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Feline idiopathic cystitis: current understanding of pathophysiology and management

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Signs referable to the lower urinary tract of indoor-housed cats have been described in the veterinary literature for at least 80 years [1]. The terms *feline urologic syndrome* (FUS) and *feline lower urinary tract disease* (FLUTD) were coined in the 1970s (FUS [2]) and 1980s (FLUTD [3]) to describe variable combinations of straining, hematuria, pollakiuria (frequent passage of small amounts of urine), and periuria (urinations in inappropriate locations) seen in cats with the disorder. No diagnosis for clinical signs of irritative voiding can be determined in approximately two thirds of cats with lower urinary tract (LUT) signs, so we refer to them as having feline idiopathic cystitis (FIC). If cystoscopy is performed and characteristic submucosal petechial hemorrhages are seen, a diagnosis of feline interstitial cystitis can be made [4]. This term was chosen because of similarities between cats and human beings with interstitial cystitis, an idiopathic pelvic pain syndrome that is characterized by difficult, painful, and frequent urinations without a diagnosable cause [5].

Pathophysiology

Two forms of interstitial cystitis are recognized in human beings, the common nonulcerative and uncommon ulcerative forms [6]. Most cats with feline interstitial cystitis have signs comparable to the nonulcerative form, although the "Hunner's ulcers" sometimes seen in human beings with interstitial cystitis have been described in a cat [7]. The term *feline idiopathic*

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cystitis is used in this article, because cats with this disorder do not commonly undergo cystoscopic evaluation (and most do not need to be subjected to this procedure).

Based on recent research we believe that FIC may include multiple complex abnormalities of the nervous and endocrine systems that likely affect more than just the urinary bladder [8]. Enhanced central noradrenergic drive in the face of inadequate adrenocortical restraint seems to be related to maintaining the chronic disease process (Fig. 1). These systems seem to be driven by tonically increased hypothalamic corticotropin-releasing factor release, which may represent the outcome of a developmental accident [8,9]. Because of these abnormalities, treatment strategies that decrease central noradrenergic drive may be important in reducing signs of FIC; those that do not address this aspect of the disease seem to be less effective. Until more effective treatments to normalize responsiveness of the stress response system are available, efforts to reduce input to this system by environmental enrichment seem reasonable [10,11].

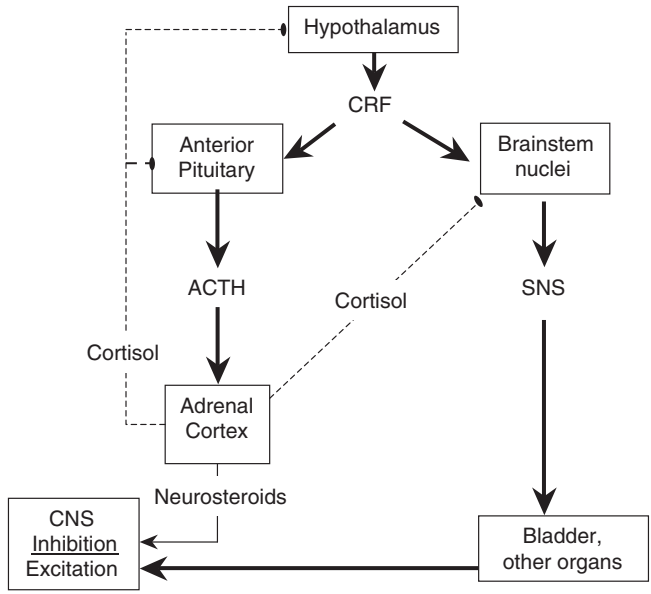

Fig. 1. Imbalanced neuroendocrine system of cats with feline idiopathic cystitis. Excitatory sympathetic nervous system (SNS) outflow is inadequately restrained by cortisol. This enhanced activity can increase tissue permeability, resulting in increased sensory afferent activity. Feedback inhibition at the level of the anterior pituitary and hypothalamus also is reduced, which tends to perpetuate corticotrophin-releasing factor (CRF) output. Neurosteroid production by the adrenal cortex, which generally enhances central nervous system (CNS) inhibitory tone during chronic stress, also may be reduced. The solid lines indicate stimulation, and the dotted lines indicate inhibition. Line thickness is intended to indicate intensity of the signal.

Environmental enrichment

Just as water is primary therapy for prevention of urinary stone recurrence, we think that environmental enrichment is primary therapy for prevention of recurrence of elimination disorders, including FIC. This opinion is based on documented neuroendocrine abnormalities suffered by cats with FIC [8,12,13] and on our clinical experience. We define environmental enrichment for indoor-housed cats to mean provision of all "necessary" resources, refinement of interactions with owners, a tolerable intensity of conflict, and thoughtful institution of change(s). Although we are not aware that a particular resource list has been validated for indoor-housed cats, some recommendations are available [11,14,15]. We have assembled a provisional list in Table 1 that could be used by owners to guide consideration of these parameters for each of their cats. The following tentative recommendations are organized to follow Table 1; more comprehensive suggestions are available in the many excellent publications [16] about cat housing and behavior that currently are available. We also recommend extending the "1 + 1" rule traditionally applied to litter boxes (one for each cat in the home plus one more) to all pertinent resources (particularly food, water, and litter containers) in the household.

Food

Behavioral and ethologic research suggest that cats prefer to eat individually in a quiet location, where they are not startled by other animals, sudden movement, or activity of an air duct or appliance that may begin operation unexpectedly [17,18]. Although canned food may be preferable for cats with FIC because of increased water content or a more natural "mouth feel," some cats may prefer dry foods. The phytoestrogen content of soy used in some cat diets also could conceivably play a role in modulating discomfort associated with the disease [19]. If a diet change is appropriate, offering the new diet in a separate adjacent container rather than removing the usual food and replacing it with new food permits the cat to express its preference. Natural cat feeding behavior also includes predatory activities, such as stalking and pouncing. These may be simulated by hiding small amounts of food around the house or by putting dry food in a container from which the cat has to extract individual pieces or move something to release the food pieces if such interventions appeal to the cat. Also, some cats seem to have specific prey preferences. For example, some cats prefer to catch birds, whereas others may prefer to chase mice or bugs. Identifying a cat's "prey preference" allows one to buy or make toys that the cat is more likely to play with. Prey preference can be identified by paying close attention to the cat's reaction to toys with specific qualities, such as those that resemble birds (feather toys), small mammals ("furry mice"), or insects (laser pointers, pieces of dry food) presented one at a time or together.

Table 1
Environmental survey for indoor-housed cats

	Yes	No
Food and water		
Each cat has its own food and water bowl in a convenient location that provides some privacy while eating or drinking and an "escape" route		
Bowls are located such that another animal cannot sneak up on the cat while it eats		
Bowls are located away from appliances or air ducts that could come on unexpectedly while the cat eats or drinks		
Food and water is kept fresh (daily)		
Bowls are washed regularly (at least weekly) with a mild detergent		
The brand or type of food purchased is changed infrequently (less than monthly)		
If a new food is offered, it is put in a separate dish next to the familiar food so the cat can choose to eat it if it wants to		
Litter box management		
Boxes are located on more than one level in multilevel houses		
Boxes are located so another animal cannot sneak up on the cat while it uses one		
Boxes are located away from appliances or air ducts that could come on unexpectedly while the cat uses one, and an "escape" route is provided		
The litter is kept clean and scooped as soon after use as possible (just like we flush after each use), at least daily		
Boxes are washed regularly (at least weekly) with a mild detergent (like dishwashing liquid) rather than strongly scented cleaners		
Unscented clumping litter is used		
The brand or type of litter purchased is changed infrequently (less than monthly)		
If a new type of litter is offered, it is put in a separate box so the cat can choose to use it if it wants to		
Each cat has its own litter box in a convenient well-ventilated location that still gives the cat some privacy while using it		
Environmental considerations		
Scratching posts are provided		
Toys are provided, rotated, or replaced regularly		
Each cat has the opportunity to move to a warmer or cooler area if it chooses to		
Each cat has a hiding area where it can get away from threats if it chooses to		
Each cat has its own space that it can use if it chooses to		
Rest		
Each cat has its own resting area in a convenient location that still provides some privacy, and an "escape" route		
Resting areas are located such that another animal cannot sneak up on the cat while it rests		
Resting areas are located away from appliances or air ducts that could come on unexpectedly while the cat rests		
If a new bed is provided, it is placed next to the familiar bed so the cat can choose to use it if it wants to		
Movement		
Each cat has the opportunity to move about freely, explore, climb, stretch, and play if it chooses to		
Social contact		
Each cat has the opportunity to engage in play with other animals or the owner if it chooses to		

Water

Cats also seem to have preferences for water that can be investigated. Water-related factors to consider include freshness, taste, movement (water fountains, dripping faucets, or aquarium pump-bubbled air into a bowl), and shape of the container (some cats seem to resent having their vibrissae touch the sides of the container when drinking). As with foods, changes in water-related factors should be offered in such a way that permits the cat to express its preferences. Additionally, food and water bowls should be cleaned regularly unless individual preference suggests otherwise.

Litter boxes

Litter boxes should be provided in different locations throughout the house to the extent possible, particularly in multiple cat households [20]. Placing litter boxes in quiet convenient locations that provide an escape route if necessary for the cat could help to improve conditions for normal elimination behaviors. If different litters are offered, it may be preferable to test the cat's preferences by providing them in separate boxes, because individual preferences for litter type have been documented. For cats with a history of urinary problems, unscented clumping litter should be considered. Litter boxes should be cleaned regularly and replaced; some cats seem quite sensitive to dirty litter boxes. Litter box size and whether or not it is open or covered also may be important to some cats.

Space

Cats interact with physical structures and other animals, including human beings, in their environment. The physical environment should include opportunities for scratching (horizontal and vertical options may be necessary), climbing, hiding, and resting. Cats seem to prefer to monitor their surroundings from elevated vantage points, so climbing frames, hammocks, platforms, raised walkways, shelves, or window seats may appeal to them. Playing a radio to habituate cats to sudden changes in sound and human voices also has been recommended, and videotapes to provide visual stimulation are available.

Play

Some cats seem to prefer to be petted and groomed, whereas others may prefer play interactions with owners. Cats also can be easily trained to perform behaviors (''tricks''); owners just need to understand that cats respond much better to praise than to force and seem to be more amenable to learning if the behavior is shaped before feeding. Cats also may enjoy playing with toys, particularly those that are small, move, and mimic prey characteristics. Many cats also prefer novelty, so a variety of toys should be provided and rotated or replaced regularly to sustain their interest.

Conflict

When cats' perception of safety becomes threatened, they appear to respond in an attempt to restore their "perception of control." During such responses, some cats become aggressive, some become withdrawn, and some become ill. In our experience, intercat conflict commonly is present when multiple cats are housed indoors together and health problems exist. Conflict among cats can develop because of threats to their perception of their overall status or rank in the home, from other animals in the home, or from outside cats [21]. With a little practice, one can recognize signs of conflict and estimate its potential role in exacerbating signs of FIC. If it is, owners usually can identify causes after signs of conflict are explained to them. Once this has been done, clients often are well on their way to reducing intensity of conflict. Of course, some conflict between housemates is normal, regardless of species. Our goal is to reduce unhealthy conflict to a more manageable level for cats involved.

Signs of conflict (Table 2) between cats can be open or silent. Signs of open conflict are easy to recognize; the cats may stalk each other, hiss, and turn sideways with legs straight and hair standing on end to make themselves look larger. If neither cat backs down, the displays may increase to swatting, wrestling, and biting. The signs of silent conflict can be so subtle that they are easily missed. The cat creating conflict (assertive cat) can be identified as the one that never backs away from other (threatened) cats, denies other cats' access to resources, stares at other cats, and lowers its head and neck while elevating its hindquarters as it approaches less confident cats. Hair along its back and on its tail and tail base may stand on end, although not to the extent of cats engaged in open conflict, and the cat may emit a low growl. The assertive cat eventually may only have to approach or stare at a threatened cat for it to leave a resource, such as food or a litter box. If the threatened cat tries to use the resource later, the assertive cat's presence alone may be enough to make it flee. Because cats do not seem to possess distinct dominance hierarchies or conflict resolution strategies, threatened cats may attempt to circumvent agonistic encounters by avoiding other cats, by decreasing their activity, or both. Threatened cats often spend increasingly large amounts of time away from the family, staying in areas of the house that others do not use, or they attempt to interact with family members only when the assertive cat is elsewhere.

Signs of conflict can result from two types of conflict: offensive and defensive. In offensive conflict situations, the assertive cat moves closer to other cats and controls the interaction. In defensive conflict situations, a threatened cat attempts to increase distance between itself and the thing it perceives as a threat. Although cats engaged in either type of conflict may spray or eliminate outside the litter box, we find that threatened cats are more likely to develop elimination problems.

Table 2
Signs of silent conflict between cats

Assertive cat	Threatened cat
Never backs away from other cats	Spends large amounts of time hiding or away from the family
Stares at other cats	Avoids eye contact with other cats
Denies other cats access resources	Yields resources to other cats
Rub cheeks, head, chin, and tail on people, doorways, and furniture at cat height	
When it sees the threatened cat	When it sees the assertive cat
Lowers its head and neck while elevating its hindquarters and stalks the other cat	Crouches, may cower, may then flee
Piloerects the hair along its back, tail base, and tail	
Growls	Does not vocalize
May spray	May spray
	May develop cystitis or other disease problem

The most common cause of conflict between indoor-housed cats that we have been able to identify is competition for resources. Cats may engage in open or silent conflict over space, food, water, litter boxes, perches, sunny areas, safe places where the cat can watch its environment, or attention from people. There may be no obvious limitation to access to these resources for conflict to develop. The change may only be the cat's perceptions of how much control it wants over the environment or its housemates' behaviors.

Open conflict is most likely to occur when a new cat is introduced into the house and when cats that have known each other since kittenhood reach social maturity. Conflict occurring when a new cat is introduced is easy to understand, and good directions are available from many sources for introducing the new cat to the current residents. Clients may be puzzled by conflict that starts when one of their cats becomes socially mature or when a socially mature cat perceives that one of its housemates is becoming socially mature. Cats become socially mature between 2 and 5 years of age and start to take some control of social groups and their activities. This may lead to open conflict between male cats, between female cats, or between male and female cats. Although clients may be surprised, "because they lived so well together for the first few years of their lives," a cat's perceptions of resource needs may expand with social maturity.

Cats that are familiar with each other but unevenly matched often show conflict in more subtle ways. One of the cats in the conflict asserts itself, and another cat is threatened by this cat's actions. Silent conflicts may not even be recognized until the threatened cat begins to hide from the

assertive cat, starts to hiss or fight back when it sees the other cat, or develops a health problem.

In addition to signs of conflict described previously, the assertive cat can be identified by its marking behavior. These cats rub their cheeks, head, chin, and tail on people, doorways, and furniture at cat height. Unfortunately, silent conflict can also involve urine, including marking by the assertive or threatened cat and cystitis in the threatened cat. Conflict-related urine marking can include spraying, where the cat treads and kneads, raises its tail, and flicks the tip of it while spraying urine on a vertical surface or squatting and urinating outside the litter box (nonspray marking). Both male and female cats may spray, and although neutering reduces frequency of spraying, it cannot eliminate the behavior. Conflict-related urine marking can be exhibited by either the assertive or threatened cat, but in our experience, FIC usually occurs in the threatened cat; we have even seen threatened male cats spray bloody urine. Cats that urinate on bedspreads or other elevated open places may do so because their access to the litter box is restricted by another cat or if they are afraid to use the box because it is placed such that a quick escape from another cat might not be possible.

Treatment for conflict between cats involves providing a separate set of resources for each cat, preferably in locations where the cats can use them without being seen by other cats. This lets cats avoid each other if they choose to without being deprived of an essential resource. Conflict also can be reduced by neutering all the cats and by keeping all nails trimmed as short as practicable. Whenever cats involved in the conflict cannot be directly supervised, they may need to be separated. This may mean that some of the cats in the household can stay together but that the threatened cat is provided a refuge from the other cats. This room should contain all necessary resources for the cat staying in it.

Cats generally require and use more space than the average house or apartment affords them. Addition of elevated spaces such as shelves, ''kitty condos,'' cardboard boxes, beds, or crates may provide enough space to reduce conflict to a tolerable level. In severe situations, some cats may benefit from behavior-modifying medications. In our experience, however, medication can help only after environmental enrichment has occurred; it cannot replace it.

Cats involved in the conflict may never be ''best friends,'' but they usually can live together without showing signs of conflict or conflict-related disease. In severe cases, a behaviorist may be consulted for assistance in desensitizing and counterconditioning of cats in conflict so they can share the same spaces more comfortably if this is desired.

Conflict with other animals, dogs, children, or adults is relatively straightforward. In addition to being solitary hunters of small prey, cats are small prey themselves for other carnivores, including dogs. Regardless of how sure the client is that his or her dog will not hurt the cat, to the cat, the

dog represents a predator. If the cat does not assert dominance over the dog, as often happens, it must be provided ways to escape at any time. For human beings, it usually suffices to explain that cats may not understand rough treatment as play but as a predatory threat.

Most cats in urban areas in the United States are housed indoors and neutered, so conflict with outside cats can occur when a new cat enters the area around the house the affected cat lives in. To cats, windows are no protection from a threatening cat outside. If outside cats are the source of the problem, a variety of strategies to make one's garden less desirable to them are available.

Because of the dearth of controlled trials, it currently is not possible to prioritize the importance of any of these suggestions or to predict which would be most appropriate in any particular situation. Appropriately designed epidemiologic studies might be able to identify particularly important factors, after which intervention trials could be conducted to determine their efficacy in circumstances in which owners successfully implemented suggested changes. Our recent clinical experience includes 76 indoor-housed cats with recurrent FIC we have been following to attempt to determine effects of environmental enrichment during a 1-year period; 17 are individually housed, and 59 live in multicat households. There are 49 male cats and 27 female cats, all neutered, ranging in age from 1 to 10 years. Based on structured interviews at the time of referral, the most common cause of clinical signs in the singly housed cats was separation anxiety; for the cats from multiple cat households, the most common cause of clinical signs was some form of conflict. At the time of this writing, 19 cats have completed the study; median time of follow-up for the 57 cats currently being studied is 6 months. In the singly housed cats, a single episode of recurrence has been observed in 2 cats (12% recurrence rate). In the cats in multiple cat households, recurrences have been reported in 7 cats (12% recurrence rate). Published recurrence rates in the absence of intervention are in the range of 50%. In all these cats, the primary chronic therapy intentionally instituted was environmental enrichment to reduce central neural arousal. These results suggest that expression of FIC may result from the presence of a susceptible cat in a provocative environment. Our challenge is to identify and change what the susceptible cat is threatened by to prevent future bouts. Moreover, only about half of clients offered this approach are amenable to it, and we have not conducted a formal intention-to-treat analysis of the results because the study is still in progress. Nevertheless, results are encouraging, and we have not encountered adverse effects related to this approach.

Additional approaches

Once environmental enrichment strategies have been implemented, additional treatments may be considered. In our experience, these

approaches are more likely to succeed after the environment has been enriched to the extent possible by the client and more likely to fail in the absence of environmental enrichment. They are listed in the order in which we consider them.

Pheromones

A novel aspect of environmental enrichment that recently has become available is the application of pheromones to the living space [22]. Pheromones are chemical substances that seem to transmit highly specific information between animals of the same species. Although the exact mechanism of action is unknown at this time, pheromones seem to effect changes in the function of the limbic system and the hypothalamus to alter the emotional status of animals. Five facial pheromones have been isolated from cats; cats deposit the F3 fraction on prominent objects (including human beings) by rubbing against the object when the cat feels safe and at ease. The function of this secretion is not only to mark objects but to serve as an antagonist for urine marking and scratching.

Feliway (Farnum Companies Inc., Phoenix, AZ) a synthetic analogue of this naturally occurring feline facial pheromone, was developed to decrease anxiety-related behaviors of cats. Although not specifically tested in cats with FIC, treatment with this pheromone has been reported to reduce the amount of anxiety experienced by cats in unfamiliar circumstances, a response that may be helpful to these patients and their owners. Decreased spraying in multicat households, decreased marking, and a significant decrease in scratching behavior also have been reported subsequent to its use. Although, Feliway is not a panacea for unwanted cat behaviors or FIC, we have used it successfully in combination with environmental enrichment or drug therapies.

Feliway is sold as a spray and as a room diffuser. The spray can be used to treat areas of the house where the cat is urinating by use of a single spray to the affected spot for 30 days. We also have found Feliway to be beneficial to decrease anxiety associated with traveling. Clients can spray the cat carrier at least 15 minutes before the trip and then place the cat in the carrier to help decrease the stress and anxiety that most cats associate with travel. Treated areas should be sprayed at least 15 minutes before the cat encounters the area, because the vehicle (ethanol) in which the pheromone is carried is offensive to most cats. The room diffuser can be placed in a room where the cat inappropriately urinates. One room diffuser is reported to cover approximately 650 square feet and to last for 30 days. This method of administering pheromone is new, and we have little experience with its use.

Analgesia

We provide short-term analgesic therapy in cases of an acute flare of signs as appropriate and sometimes recommend pharmacotherapy in refractory cases after all previous recommendations have been instituted to the extent

possible, because we have not found a drug that is more effective than environmental enrichment. Drugs that might be considered include tricyclic "antidepressants" and other autonomic nervous system modulators, glycosaminoglycan-replacing compounds, sedatives, gamma-aminobutyric acid-A ($GABA_A$) agonists, and neuroactive steroids. Many aspects of this therapy, which is rapidly evolving, have not been adequately tested to permit evidence-based recommendations. Because placebo response also may be mediated by a reduction in this drive, differentiating placebo effects from drugs effects can be difficult. In most studies of human patients with interstitial cystitis, the placebo response rate is in the range of 50%.

Treating the owner

Finally, decreasing central neural drive in the cat may require reducing the level of arousal of the owner to the situation, as has been reported in human beings (parents and children [23]). We try to follow recommendations [24] for improving client satisfaction with our suggestions by attempting to ensure that clients leave the encounter with us feeling that they:

1. Were listened to
2. Received an explanation for the problem that made sense to them
3. Felt care and concern being expressed by the caregivers and others in the clinic
4. Left with an enhanced sense of mastery or control over the cat's illness or its signs

Because FIC can be a chronic frustrating disease, we have found that keeping these four points in mind when communicating with clients is beneficial for the client, pet, and clinician. We have also established a technician program in which a staff member follows only these patients as often as necessary to be sure their cat's problems are explained thoroughly and the clients gain enough understanding of the disease process to feel comfortable with managing their cat's disease.

Once clients have identified areas for improvement in resource availability, they may need help in instituting changes. In our experience, veterinary technicians are invaluable in helping clients with all aspects of this change process, because they often have more time available to answer questions and provide guidance. We also recommend that environmental modifications be instituted slowly, one at a time, and in a way that permits the cat to express its like or dislike for the change. For example, new diets or litter should be offered in separate containers next to the usual food or litter so the cat can express a preference.

Summary

Many indoor-housed cats seem to survive perfectly well by accommodating to less than perfect surroundings. Neuroendocrine abnormalities in

the cats we treat, however, do not seem to permit adaptive capacity of healthy cats, so these cats may be considered a separate population with greater needs. Moreover, veterinarians are concerned more with optimizing environments of indoor cats than with identifying minimal requirements for indoor survival. Further information about environmental enrichment and conflict is available at: http://www.nssvet.org/ici/.

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