



FLUTD can be seen in cats of any age although it usually affects middle-aged, overweight cats which take little exercise, use an indoor litter tray, have restricted access to the outdoors and eat a dry diet. Picture, Ralston Purina

Feline lower urinary tract disease: an update

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FELINE lower urinary tract disease (FLUTD) describes a collection of conditions that can affect the bladder and/or urethra of cats. Unfortunately, since the urinary tract can respond to insult in only a limited number of ways, the clinical signs are rarely indicative of a particular disease. While there are many conditions that can result in signs of FLUTD, the vast majority of cases are idiopathic. This article discusses possible aetiologies and describes a stepwise approach to diagnosis and management.

CLINICAL SIGNS OF FLUTD

Cats with FLUTD usually present with signs of dysuria (difficult urination), pollakiuria (increased frequency of urination), haematuria, urethral obstruction and/or periuria (inappropriate urination). In some cases the owner is unaware of an underlying urinary tract problem, and they present the cat for investigation of behavioural changes, loss of litter tray training and/or aggression.

The annual incidence of FLUTD in British cats is believed to be around 1 per cent. While FLUTD can be seen in cats of any age, it is most frequently seen in middle-aged, overweight cats which take little exercise, use an indoor litter tray, have restricted access to the outdoors, and eat a dry diet. Persian cats appear to be predisposed, while the condition is rarely seen in Siamese cats. FLUTD occurs equally in male and female cats although neutered cats are more susceptible to the disease and the risk of urinary tract obstruction is greatest in males.

CAUSES OF FLUTD

IDIOPATHIC CYSTITIS

In the majority of cases of FLUTD, no underlying cause can be found. Research over the past 30 years has failed to find a consistent cause for the inflammation. However, a recent hypothesis suggests that feline idiopathic cystitis (FIC) may result from alterations in the interaction between the neuronal supply, the protective glycosaminoglycan (GAG) layer that lines the bladder, and compounds within the urine (see box on the facing page). It has also been suggested that FIC has similarities to an idiopathic non-malignant bladder disease in humans, known as 'interstitial cystitis'.

None of the drugs mentioned in this article are licensed for use in cats. Readers are advised to consult the data sheets and texts such as The Veterinary Formulary or the BSAVA Small Animal Formulary for more information and potential side effects.

Much of our understanding of FIC has come from studying the histopathology of bladder wall biopsies. These biopsies usually reveal a relatively normal epithelium and muscularis, with submucosal oedema and vasodilation but without an obvious inflammatory infiltrate; however, large numbers of mast cells are frequently present. In addition, biopsies often reveal increased

CAUSES OF NON-OBSTRUCTIVE FLUTD

	Relative frequency
Non-obstructive idiopathic cystitis	65%
Urolithiasis	15%
Anatomical defects/neoplasia/other	10%
Behavioural problems	<10%
Bacterial infection	<2%
From Buffington and others (1997)	

CAUSES OF OBSTRUCTIVE FLUTD

	Relative frequency
Obstructive idiopathic cystitis	29%
Urethral plug	59%
Uroliths	10%
Uroliths and bacterial infection	2%
From Kalkstein and others (1999) and Kruger and others (1991)	

numbers of pain fibres (C-fibres) and pain receptors (substance P receptors).

It is now known that stimulation of the C-fibres by a central or local triggers can cause the release of substance P (and other neuropeptides), which can in turn result in pain, vasodilation of the intramural blood vessels, increased vascular and bladder wall permeability, oedema of the submucosa, smooth muscle contraction, and mast cell degranulation. Mast cell degranulation results in the release of a variety of inflammatory mediators (including histamine, heparin, serotonin, cytokines, and prostaglandins) which can further exacerbate the effects of the C-fibres. Stimulation of C-fibres can therefore explain many aspects of the changes recorded in FIC. The nerve endings can be stimulated in response to central triggers (such as 'stress'), or via compounds within the urine (eg, acid pH, potassium, magnesium and calcium ions). This in turn may result in further recruitment of C-fibres, and intensification of the disease.

A thin layer of mucus composed of GAG covers the bladder epithelium. This layer helps to prevent microbes and crystals from sticking to the bladder lining. It has been shown that some cats with FIC have decreased urine concentrations of GAG and increased urinary bladder wall permeability. While it has not been proven, it has been suggested that defects in this protective layer may result in increased bladder wall permeability, allowing noxious substances within the urine to pass through the urothelium and cause inflammation.

While it appears that neurogenic inflammation may play an important role in the development of the clinical signs of FLUTD, it is unclear whether or not it is a primary factor, or a secondary event, perhaps triggered by an as yet unidentified, infectious agent.

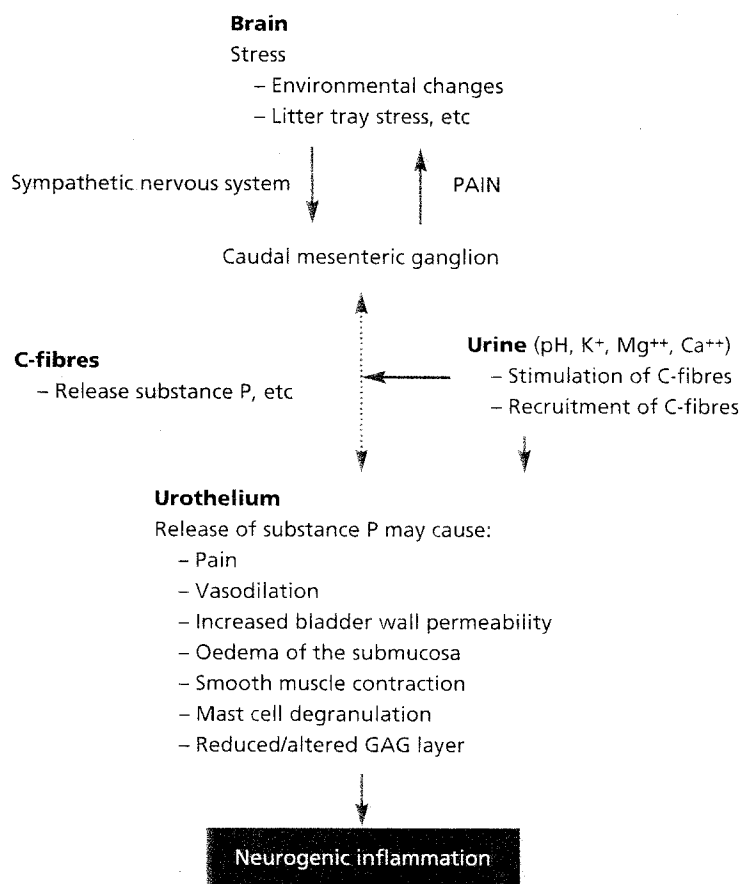
UROLITHIASIS

Urolithiasis is defined as the formation of urinary calculi (eg, uroliths, stones). Uroliths can vary in their mineral composition, with struvite and oxalate forms being seen most commonly in cats. Over the past few years much interest has been targeted by the food companies at designing diets that will aid the dissolution of struvite stones. However, while this has resulted in a decline in the incidence of struvite urolithiasis it has resulted in an increase in oxalate urolithiasis. Unfortunately, oxalate uroliths are not dissolvable in cat urine, and so must be removed surgically.

URETHRAL PLUGS

Urethral plugs occur with approximately the same frequency as uroliths and are of particular importance because they are associated with urethral obstruction. They are composed of varying combinations of a colloid matrix (eg, mucoproteins, albumin, globulin and cells) and crystalline material (most typically struvite). The colloid matrix is believed to 'leak' from the bladder wall as a result of inflammation. This inflammation may be neurogenic or idiopathic, or it may occur secondarily to

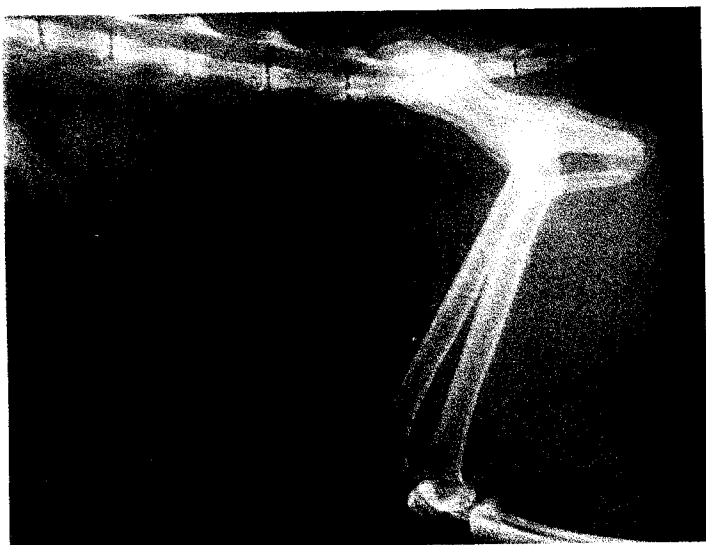
Current hypothesis for neurogenic inflammation of FIC



Adapted from Buffington and others (1996)



(left) Pneumocystogram and (right) double contrast cystourethrogram of a six-year-old neutered male Persian cat with FLUTD. Oxalate uroliths are present, and the ventral aspect of the bladder wall is thickened. The uroliths are more readily apparent in the double contrast cystogram



Pneumocystogram of an eight-year-old neutered male domestic shorthaired cat with severe FIC, showing extreme bladder wall thickening. This was the full extent to which the bladder could be distended



Double contrast cystogram of a three-year-old neutered male domestic longhaired cat with FIC, showing thickening of the bladder wall. Air bubble artefacts can be seen along the ventral wall

infection, neoplasia or uroliths. Thick colloid may cause urethral obstruction without evidence of crystalluria. However, where crystalluria is also present, the crystals may become trapped within the matrix, and add to the obstruction. It is therefore the colloid that is of primary importance, rather than the presence of crystals per se.

INFECTIOUS CAUSES

So far, no bacterial, fungal or viral organisms have been consistently shown to induce FLUTD. However, it is still possible that a very fastidious organism could be involved. Bacterial infection is a rare cause of FLUTD. Where it is seen, it is usually iatrogenic, or secondary to urolithiasis, an anatomical defect or neoplasia. Older cats, particularly those with concurrent renal failure, have an increased risk of bacterial infection. However, FLUTD is rarely seen in cats of this age group.

INTERACTING COMBINATIONS

The different causes of FLUTD may occur individually or in various interacting combinations. For example, the formation of urethral plugs may result from concurrent,

but not necessarily related, disorders (eg, the simultaneous occurrence of urinary tract inflammation and crystalluria; see box below). While obstruction most typically results from the formation of urethral plugs, it may also be caused by the passage of small uroliths, or from pain-induced urethral spasm. Although inflammation without crystalluria can result in obstruction with colloid matrix, it more typically causes haematuria and dysuria. Crystalluria is often clinically silent but, if persistent, may predispose to the development of uroliths, and these, in turn, can lead to urethral obstruction and bladder inflammation.

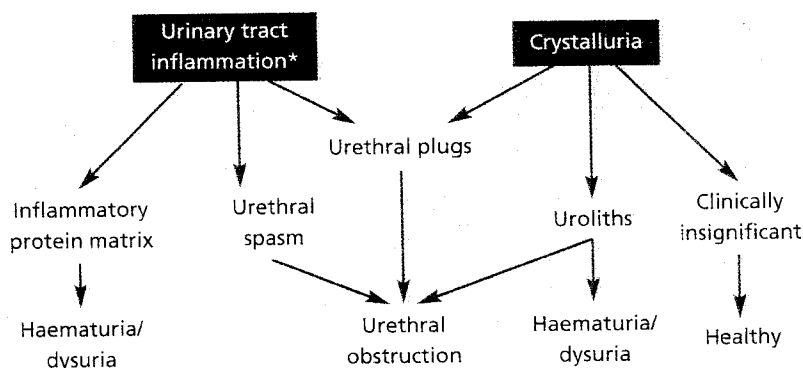
DIAGNOSIS OF IDIOPATHIC CYSTITIS

A diagnosis of FIC is made by excluding all other causes of dysuria, pollakiuria, haematuria and periuria. This requires a practical, stepwise approach (see below). Unless there is evidence of concurrent systemic disease or urethral obstruction, cats with FLUTD typically have unremarkable serum biochemistry and haematology.

STEPWISE APPROACH

- STEP 1: RULE OUT URETHRAL OBSTRUCTION.
- STEP 2: COLLECT URINE SAMPLE.
- STEP 3: CHECK URINE SPECIFIC GRAVITY (SG). If SG is less than 1.025, then rule out systemic disease (eg, renal disease or other causes of dilute urine). If SG is more than 1.025, carry out urinalysis (STEP 4).
- STEP 4: URINALYSIS. Assess the urine for crystals, protein, red blood cells and white blood cells. Care should be taken when interpreting the findings of urinalysis. If obtained by cystocentesis, blood contamination may increase the red blood cell and white blood cell numbers. When looking for crystals, the urine should be examined within two hours of collection. This is because crystals precipitate rapidly in cat urine as it cools to room temperature. Struvite crystals are common in normal cat urine, especially if the cat is fed a dry diet. Therefore, their presence without evidence of stone formation or secondary infection does not necessarily require the introduction of an acidifying diet. Urine from cats with FIC is usually concentrated and is of acid pH

Interaction between urinary tract inflammation and crystalluria



From Osborne and others (1992)

*Urinary tract inflammation may be neurogenic, idiopathic or secondary to infection, neoplasia or uroliths



Double contrast cystourethrogram of an adult neutered male domestic shorthaired cat with FIC, showing leakage of air and contrast medium into the bladder wall. Picture, Ivan Clark



Positive contrast cystogram of a two-year-old neutered male Burmese cat with severe FIC, showing leakage of the contrast medium throughout the abdominal cavity. Exploratory laparotomy revealed no gross bladder defects. Histopathology revealed severe interstitial cystitis. Picture, Ian Hemsley

with haematuria and proteinuria, but without significant pyuria or bacteriuria. Care should be taken when assessing urine pH as stress and hyperventilation can cause the urine to become alkaline.

■ **STEP 5: QUANTITATIVE URINE CULTURE AND SENSITIVITY.** This analysis should always be performed using a sample obtained by cystocentesis. The number of positive results will be low as urinary tract infections are uncommon in cats. If positive, the cat should be treated with antibiotics selected on the basis of the culture and sensitivity findings. If negative, abdominal radiographs should be carried out (STEP 6).

■ **STEP 6: SURVEY ABDOMINAL RADIOGRAPHS.** Rule out radiopaque calculi (eg, struvite and oxalate uroliths). If positive, struvite uroliths should be treated by dietary means; oxalate uroliths need to be surgically removed. If no abnormality is found then further diagnostic imaging should be undertaken (STEP 7).

■ **STEP 7: FURTHER DIAGNOSTIC IMAGING.** This should include radiographic contrast studies (see box on the right) and abdominal ultrasonography, if appropriate. Rule out conditions such as radiolucent calculi, bladder diverticula, strictures, anatomical defects, neoplasia and polyps.

Radiographs of cats with FIC are frequently unremarkable. Changes that may be seen on double contrast cystourethrogram include diffuse bladder wall thickening (particularly affecting the apical area), mucosal irregularities, urethral narrowing and, occasionally, leakage of contrast media through the layers of the bladder wall. Ultrasonography may reveal hyperechoic material (possibly crystals), blood clots, mural irregularities or thickening of the bladder wall.

FURTHER DIAGNOSTIC AIDS

Where available, cystoscopy can be very useful. It may reveal evidence of increased mucosal vascularity, urothelial ulceration or focal areas of submucosal haemorrhage ('glomerulations'). However, these changes are not pathognomonic for FIC.

Histopathology of a full-thickness bladder wall biopsy is required to confirm the diagnosis of idiopathic cystitis. However, in many cases, once all other causes of FLUTD have been ruled out, it is often appropriate to treat as FIC presumptively.

If no lesions are identified on a full work-up then a purely behavioural problem should be considered. However, if the cat is not currently symptomatic, repeating the investigation when the cat is showing clinical signs may reveal more obvious bladder pathology. It is interesting to note that many cats which are believed to have a behavioural problem have a history of FLUTD at some time in their past.

Double contrast cystourethrogram

Double contrast cystourethrogram is the diagnostic method of choice for the assessment of the urinary bladder and urethra. The technique can be used to assess the position and integrity of the bladder and urethra, bladder distensibility and wall thickness, and to detect intraluminal and intramural lesions such as tumours, polyps, diverticula or calculi.

Method

- In preparation, allow a 24-hour starvation and give enemas to ensure that the colon and rectum are empty
- Sedate, or preferably anaesthetise, the cat
- Take survey abdominal radiographs
- Catheterise and empty the bladder using an aseptic technique
- If necessary, flush the bladder with warm saline to remove blood clots
- Infuse gas to distend the bladder. Generally about 2 to 4 ml/kg bodyweight is required. The bladder should be palpated to avoid over-distension. It is preferable to use carbon dioxide or nitrogen monoxide rather than room air, as these gases are less soluble
- Inject about 1 to 2 ml/cat of iodinated contrast medium (50:50 Urografin [76 %], Schering-Plough) into the bladder
- Roll the cat 360° to ensure that the entire bladder mucosa is coated
- Obtain lateral and ventrodorsal projection radiographs
- Inject additional gas if further bladder distension is required. Care is needed when adding the gas as air bubbles can produce misleading images
- Assessment of the urethra can be carried out either with the use of a voiding study or a retrograde urethrogram. A voiding study can be performed by filling the bladder with contrast medium and obtaining lateral and/or oblique projections while expressing the bladder by abdominal compression (eg, placing a light sandbag across the abdomen). A retrograde urethrogram can be obtained using either a small Foley catheter in female cats, or an open-ended tom cat catheter in male cats. Place the catheter as distally in the urethra as possible, and obtain lateral radiographs as 1 to 2 ml of the iodinated contrast medium is injected

Unfortunately, few treatments for FLUTD have been investigated by controlled, double-blinded experimental studies. Most recommendations are therefore based on clinical observations and personal opinion. Also, as FLUTD is usually self-limiting, many treatments may appear to be effective when they actually have no positive effect. All treatments should therefore be considered with appropriate caution.

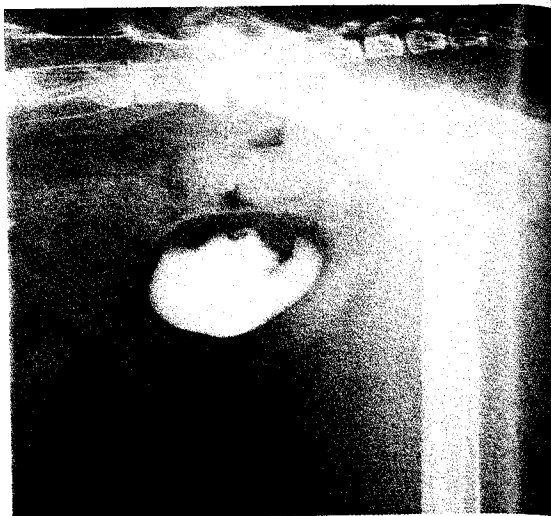
As more drugs are tried, the list of those that are either unhelpful, or even harmful, is growing. Among the treatments that have been critically assessed are certain antibiotics, and corticosteroids. The former have been shown to have no beneficial effect except in those rare cases where bacterial infection is present. Corticosteroids have also been found to have no positive effect. A number of drugs should never be given to cats. These include the urinary tract antiseptic, methylene blue, and the urinary tract analgesic, phenazopyridine, both of which can result in severe Heinz body anaemia.

The entire list of medications and interventions that have been considered for the treatment of FLUTD is far too extensive to be reviewed in this article. Instead, the author suggests therapeutic management of FIC which is aimed at addressing the factors underlying the disease (ie, altering the nature of the neurological input to the bladder, the protective GAG layer, and the content of the urine).

ALTERING THE NEURONAL SUPPLY

Reducing stress

Stress plays a key role in the pathophysiology of FIC and has been identified as a 'flare factor' that can precipitate a recurrence of clinical signs. Recognised stressors include abrupt changes in diet, environment or weather, overcrowding, owner stress, or the addition to the household of new pets or people. Stress associated with urination can be particularly significant (eg, an unsuitable position or content of the litter tray, competition for the litter tray,



Positive contrast cystogram of an 11-year-old neutered male Siamese cat with severe FLUTD, showing an irregular soft tissue mass associated with the dorsal bladder wall. Histopathology revealed a transitional cell carcinoma

or aggressive behaviour by other cats while the cat is trying to use the litter tray or when urinating outside).

It is essential to reduce the level of stress to which the cat may be exposed. Providing a safe, clean area in which the cat can urinate, reducing overcrowding or bullying, and reassuring the cat as much as possible may help to achieve this.

Tricyclic antidepressants

Tricyclic antidepressants have been found to be beneficial in the treatment of humans with interstitial cystitis and also in a number of cats with FIC. This group of drugs has both behavioural and organic effects. They have anticholinergic (including increasing bladder capacity), anti-inflammatory (including preventing histamine release from mast cells), anti-alpha-adrenergic, analgesic and antidepressant effects. These products are usually reserved for those cats with very severe or chronic disease and should be used with caution.

One product available for use is amitriptyline hydrochloride, administered at a dose of 2.5 to 10 mg/cat orally every 24 hours in the evening. The side effects of this drug include somnolence, urinary retention (due to its anticholinergic effects) and elevation in liver enzymes. Liver function should be assessed prior to starting therapy, reassessed one month later and then every six to 12 months while the cat is on the treatment. The drug action can be rapid and it is therefore possible for owners to start medication as soon as they observe the clinical signs of FIC. This may provide rapid regression of clinical signs. In some cats the drug may be given episodically, while others may need more protracted courses or continuous therapy.

Analgesia

Analgesia alone may reduce the severity of the clinical signs, but is rarely sufficient. Butorphanol, or fentanyl patches (which can be attached to a shaved area on the back of the neck) may have some positive effect.

THE PROTECTIVE GAG LAYER

In theory, therapy to replace the GAG layer should be very beneficial. It relies on the assumption that exogenous GAG will attach to the defective urothelium and

Indications for treatment

Most cases of non-obstructive FLUTD are self-limiting and usually resolve within five to 10 days. However, most affected cats have episodes of clinical signs which recur with variable frequency. The recurrent episodes generally tend to decrease in frequency and severity over time.

Despite the likelihood of spontaneous resolution, treatment is recommended for a number of reasons:

- FIC is very painful and distressing for the cat
- Cats with FIC may self-traumatise their perineal region
- Cats with FIC may become anorexic
- Male cats with FIC are at risk of developing urethral obstruction, which can present as a medical emergency
- Cats with FIC may develop behavioural changes, become aggressive to their owners or other cats within the household, or may lose their litter tray training
- Having a cat with FIC is very distressing for an owner

decrease bladder wall permeability. GAGs may also have analgesic and anti-inflammatory effects. However, while these compounds have shown some positive responses in humans with interstitial cystitis, controlled studies in cats are currently lacking. From human studies, it appears that there are differences in the relative efficacy of different GAGs, and the same is likely to be true in cats.

Although controlled studies have not yet been performed, the author has been using GAG supplementation, and has generally been pleased with the response. Supplementation can be given parenterally or orally and should begin with a higher dose at the time of initial presentation. This can then be reduced to a maintenance level. For those cats where oral supplementation is not possible, and repeated visits to the veterinary practice cause distress, pentosan polysulphate sodium (Cartrophen Vet; Arthroparm) can be dispensed for home-medication (in a similar fashion to insulin therapy).

Observant owners may notice that some cats show prodromal signs before an episode of FIC. The duration of these signs can vary from a few hours to a few days. Signs may include increased perineal licking and hind-end grooming, or inter-cat aggression initiated by the FIC sufferer. These signs may relate to increasing perineal pain. The instigation of treatment or increasing the dose of medication at this time may help to reduce the severity and duration of the episode, or prevent it from occurring altogether. This approach can also be used if a stressful episode is anticipated (eg, a visit to the vet, a stay in a cattery or buildiers in the home).

Products available for use include:

- Pentosan polysulphate sodium (Cartrophen Vet). This is a semisynthetic polymer that is given parenterally by subcutaneous injection at a dose of 3 mg/kg on days 1, 2, 5 and 10 and then every five to 10 days.
- N-acetyl glucosamine, the precursor of GAG. It can be given as a number of different food supplements. The author's preference is to use Acetylator (Vetri-Science Laboratories). A quarter to half of the contents of a capsule should be given per cat, orally, every 24 hours (each capsule contains 250 mg N-acetyl glucosamine, 100 mg alfalfa, *Lactobacillus acidophilus* 14 million microorganisms [non-dairy] and 45 mg proteolytic enzymes [pepsin, papain, bromelain]).

The possible side effects of GAG supplementation include prolonged bleeding times, inappetence, diarrhoea and, possibly, insulin resistance.

URINE

The easiest way to modify the content of urine is by altering the diet of the cat. Dietary changes can affect urine concentration, volume, pH and mineral content. While much interest has been directed at altering urine pH, and the magnesium and calcium content of urine, it is now believed that the single most important factor is the rate of water turnover. The aim of dietary manipulation is therefore to increase water turnover and dilute any noxious components within the urine. Rather than altering the content of a dry diet, it makes much more sense to simply feed a wet one! However, wet diets vary in their composition. Care should be taken when feeding high-fibre diets since they result in increased faecal fluid loss, and therefore reduced urine production. Where significant struvite crystalluria and/or urolithiasis is present, feeding an acidified wet diet may be useful.



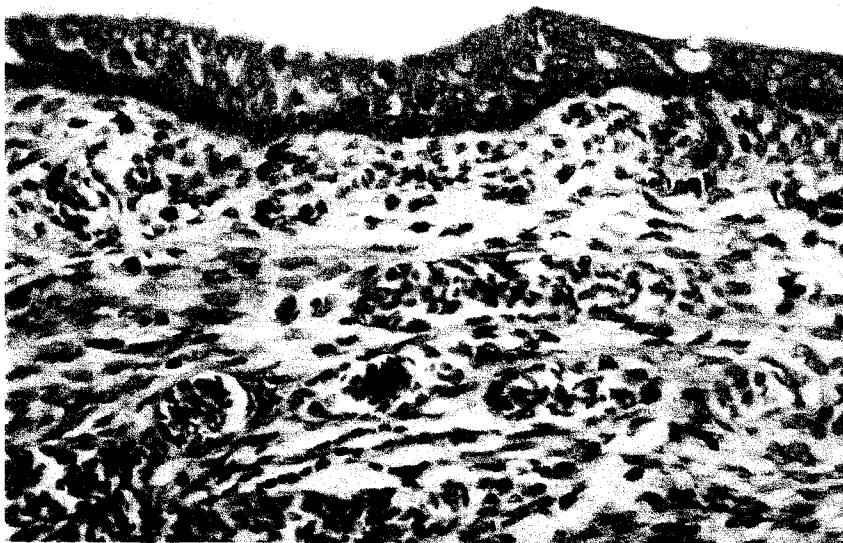
Positive contrast urethrogram of a three-year-old neutered male domestic shorthaired cat with clinical signs of FLUTD, revealing no abnormalities

Dietary recommendations

- Change diet to canned food (or moisten dry food).
- Supply free access to water and encourage the cat to drink.
- Do not feed an acidified diet if the urine is acid and struvite uroliths are not a problem.
- Long-term use of highly acidified diets is not recommended. They can result in metabolic acidosis, hypokalaemia, renal damage and loss of bone density, especially when fed to immature cats. They also increase the risk of oxalate urolithiasis.

URETHRAL SPASM

Urethral spasm may cause significant dysuria, often immediately after a urethral obstruction has been relieved using a catheter. Where this occurs, antispasmodics may be beneficial. Since both smooth and skeletal muscle fibres are responsible for generating urethral tone, it may be beneficial to give drugs to counter both of these effects. Injectable drugs, such as acepromazine, diazepam



Histopathology of a bladder wall biopsy from a six-year-old domestic shorthaired cat with clinical signs of FLUTD. The changes are consistent with idiopathic interstitial cystitis, and include a relatively normal epithelium and muscularis, submucosal oedema and vasodilation, but minimal inflammatory infiltrate. Haematoxylin and eosin x125

and dantrolene, may be given at the time of relieving the obstruction, after which the author commonly prescribes a short course (of about five days) of phenoxybenzamine or prazosin, together with dantrolene (ie, a smooth muscle antispasmodic plus a skeletal muscle antispasmodic).

Significant over-distension of the bladder during urethral obstruction can result in transient or, occasionally, permanent lack of bladder contractility. In these cases, the administration of bethanechol (0.1 to 0.2 mg/kg, given orally every eight hours) may be helpful in increasing bladder contraction. However, since bethanechol also increases proximal urethral tone, it is important that an anti-alpha-adrenergic smooth muscle antispasmodic (eg, phenoxybenzamine) is given at the same time.

SUMMARY

It is important to note that all current treatments for FLUTD are merely palliative. The best results are gained by instigating a number of changes (ie, reducing stress, feeding a wet diet, replacing GAGs and, if necessary, relieving urethral spasm). In the vast majority of cases, when tailored to the individual cat, this will reduce or prevent further clinical signs. Tricyclic antidepressants should only be used in very severe recurrent cases.

Antispasmodics

Smooth muscle antispasmodics

- Phenoxybenzamine administered orally at a dose of 0.5 to 1.0 mg/kg every 12 hours. This drug should be given for five days before evaluating efficacy
- Acepromazine administered intravenously, intramuscularly and subcutaneously at a dose of 0.05 to 0.2 mg/kg or given orally at a dose of 1 to 3 mg/kg
- Prazosin given orally at a dose of 0.25 to 0.5 mg/cat every 12 to 24 hours

Skeletal muscle antispasmodics

- Dantrolene administered intravenously at a dose of 0.5 to 1.0 mg/kg or given orally at a dose of 0.5 to 2.0 mg/kg every 12 hours. It should be noted that this product is very expensive
- Diazepam administered intravenously at a dose of 0.1 to 1.0 mg/kg or given orally at a dose of 1.0 to 5.0 mg/cat every eight to 12 hours

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