FROM FUS TO PANDORA SYNDROME,
PART 3: CHRONIC TREATMENT AND PROGNOSIS

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Diet and feeding management - Some dietary modifications may reduce the risk of recurrence of clinical signs in affected cats. Efforts to acidify the urine using dry foods have no demonstrated value in treatment of cats with idiopathic cystitis. In fact, no known benefit to acidifying the urine or restricting magnesium has been identified in cats with this problem. No available evidence supports the idea that struvite crystalluria causes any damage to the underlying urothelium or worsens clinical signs, although crystals can be incorporated into the urethral plugs that form in cats with obstructed cats.

Increasing water intake may be beneficial for cats with LUTS, and consumption of a canned food is one way to accomplish this. One study found that LUTS recurred in only 11% of affected cats during one year of feeding the canned formulation of a dietary product. Recurrence occurred in 39% of cats fed the dry formulation of the same food, suggesting that both constancy and consistency (i.e., increased water intake) may be important, but the reasons for this effect remain to be determined. Increasing water intake will decrease the urine specific gravity and potentially decrease the concentration of noxious substances within the urine. Currently, no studies of the efficacy of any other diet marked for cats with idiopathic cystitis have been reported to my knowledge.

Some cats do not seem to like canned cat foods, and some cat’s owners do not like to feed them. Because of the stress-responsive nature of the disorder, I only recommend offering canned food if the owner is amenable to the change to avoid creating annoyance in the owner that the cat may perceive. If acceptable to the client, they can offer the canned food (no currently available evidence permits informed recommendations for any particular diet) to the cat in a separate container next to its usual food to permit it to express its preference. If the cat eats the new food readily, the old food can simply be removed over the next day or two. If the cat doesn’t eat the new diet after an hour, the food should be removed until the next feeding and another attempt made at that time, always providing fresh food at each new feeding. Once new diets become familiar to cats, they generally eat them more readily. When this occurs, the amount of the old food offered may be decreased by about 25% each day until the change is complete. If necessary, small quantities of the cat’s favorite food, such as meat or fish juice, can be mixed with the new preferred food to increase the cat’s interest in the diet. Meal feeding is generally an easier way to provide a change in a cat’s diet, and may provide more interaction with the owner and the cat, which could be beneficial as long as it does not create additional anxiety. If a diet change seems appropriate, I only attempt to implement it after the cat has returned home and is feeling better to reduce the risk of inducing a learned aversion to the new food.
**Pharmacotherapy** - Administration of the tricyclic antidepressants (TCAs) may be helpful in selected chronic cases of idiopathic cystitis when environmental enrichment and diet therapy fail to resolve clinical signs. Amitriptyline (Elavil®), and probably all TCAs, are inappropriate for acute management, and may increase the risk of recurrence. Amitriptyline has been reported in uncontrolled trials to successfully decrease clinical signs of severe, recurrent FIC. It was shown in this series of cats that the clinical signs of 9 of 15 cats treated resolved with amitriptyline treatment during a 12-month period. Amitriptyline may provide analgesia by inhibiting norepinephrine reuptake at noradrenergic nerve terminals, and possibly due to inhibition of wide dynamic range nociceptive neurons. I usually begin at the low end of the dose range, and recommend that the medication be administered in the evening. The dosage can be slowly increased until the desired effects are achieved. If a favorable response is not achieved with this drug, it should be tapered slowly, over several weeks, and then discontinued. Side effects can include lethargy, weight gain, urine retention, and even transient urinary stone formation because of the anticholinergic effects of this drug.

Clomipramine (Clomicalm®, veterinary label; and Anafranil®, human label) is also a tertiary amine like amitriptyline, but has more selectivity for blocking the reuptake of 5-HT. This drug has been shown to significantly decrease the number of episodes of urine spraying in cats. In that study, the initial dose used was 0.25-0.5mg/kg orally once daily. Clomipramine has fewer anticholinergic properties than does amitriptyline, however sedation is a common side effect of this drug as well. Clomipramine, in conjunction with environmental modification, also has been described to successfully decrease anxiety related and obsessive compulsive disorders in cats. I have prescribed this Clomipramine in some recurrent cases of idiopathic cystitis, and received anecdotal reports of improvement from some patients. Given the large response of cats with this syndrome in the placebo arm of a recently reported randomized controlled trial, little credence should be ascribed to such reports, however. Fluoxetine (Prozac®) has been reported to help cats with inappropriate urinations with variable success rates. Fluoxetine was used to help decrease the rate of urine marking after environmental alterations such as litter box hygiene and appropriate cleaning strategies.

Cats with idiopathic cystitis reportedly have decreased urinary glycosaminoglycan (GAG) excretion. GAGs form a protective “slime” layer over the urothelium that forms part of the barrier to reabsorption of constituents of the urine. A defective GAG layer or damaged urothelium can permit hydrogen, calcium, potassium ions, or other constituents of urine to come into contact with sensory neurons innervating the urothelium. Because of this, GAG replacers such as pentosan polysulfate (Elmiron®) have been used to treat cats with FIC. In a placebo controlled study in which the effectiveness of oral glucosamine for the management of cats with FIC was evaluated, no significant differences were found between the two groups. However, we did observe a large placebo effect, wherein cats in both groups improved significantly over the course of the study. One potential explanation was that more positive (and/or fewer threatening) interactions occurred with the cat, thereby decreasing stress and the resulting signs of the syndrome.

During the study, the treatments were mixed with a savory canned food, and then given to the cat by the owner. This regular, positive, interaction between the owner and the cat also may have altered the cat’s perceptions of its environment (and the owner?). This speculation has led us to try offering a treat to cats twice a day before feeding to mimic the placebo arm of the trial. We use “Pill-Pockets”, which many cats seem to like, so if medications are eventually
necessary the cat has been habituated to this approach and pills may be added. If successful, such an approach may be worth trying in a broader range of situations.

**Treating the environment, follow-up, and prognosis**

**Environmental Enrichment**

Environmental enrichment is primary therapy for prevention of recurrence of Pandora Syndrome (PS). This opinion is based on the documented neuroendocrine abnormalities suffered by cats with PS, 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 in the many excellent publications about cat housing and behavior that currently are available. We also recommend extending the “1+1” rule traditionally applied to litter boxes (1 for each cat in the home, plus 1 more) to all pertinent resources (particularly food water and litter containers) in the household.

**Food** - Cats prefer to eat individually in a quiet location where they will not be startled by other animals, sudden movement, or activity of an air duct or appliance that may begin operation unexpectedly. Although canned food may be preferable for cats with PS due to the increased water content or a more natural “mouth feel”, some cats may prefer dry foods. 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 the new food will permit 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 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, while others may prefer to chase mice or bugs. Identifying a cat’s “prey preference” allows one to buy or make toys that the cat will be more likely to play with.

**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 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. Placing litter boxes in quiet, convenient locations that provide an escape route if necessary for the cat could help 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, since 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 both the physical structures and other animals, including humans, in their environment. The physical environment should include opportunities for
scratching (both horizontal and vertical 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 that 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 are present. 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. With a little practice, one can recognize the signs of conflict and estimate its potential role in exacerbation of signs of PS. If it is, owners usually can identify the causes after the signs of conflict are explained to them. Once this has been done, clients often are well on their way to reducing the 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 the cats involved.

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 the cats avoid each other if they choose to without being deprived of an essential resource. Neutering all of the cats also can reduce conflict, and keeping all nails trimmed as short as practicable reduces the risk of fight wounds. Whenever the 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. The 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.

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 their 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 humans, 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 ones 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 epidemiological studies might be able to identify particularly important factors, after which intervention trials could be conducted to determine their efficacy in circumstances where owners successfully implemented the suggested changes.

**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 application of pheromones to the living space. 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 appear to effect changes in the function of both the limbic system and the hypothalamus to alter the emotional status of the animals. Five facial pheromones have been isolated from cats; cats deposit the F3 fraction on prominent objects (including humans) 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 also as an antagonist for urine marking and scratching.

Feliway®, 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 multi-cat households, decreased marking, and a significant decrease in scratching behavior also has been reported subsequent to its use. Although, Feliway is not a panacea for unwanted cat behaviors or PS, we have used it successfully in combination with environmental enrichment, and/or drug therapies.

Feliway® is sold as both a spray and 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 prior to the trip and then place the cat in the carrier to help decrease the stress and anxiety most cats associate with travel. The treated areas should be sprayed at least 15 minutes prior to the cat encountering the area because the vehicle (ethanol) the pheromone is carried in 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 last for 30 days. This method of administration of the pheromone is new and we have little experience with its use.

**Conclusions**

Many indoor-housed cats appear to survive perfectly well by accommodating to less than perfect surroundings. The neuroendocrine abnormalities in the cats we treat, however, do not seem to permit the adaptive capacity of healthy cats, so these cats may be considered a separate
population with greater needs. Moreover, veterinarians are concerned more with optimizing the environments of indoor cats than with identifying minimum requirements for indoor survival. Additional information about environmental enrichment is available at: http://indoorpet.osu.edu/

References