.

Stone type	Canine (%)	Feline (%)
Struvite[a]	39.0	48.6
Calcium oxalate	41.3	40.8
Urate	5.0	4.9
Cystine	1.1	< 0.1
Mixed	2.8	0.7
Compound	9.1	3.2

Percentages are calculated from a total of 40,612 canine and 11,174 feline uroliths evaluated at the Minnesota Urolith Center by polarising light microscopy or infrared spectroscopy in 2007 (Osborne et al., 2008). Mixed uroliths were defined as those in which no nucleus or shell was detected and they did not contain > 70% of any individual mineral type. Compound uroliths contained an identifiable nucleus and at least one surrounding layer of a different mineral type.

Data are only reported for stones comprising at least 1.0% of the total in either the dog and/or cat. Other documented stone types included; calcium phosphate, silica, magnesium hydrogen phosphate, drug metabolites, calcium carbonate, magnesium phosphate, matrix and dolomite.

[a] Struvite stones are usually infection-related in dogs but sterile in cats.

analysis. Struvite stones in dogs (male and female) usually develop due to a UTI with urease-producing bacteria; *Staphylococcus* species are most commonly responsible in dogs. Struvite stones are much more common in bitches than male dogs because females are more likely to develop UTI. By contrast, struvite stones in cats are usually sterile and as a result are evenly represented in males and females.

Struvite stones are amenable to medical dissolution. In dogs the most important component of therapy is treatment of the UTI with appropriate antimicrobial agents, chosen on the basis of culture and sensitivity. These drugs must be continued throughout the period of medical dissolution because of the continual liberation of viable bacteria from within the dissolving uroliths. Dissolution is aided by dietary therapy. Diets for the dissolution of struvite calculi are designed to result in urinary acidification, production of a large volume of dilute urine, and a low concentration of constituent crystalloids (i.e., magnesium and phosphate) and crystalloid precursors (i.e., urea). This is typically achieved by feeding prescription diets that are specially formulated for this purpose; these contain calcium sulphate and DL-methionine to achieve a target pH of ≈6.0, low concentrations of magnesium and phosphate to reduce their concentration in the urine, and a low protein content which results in a reduction in the concentration of urea. The low urea level, in addition to reducing the substrate for the urease enzymes, reduces the medullary concentrating gradient, resulting in the formation of more dilute urine. In dogs the average time to dissolve struvite stones using antimicrobial agents and diet is ≈3 months and treatment is not always successful [7]. Treatment can fail due to the presence of a calcium phosphate shell. The relatively high cost of prescription diets and antimicrobial agents (especially in large dogs), concern about the risk of urethral obstruction if the stones reduce in size, failure to identify that medical dissolution is possible, and the uncertain success of this approach, mean that it is probably relatively under-used in general practice.

The dissolution of struvite nephroliths in dogs with bacterial pyelonephritis has been reported [8]. To be effectively managed medically the stones must not be obstructive, as for dissolution they must be continually bathed in urine that is under-saturated with respect to magnesium-ammonium-phosphate.

In cats sterile struvite stones can be dissolved with diet alone, and this process is relatively rapid, taking on average just over a month [9]. Despite the relative ease with which these stones can be dissolved, and the very high success rates with dietary therapy alone, this approach is often not considered by general practitioners, and cystotomy is performed instead.

In addition to developing sterile struvite stones, male cats are also vulnerable to the development of urethral plugs which cause acute urethral obstruction. Urethral plugs are predominantly composed of a proteinaceous matrix often with embedded struvite crystals. Plugs tend to form in male cats with signs of idiopathic feline lower urinary tract disease, a sterile condition that has been considered analogous to interstitial cystitis in women, except that in cats it occurs in both sexes (although females do not become obstructed). It is unclear whether struvite crystals actually play a role in the aetiopathogenesis of plug formation or are essentially caught up in the inflammatory milieu, as struvite crystals are present in the urine of more than half of normal cats even when no lower urinary tract signs are present [10]. Urethral plugs cause acute urethral obstruction with the life-threatening consequences of post-renal azotaemia and severe hyperkalaemia. Death occurs rapidly if the obstruction is not relieved. An interesting and unexplained observation is that although calcium oxalate stones have dramatically increased in prevalence over the last 30 years, calcium oxalate crystals are very rarely found in urethral plugs, and any mineral component is almost invariably struvite [1]. In recent years there seems to have been a shift away from urethral obstruction due to plug formation, with cats tending to have functional urethral spasm rather than a mechanical lesion [4].

Calcium oxalate

Calcium oxalate stones are the second most common type found in companion animals; in 2007 they accounted for 41.3% of stones submitted from dogs and 40.8% of stones from cats [1]. This has not always been the case. In 1981 calcium oxalate accounted for only 2% of feline and 5% of canine uroliths submitted to the same centre. The prevalence of calcium oxalate stones in dogs has increased fairly steadily over the last three decades (Fig. 3a) while the prevalence in cats increased dramatically between 1981 and 2002 to a maximum of 55%, and has since declined slightly (Fig. 3b). Other laboratories reported broadly similar results [5,6]. There are several postulated reasons for the increasing occurrence of calcium oxalate stones; the most likely seems to be a change in dietary composition to try to prevent struvite stones and urethral plugs forming. In the 1980s most commercial brands of pet-food (especially feline diets) were essentially reformulated to be more acidifying and to contain less magnesium. It is possible that there was also a shift in owner-preference to feeding more dry (i.e., 'kibble') rather than moist (i.e., canned or sachet) formulations. Changes in breed popularity might also have played a role. Other postulated influences are the increasing problems of obesity and sedentary lifestyles in both dogs and cats [11].

The increase in calcium oxalate stones in cats has resulted in a parallel increase in the occurrence of ureteroliths and nephroliths in this species. Feline nephroliths

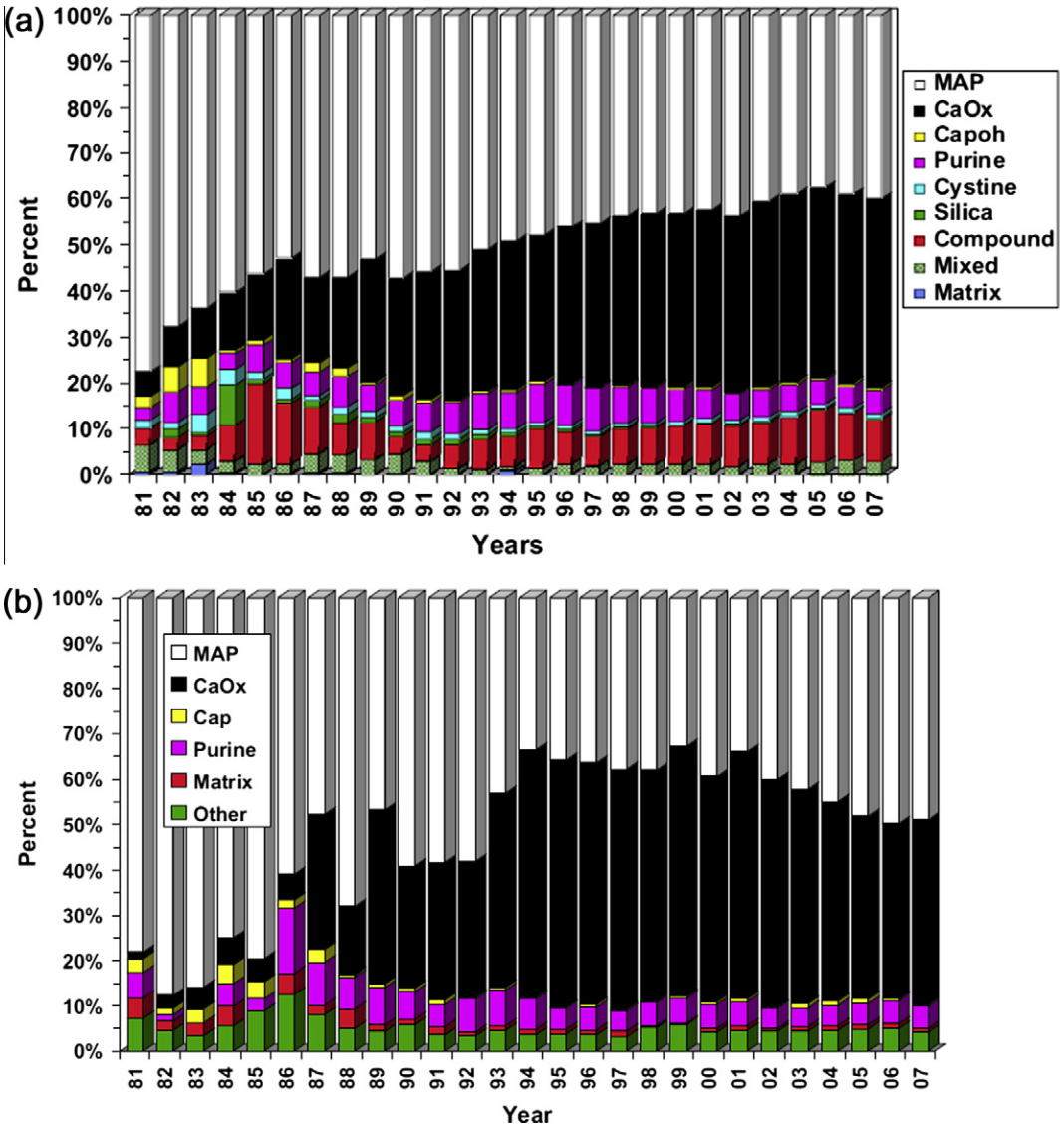

Figure 3 Distribution of (a) canine uroliths and (b) feline uroliths, analysed at the Minnesota Urolith Center between 1981 and 2007. Figure reproduced from Osborne et al. 2009 [1] (with permission).

and ureteroliths that have been submitted for analysis are almost invariably calcium-containing (usually calcium oxalate, occasionally calcium phosphate) with only 8% of them composed of struvite. By contrast, nephroureteroliths that are removed from dogs have a more variable mineral composition, and anecdotally the relative occurrence of upper urinary tract stones does not seem to have increased as dramatically over time.

In both dogs and cats those at greatest risk of developing calcium oxalate stones are old and male. Neutered male dogs are at greater risk than those that are sexually intact [12]. There are also breed-based predispositions towards the development of calcium oxalate stones. In dogs many of the commonly affected breeds are small, including the miniature schnauzer, Lhasa apso, Yorkshire terrier, bichon frise and miniature poodle. Although all small in stature they are not closely genetically related, originating from different evolutionary clusters [13]. Keeshonds (a larger breed) have also been found to be over-represented among calcium oxalate stone-forming dogs, which is probably due to this breed's known predisposition to the development of primary hyperparathyroidism [14]. In cats breed predisposition towards calcium oxalate stones is less well defined, in part because most pet cats are from an out-bred population described as domestic shorthair or domestic longhair. Even so, there is a suggested predisposition of certain related breeds (Persians, Himalayans) [6].

Hypercalciuria is reportedly common in dogs with calcium oxalate stones, and in one small study of miniature schnauzers this was found to be due to increased intestinal absorption (absorptive hypercalciuria) [15].

Calcium oxalate stones are not amenable to medical dissolution and must be removed by mechanical means.

Once the patient is stone-free recommendations are made to prevent recurrence, which is reported to occur in up to half of the affected dogs within 3 years [16]. Several prescription diets are marketed for this purpose. In general these diets have not been extensively tested in the field and therefore their efficacy is unknown. Much of the purported efficacy of these diets is based on the calculation of activity product ratios or relative supersaturation (RSS) in the urine of animals eating these diets. These data might be limited by the fact that samples are often obtained from clinically healthy dogs and cats rather than stone-formers. Also these analyses are usually funded by the pet-food manufacturers, so the diets investigated typically will have several differences from a maintenance food, making it difficult to determine the importance of any individual modification in dietary composition.

The one uncontroversial recommendation for preventing the recurrence of calcium oxalate stones is to increase the urine volume. Cats evolved as a desert species and if they are young, have good renal function, and are eating a dry diet they will commonly produce urine with a specific gravity as high as 1.060–1.070. In dogs the urinary specific gravity is more variable, but typically in the region of 1.025–1.045. Dogs that produce more concentrated urine and that urinate less frequently might be predisposed to calcium oxalate formation [17]. There are various methods that are used to increase water intake. If the cat or dog is eating a dry food then this should be changed to a moist formulation if possible, but some cats are very resistant to this if they have habitually eaten an all-dry diet. Water can also be gradually added to the food over a period of a few weeks until the patient is essentially lapping gruel. This approach is more successful in dogs than cats. Some of the formulated prescription diets have added salt to increase thirst and so decrease urine concentration. Initially it was considered that adding salt would be detrimental due to the resultant increase in calcium excretion. However, although the 24-h excretion of calcium is increased by salt-supplementation, the volume of urine produced also increases, such that the RSS for calcium oxalate actually reduces [18]. However, salt supplementation remains controversial, with concerns about the effects on renal function and blood pressure [19] that largely appear to be unfounded [20].

Many of the diets recommended for preventing calcium oxalate stones are relatively protein-restricted. The benefit to this is uncertain, as the only epidemiological study that examined the association of stone formation with protein intake actually found an increased risk in dogs fed a low-protein diet [21]. This might have been as a result of the diet being changed because stones were detected, rather than being truly associated with their formation. Alternatively, the association of low protein intake with the development of calcium oxalate stones, which differs from what has been found in humans, might be because of the concurrent reduction in phosphate intake or the fact that urinary pH can be manipulated in the process used to manufacture pet-food, independent of protein intake. In dogs, urinary citrate excretion is much lower than it is in humans, with $<1\%$ of filtered citrate actually excreted in the urine, although this increases dramatically with metabolic alkalosis [22]. The diets have typically been supplemented with potassium citrate with the aim of producing a diet that results in urine being produced with a pH of 6.5–7.5.

Treatment with hydrochlorothiazide has also been suggested as a means to reduce the risk of calcium oxalate recurrence in both dogs and cats. Although this approach has been shown to decrease urinary calcium concentration [23] and RSS [24] there are no studies evaluating the effectiveness in clinical patients.

Urate

Most dogs and cats are relatively protected from forming uric acid-containing uroliths because, in common with most mammals, uric acid is converted to allantoin by uricase (uric acid oxidase) within hepatocytes. Allantoin is much more soluble in urine than uric acid. The uricase enzyme is absent in humans and great apes. Dogs and cats with hepatic failure or portosystemic shunts might form urate stones due to a lack of functional hepatic tissue.

Many urate stones that are submitted for analysis come from Dalmatian dogs [25]. This breed has an inherited tendency to form uric acid stones that was first described in the early 20th century [26]. What is unusual about the genetic defect in Dalmatians is that although it is inherited in an autosomal-recessive manner, all pure-bred Dalmatians excrete excessive quantities of uric acid (and therefore have two abnormal copies of the gene). When serum and urine concentrations of uric acid in Dalmatians and humans are compared (Table 2) [27,28] it is apparent that although the urinary concentrations in the two species are similar, the serum concentration in Dalmatians, while greater than normal dogs, is lower than that of humans. This explains why Dalmatians (in common with other breeds of dog) do not get

Table 2 Comparison of uric acid concentrations in humans, dogs and Dalmatians.

Uric acid (mg/dl)	Human	Dog	Dalmatian
Serum	5–6	0.5	1.3
Urine	~33.3	~9.5	~37.8

Data from Moulin and colleagues [50] cited by Bannasch and Henthorn [41].

gout. The defect in Dalmatians is not due to a lack of uricase; if hepatocytes from this breed are homogenised so that the contents of the cells are liberated, the production of uric acid is similar to that of other breeds of dog [29]. In Dalmatians the stones form due to a failure of uric acid transport, both into hepatocytes for conversion to allantoin and out of the proximal tubule [30]. This explains why urinary concentrations of uric acid are high despite only a modest elevation in serum concentration.

The genetic basis for defective urate transport in Dalmatians was recently elucidated and elegantly shows the power of analysing the canine genome for unravelling the causes of inherited diseases and, as a result, providing a greater understanding of normal physiology [31]. Following an unsuccessful candidate-gene approach a genome-wide association study was conducted to map the hyperuricosuria locus. This was made possible because of a population of back-cross dogs that had been developed by initially crossing a Dalmatian with a pointer, and then crossing the resulting progeny with a pure-bred Dalmatian. This was repeated for many consecutive generations, at each step selecting the heterozygous offspring that excreted low concentrations of uric acid. The end result of this project was a population of dogs that were >99% Dalmatian, retaining all the normal phenotypic features of the breed, including the distinctive pattern of spotting, but that were heterozygous for the abnormal gene. Screening 148 markers on 25 members of this back-cross family identified a marker on canine chromosome CFA03 that was linked to the hyperuricosuria locus. Additional genetic markers were then used to localise the area of interest to a stretch of the genome containing 19 candidate-genes. The search could then be refined further to an area containing only four genes, because of the knowledge that all pure-bred Dalmatians are homozygous for the hyperuricosuria locus. An area of the chromosome was identified where all markers were identical. Finally, sequence analysis revealed a mutation in one gene (*SLC2A9*) that completely segregated with the hyperuricosuria trait in Dalmatian and back-cross dogs and was absent from 300 non-Dalmatians. This gene is now known to encode a urate transporter (it had previously been thought to transport glucose) and has been associated with serum uric acid concentrations in humans [32]. Subsequently this same mutation has been identified in other breeds of dog that sporadically form uric acid stones, such as the bulldog and the black Russian terrier; in these breeds the mutation is present in a much smaller segment of the population, explaining the much lower prevalence of uric acid stones [33].

Not all dogs with hyperuricosuria will form stones. It has been estimated that 25% of male Dalmatians will develop clinical signs related to urolithiasis but very few females will, probably because of the lower risk of urethral obstruction, although other factors, such as excretion of Tamm–Horsfall protein, might also play a role [34]. The risk of stone formation is reduced by feeding low-protein or vegetarian diets containing relatively low amounts of purine precursors. Other methods for reducing the risk of stone formation (or even promoting the dissolution of stones) are to alkalinise the urine to a pH of ≈7.0 by adding potassium citrate or sodium bicarbonate to the diet and encouraging water intake. Allopurinol can also be used to dissolve or prevent stone formation. This drug must be used in combination with a reduction in dietary protein intake, otherwise xanthine stones will form [35].

The identification of the underlying genetic defect responsible for uric acid stone formation also means that the problem could be eradicated by selective breeding. This approach is much easier in breeds of dog where the mutation is uncommon; in these breeds heterozygotes can be identified by genetic testing and not used for breeding. In the Dalmatian, eradication will be more difficult because all dogs (other than the back-cross progeny) are homozygous for the defective gene. Unfortunately, plans to breed from the back-cross dogs (that are >99% Dalmatian and heterozygous for the mutation) have met with resistance from Dalmatian breed societies that object to the fact that these dogs are not 'pure'. If the mutation is to be eliminated from this breed, a step-wise process will be required to first create a very large population of heterozygous dogs for breeding before eventually selecting for dogs that do not have the mutation at all; if this second step is undertaken prematurely then a genetic bottleneck will be created with probable adverse consequences for the breed in relation to other inherited diseases.

Cystine

Cystine urolithiasis occurs predominantly (98%) in male dogs [36]. Somewhat surprisingly, cystine uroliths are not common in very young dogs but tend to occur in middle-age. Cystine uroliths have been reported in many breeds of dog, including English bulldogs, Newfoundlands, dachshunds and Staffordshire bull terriers [5,37,38]. The prevalence of cystine urolithiasis is highly dependent on geographical location, with a higher reported prevalence in dogs in Europe than dogs from the USA [39].

Cystinuria is an inherited defect that results in the abnormal transport of the dibasic amino acids cystine, ornithine, lysine and arginine in the kidney (proximal tubules) and intestines. Clinical signs of deficiency do not occur, but instead signs are related to the precipitation of cystine within the urine due to its relatively low solubility, particularly at an acidic pH. In humans the clinical phenotypes have been divided into type-1 (caused by autosomal-recessive mutations in the *SLC3A1* gene, encoding rBAT) and non-type 1 (usually caused by

incompletely recessive mutations in *SLC7A9*, encoding $b^{o,+}$AT). The two proteins rBAT and $b^{o,+}$AT heterodimerise to form the basic amino acid transporter $b^{o,+}$.

Cystinuria in dogs is quite heterogeneous, with differences in both the type and quantity of amino acids excreted in the urine [40]. Newfoundlands with an autosomal-recessive form of cystinuria develop urolithiasis at a comparatively young age (a few months), and in contrast to other breeds the females can be affected as well as males [27]. The molecular basis of the defect has been identified in this breed as a nonsense mutation in exon 2 of *SLC3A1* which results in formation of a severely truncated protein product [41]. A different mutation in this gene has also been reported in Labrador retrievers [42]. However, in other breeds of dog with cystinuria no mutation in *SLC3A1* has been identified, indicating that the molecular pathogenesis of cystinuria in the dog is likely to be heterogeneous, as it is in humans. To date, deleterious mutations in *SLC7A9* have not been identified in cystinuric dogs [43]. It is possible that mutations in non-coding regions relating to *SLC3A1* or *SLC7A9* are responsible for causing cystinuria in dogs, or that an entirely different gene is responsible. If this is the case then unravelling the causes of cystinuria in dogs could have comparative value by increasing the understanding of cystinuria in humans.

Cystine uroliths are amenable to medical dissolution. As with all uroliths, augmenting the urinary volume is likely to be beneficial. Also, the solubility of cystine can be increased by increasing the urinary pH to 7.0–7.5, either by dietary therapy or by treatment with potassium citrate. Protein restriction is also advocated to reduce the intake of cystine precursors. Thiol-containing drugs have been used for dissolving cystine stones in dogs. Unfortunately d-penicillamine is not that effective and is associated with a high incidence of side-effects, which effectively limits its use. The drug N-(2-mercaptopropionl)-glycine (Thiola) is more effective but not widely available [44]. Sadly, many cystinuric dogs are euthanised due to a failure to prevent repeated episodes of urethral obstruction.

Potential benefits and limitations to the study of stone disease in animals

Epidemiological studies

Studies of stone disease in animals are facilitated by the submission of many stones to relatively few laboratories, as illustrated by the data in Table 1 and Fig. 3a,b. This has allowed the study of various risk-factors for stone formation, including the effects of age, gender and breed, as described above, together with influences such as geographical location, presence of UTI and dietary history [45].

One limitation to the study of risk-factors for urolithiasis in animals is a lack of knowledge about the size of the population at risk. The numbers of dogs and cats living in most countries are not recorded. As a result many studies of stone-formers have identified only the most commonly affected breeds rather than those that are truly over-represented.

Genetic studies

The dog is an ideal model for mapping genetic diseases [46]. The domestic dog shows profound phenotypical variation with >400 identified breeds. Each of these breeds has been developed by strong artificial selection over a relatively short period, most breeds of dog having been created in the Victorian era. This selective breeding has created population bottlenecks with long haplotype blocks and marked linkage disequilibrium, making dogs particularly amenable to genome-wide association studies. However, large haplotype blocks also mean that any trait region identified within a single breed can incorporate hundreds of genes. In many instances this problem can be overcome when a particular trait is evident in several breeds, allowing a comparison between them and so narrowing the region of interest.

The dog genome is very similar to the human genome, with an average nucleotide divergence of ≈ 0.35 substitutions per site (less than the mouse) and a similar number of genes, most of which are 1 : 1 orthologues. There are now several canine single-nucleotide polymorphism arrays with thousands of loci. A comprehensive linkage map for all dog chromosomes is available that can be used in conjunction with whole-genome mapping. There is also a great deal of medical knowledge about dogs; there are extensive lists of known disorders that are thought to be inherited, for example on the Inherited Diseases in Dogs Database (http://server.vet.cam.ac.uk/index.html). In addition to the examples of uric acid stones in Dalmatians and cystine stones in Newfoundlands that are described above, there are also instances where the canine genome has successfully been used to elucidate disease mechanisms in humans (e.g., discovering a novel photoreceptor gene, *PCRD*, involved in retinitis pigmentosa [47]) or to understand complex phenotypic traits with multiple gene effects (e.g., coat appearance [48]).

Technical challenges

The treatment of stone disease in dogs and cats can be very technically challenging because they are relatively small; this is particularly true of cats with obstructive ureterolithiasis. These animals are often very clinically unstable due to the obstruction of their only functional kidney. Although microsurgical techniques have been described for ureterotomy, this approach has now lar-

gely been superseded by placing ureteric stents. This has been aided by the development of 2.5 F ureteric catheters specially designed for use in the cat. However, even stents of this size are difficult to pass, and although endoscopic placement has been described, open surgical placement is more common. Even then placement is most often accomplished via pyelocentesis (antegrade placement) rather than via cystotomy (retrograde placement). In one series of cases, the placement was successful in 98% of 84 dogs and 94% of 62 cats [49]. Unfortunately, once placed, ureteric stents can typically not be removed, at least from cats. The very small ureter means that the trauma and resulting mucosal swelling associated with stent removal results in ureteric obstruction. It has been suggested that stent encrustation is less of a problem in cats and dogs than it is in humans, allowing the stents to remain in place in the long-term [49]. However, a preliminary study of an *in vitro* model of encrustation indicated that the behaviour of artificial feline and human urine was no different. An alternative approach to stenting that has been developed for use in cats is the creation of a subcutaneous ureteric bypass system [3].

ESWL has been used successfully to treat nephro-ureteroliths in dogs but has had very limited success in the cat. One potential explanation is that impacted ureteroliths are more difficult to fragment because they are not surrounded by sufficient urine for cavitation bubbles to form on the near side of the ureterolith. However, it also seems that feline calcium oxalate stones are inherently less susceptible to fragmentation than canine (and presumably human) stones [49]. It was postulated that this difference is attributable to differences in the organic matrix component of the uroliths.

Ongoing work to overcome the challenges of ureteric stone disease in veterinary patients might result in advances in technology that can then be used in human medicine. A comparison between species could also result in a greater understanding of the biomechanical properties of uroliths.

Sentinel population

A final example of the potential benefit to the study of disease in dogs and cats is provided by the recent epidemics of stone disease due to contamination of food stuffs with melamine and/or cyanuric acid. The detection and recognition of the food contaminant in Chinese baby-food was facilitated by the preceding outbreaks of renal failure in dogs and cats associated with contaminated pet-food [28].

In summary, there are numerous advantages to studying naturally occurring disease in dogs and cats, not just for the benefit of the patients themselves but also potentially for the advancement of human medicine. Some of these are listed in Box 1.

Box 1

A summary of potential advantages of the study of naturally occurring disease in companion animals.

- Reduction in the number of animals used in experimental research.
- Development of better animal models for development of human drugs and devices.
- Direct benefit to pets and their owners as new drugs, devices and diagnostic procedures are developed and tested.
- Promotion of evidence-based veterinary medicine to improve the quality of clinical veterinary care.
- Reduced cost of veterinary care to owners whose pets are enrolled in clinical studies.
- Availability of leading edge veterinary care for animal patients who are enrolled in clinical studies.
- Identification of new, relevant models of spontaneous disease for drug development and device testing.
- Improved human and animal health.

Conflict of interest

None.

Source of funding

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