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Idiopathic Cystitis in Domestic Cats—Beyond the Lower Urinary Tract

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Signs of lower urinary tract (LUT) disease in domestic cats can be acute or chronic, and can result from variable combinations of abnormalities within the lumen of the LUT, the parenchyma of the LUT itself, or other organ system(s) that then lead to LUT dysfunction. In the majority of cats with chronic signs of LUT dysfunction, no specific underlying cause can be confirmed after standard clinical evaluation of the LUT, so these cats typically are classified as having idiopathic cystitis. A syndrome in human beings commonly known as interstitial cystitis (IC) shares many features in common with these cats, permitting comparisons between the two species. A wide range of similarities in abnormalities has been identified between these syndromes outside as well as inside the LUT. A variety of potential familial and developmental risk factors also have been identified. These results have permitted generation of the hypothesis that some of these people have a disorder affecting the LUT rather than a disorder of the LUT. This perspective has suggested alternative diagnostic strategies and novel approaches to treatment, at least in cats. The purpose of this review is to summarize research investigations into the various abnormalities present in cats, to compare some of these findings with those identified in human beings, and to discuss how they might modify perceptions about the etiopathogenesis, diagnosis, and treatment of cats with this disease.

Dedication: I dedicate this contribution to Professor Dennis J. Chew, whose collaboration, patience, and support made it all possible.

Key words: Comorbidity; Developmental biology; Etiology; Phenotype; Syndrome.

Signs of lower urinary tract (LUT) dysfunction in domestic cats (*Felis silvestris catus*) include variable combinations of dysuria, hematuria, periuria, pollakiuria, and stranguria.[1] A review article published in 1996 listed some 36 confirmed causes of LUT signs.[2] These signs can be acute or chronic, and can result from variable combinations of abnormalities within the lumen of the LUT (local external abnormalities), in the LUT itself (intrinsic abnormalities), or other organ system(s) that then lead to LUT dysfunction (internal abnormalities). In the majority of cats with chronic signs of LUT dysfunction, however, no specific underlying cause can be confirmed after standard clinical evaluation of the LUT. These cats typically are classified as cases of idiopathic causation, hence the name idiopathic cystitis.[1]

Beginning in 1993, results of a series of studies using cats with chronic idiopathic LUT signs donated by owners for whom they no longer were acceptable pets have been published. Initial studies of these cats focused on identification of abnormalities of the LUT because the affected cats were proposed to represent a naturally occurring model of a chronic LUT syndrome in human beings called interstitial cystitis (IC).[3,4] These studies led to the proposal in 1996 that cats having chronic idiopathic LUT signs be described as having "feline interstitial cystitis" (FIC).[5]

During the ensuing years, evidence also has accumulated that additional problems outside the LUT are commonly present in these cats, as well as in most patients with IC. This evidence has led to reconsideration of the cause(s) of the syndrome in these individuals, as well as to considerable debate about the most appropriate name, diagnostic approach, and treatment recommendations. This reconsideration is ongoing, and has resulted in the generation of new hypotheses related to the etiopathogenesis of the signs and symptoms in both cats and human beings with this problem, as well as novel approaches to treatment, at least in cats.

Abbreviations:

ACTH	adrenocorticotropic hormone
FIC	feline interstitial cystitis
GAG	glycosaminoglycan
IC	interstitial cystitis
KCl	potassium chloride
LUT	lower urinary tract
SRS	stress response system
UTI	urinary tract infection

The purposes of this review are to summarize some of the many research investigations into the external, intrinsic, and internal abnormalities that are present in these cats (this organization was chosen because it roughly parallels the chronology of studies of the syndrome over the past 3 decades), to compare these findings with those identified in human beings with IC during this time, and to consider how these results might modify perceptions about the diagnosis and treatment of cats with this problem.

Nosology

Nosology refers to the naming of diseases. Diseases can be named according to etiology, pathogenesis, and affected organ system(s), and by presenting signs and symptoms. A significant challenge to accurate nosology exists because diseases can be named based on prominent signs and symptoms long before research identifies the etiology and pathogenesis. Whereas presenting signs sometimes result in naming a disease for the organ associated with the signs, the disease might not originate

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in the affected organ, and many diseases affect more than one organ. Thus, the name could reflect a subset of the problems associated with an underlying disease. This could have affected the nosology describing cats with chronic idiopathic LUT signs[6] and human beings with IC.[7] Feinstein[8] recently concluded that "an important principle in naming apparently new ailments is to avoid etiologic titles until the etiologic agent has been suitably demonstrated. A premature causal name can impair a patient's recovery from the syndrome, and impede research that might find the true cause."

Although terms such as "feline urological syndrome,"[9] "feline lower urinary tract disease,"[10] and "feline interstitial cystitis"[11] fairly accurately capture the currently recognized diagnostic criteria for LUT disorders, they no longer seem to capture the extent of the problems occurring in many cats. These terms all focus on the LUT, reflecting the prominent presenting signs and LUT-focused diagnostic testing rather than a thorough evaluation of the entire cat. In human beings, more comprehensive investigations of patients with IC and a variety of other chronic idiopathic disorders have resulted in the suggestion of names such as "medically unexplained syndrome,"[12] "functional somatic syndrome,"[13] or "central sensitivity syndrome"[14] to describe the multiple abnormalities observed in these patients by physicians. The list of chronic disorders proposed to be covered by these names is long, and includes problems addressed by most of the medical subspecialties. These names also seem to violate Feinstein's admonition, however, and it seems that some generic umbrella term comparable to "cancer" or "infection" might be more appropriate. One possibility, which I will use in this review when it seems appropriate, is to adopt an interim name such as "Pandora" syndrome until the most biologically appropriate nosological term is identified. Tentative criteria for diagnosis of a "Pandora" syndrome include:

1. Presence of clinical signs referable to other organ systems *in addition to* the chronic idiopathic signs prominently referable to a particular organ for which the patient is being evaluated. For example, variable combinations of clinical signs referable to other organ systems such as the gastrointestinal tract, skin, lung, cardiovascular, central nervous, endocrine, and immune systems have been identified in cats with chronic idiopathic LUT signs.[15,16]
2. Waxing and waning of severity of clinical signs associated with events that (presumably) activate the central stress response system (SRS).[15,17,18]
3. Resolution of signs associated with effective environmental enrichment.[15,17,18]

A name like "Pandora" syndrome seems appropriate for at least 2 reasons. First, it does not identify any specific cause or organ, and second, it seems to capture the dismay and dispute associated with the identification of so many problems (evils) outside the organ of interest of any particular subspecialty.

Regardless of the name eventually chosen to describe cats with chronic idiopathic LUT and other clinical signs, current evidence suggests that restriction of the *description* of these cats to their LUT signs does not capture all currently recognized features of the syndrome.[15,16,18] Regardless of agreement on an accurate descriptive term for the syndrome, it seems appropriate for clinicians to conduct a more comprehensive evaluation of cats presented with these and other chronic idiopathic signs to determine whether only these signs occur, or whether variable combinations of comorbid somatic and behavioral abnormalities also are present. Such an evaluation could result in a more complete diagnosis and implementation of additional approaches to treatment for some cats, which has been associated with better outcomes.[15] For the purposes of this review, I will retain the terminology used to describe patients in the studies referenced, since it was what was used at the time the results were published. This is done with some trepidation because of the risk of reinforcing the focus on the LUT rather than a more comprehensive assessment of the problem list of the patients, but such was, and to a greater or lesser extent still is, how studies have been reported.

Abnormalities Identified in FIC and IC

Many features in common have been identified in cats and human beings with the syndrome.[19] Variable combinations of LUT abnormalities have been identified in patients of both species, who also often suffer multiple comorbid disorders.[16,20] Moreover, the occurrence of comorbid disorders often precedes the occurrence of LUT signs and symptoms (C.A.T. Buffington, unpublished observation).[21,22] These comorbid disorders also appear to occur more commonly in close relatives of human patients,[23,24] and evidence of adverse early experiences has been reported in patients with FIC[25] and IC.[26]

Two LUT forms of the syndrome have been reported, nonulcerative (Type I) and ulcerative (Type II); other forms also could exist.[20] Cats almost always present with the Type I form, although the Type II form has been described,[27] and in human beings, approximately 90% of patients have the Type I form.[28] The etiopathogenesis of these 2 forms differs. The Type II form appears to be an inflammatory disease intrinsic to the bladder, whereas the Type I form might be neuropathic in origin.

Owners commonly request evaluation of obvious LUT signs they observe in their cats, so a large amount of research has been directed toward the bladder, resulting in identification of a variety of abnormalities. The bladder is a deceptively sophisticated organ.[29,30] Its internal covering consists of an epithelium with its underlying neurovascular supporting tissue, which is surrounded by both smooth and striated muscle.[31] These structures engage in complex neuroendocrine communication with the rest of the body to determine the appropriate conditions and timing for voiding. Bladder neural connections include sensory afferent, central, and somatic, sympathetic, and parasympathetic efferent neurons that interact throughout the neuraxis between the urothelium and the cerebral cortex.[32] In addition to a variety of

neurotransmitters, bladder function also is influenced by both adrenocortical and sex hormones.[33]

Local External Abnormalities

Toxic and Protective Factors. The presence of some toxin,[34] abnormality of some protective factor,[35,36] or presence of some microorganism[37,38] in the urine has been proposed to explain the LUT signs and symptoms in patients with FIC and IC. An abnormality of Tamm-Horsfall protein that results in loss of protection of the urothelium,[39] the appearance of an "anti-proliferative factor" and local growth factor abnormalities that might disrupt cell signaling,[40] and other changes in the urine of patients with IC have been identified and are being investigated.[41,42] Whether these play causative roles in FIC or IC remains to be determined, although the relevance of the Tamm-Horsfall protein abnormality was diminished by the report of absence of voiding dysfunction or compatible histological abnormalities in Tamm-Horsfall protein knockout mice.[43]

Microbial Agents. Given the similarity in symptoms between cystitis resulting from bacterial urinary tract infection (UTI) and FIC and IC, researchers have considered infection to be a cause of the LUT signs and symptoms for nearly 100 years. Guy Hunner, for whom the "Hunner's ulcer" of the Type II form of the syndrome was named, publically speculated that a bacterial infection was the cause of "a rare type of bladder ulcer in women" in 1915.[44] If microbes are associated with FIC or IC, they could either cause the disorder, or be associated with it in some noncausal way.

A role for infectious agents such as viruses in the LUT signs observed in cats has been investigated,[37,45] although what relationship viruses play in the etiopathogenesis of these signs in cats with naturally occurring FIC remains unclear at this time.[46] Moreover, investigations of what role infectious agents might play in the systemic manifestations of the syndrome are yet to be reported.

In human beings, 2 recent studies concluded that "IC is not associated with persistence of viral and bacterial DNA in the bladder. A chronic infective etiology for the condition is excluded by these findings,"[47] and, "these data suggest that the symptom flares of IC are not usually associated with recurrent UTI and, therefore, are likely due to a triggering of the other painful mechanisms involved in IC patients who are culture-negative."[48] Thus, the probability that an infectious agent commonly causes the symptoms present in these patients seems quite small.

Although microorganisms in the LUT might not commonly cause FIC or IC, this does not mean that microbes have no association with the syndromes. A recent report of 134 cats in Norway evaluated for LUT signs found bacteriuria exceeding 10^3 CFU/mL in 44 (33%) cats, and exceeding 10^4 in 33 (25%), either alone or with variable combinations of crystals and uroliths.[49] These results suggested a prevalence of bacteriuria higher than reported previously, which the authors speculated might have resulted from differences between cases diagnosed at primary and tertiary care facilities. Other variables, such as the number of previous treatments, including catheterization of male cats, also might have influenced their results. Other studies have reported prevalence rates of UTI from 15 to 43% in cats with compromised urinary tract defense mechanisms, and 1 study reported a prevalence of 22% in cats with no apparent predisposing factors.[50] Some evidence suggests that colonization may result from an underlying vulnerability in affected cats. Perineal urethrostomy did not lead to postoperative bacterial infection in healthy cats, whereas it occurred postoperatively in 22% of cats with histories of recurrent or persistent urethral obstruction.[51]

There also might be a relationship between IC and UTI in human beings. One recent study found evidence of UTI within the past 2 years in 38% of the IC/painful bladder syndrome patients they studied,[52] although, " . . . the infection domain was not associated with any increased symptoms." Additionally, retrospective data suggest that a proportion, probably a minority, of women had evidence of UTI or inflammation at the onset of symptoms of IC/painful bladder syndrome.[53] It also has been speculated that intrinsic abnormalities make the LUT more vulnerable to microbial colonization,[38] which might be consistent with the observation of increased risk for bacterial UTI in these patients.

Intrinsic Abnormalities

The Glycosaminoglycan (GAG) Layer. The internal surface of the LUT is coated by a GAG layer that might be abnormal in patients with FIC or IC. A wide variety of sometimes-conflicting changes in the quantity and quality of the GAG layer in patients with IC is reported.[54–56] Decreased total GAG,[35,57] and a specific GAG known as GP-51,[58] has been reported in cats with FIC. One group of investigators also found chondroitin sulfate in the plasma of cats with feline urologic syndrome, leading them to conclude that the decreased chondroitin concentration they found in urine could have resulted from reabsorption back across a more permeable urothelium.[57] Limitations of most studies of urine GAG include the difficulty of the GAG assay and the variety of methods used, so what role the GAG layer plays in these disorders currently remains unresolved.[59]

Experimental attempts to replenish the GAG layer also have been reported. In cats, 2 studies of the effects of GAG replacement therapies have been investigated, but no benefit beyond placebo was found in either study.[60,61] In human beings, the beneficial effects of polysulfated[62,63] and other GAGs[64] on symptoms of IC or painful bladder syndrome/IC also appear to be small. As noted in a recent editorial commentary, the shift in perspective toward a more systemic view of IC "calls local treatments into question."[59]

Urothelium. A specialized epithelium called the urothelium lines the distal portion of the urinary tract, including the renal pelvis, ureters, bladder, upper urethra, and glandular ducts of the prostate.[65] The urothelium is composed of a basal cell layer attached to a basement membrane, an intermediate layer, and a superficial apical layer.[66] Although healthy urothelium maintains a tight

barrier to ion and solute flux, factors such as altered pH or electrolyte concentrations, mechanical, chemical, or neurally mediated stimulation, and infectious agents all can impair the integrity of the barrier.[67]

Both functional and anatomical abnormalities of the urothelium have been reported in FIC and IC, although their cause and significance are unknown. In cats with FIC, significantly higher bladder permeability to sodium salicylate,[68] as well as reduced transepithelial resistance and increased water and urea permeability after hydrodistention of the bladder, has been reported.[69] A denuded urothelium with appearance of underlying cells also was found in these cats by scanning and transmission electron microscopy, leading the authors to conclude that the urothelial damage and dysfunction identified might "suggest novel approaches toward examining the etiology and therapy of IC."[69] Ironically, a paper published the same month[70] reported strikingly similar electron microscopic findings—in healthy female mice exposed to constant illumination for 96 hours, after which they were returned to conventional day-night illumination for 7 days before being killed. This report showed that comparable urothelial injury also could occur in healthy animals exposed to stressful external events. Neither of these studies examined any other tissues to determine if the observed abnormalities were restricted to the bladder or had a more widespread distribution.

Recent studies have revealed that urothelial cells express a number of molecular "sensors" that confer properties similar to both nociceptive and mechanosensitive type neurons on these cells. Thus, like superficial cells on other epithelial surfaces,[71,72] urothelial cells possess specialized sensory and signaling properties that allow them to respond to their environment and to engage in reciprocal communication with neighboring urothelial and nerve cells.[73] Alterations in the expression of various receptors, channels, and transmitters involved in both the "sensor" as well as "transducer" properties of the urothelium at both gene and protein levels have been found in urothelial cells from both cats and human beings with the syndrome.[30] Alterations in stretch-mediated release of transmitters from the urothelium, including increased nitric oxide[74] and adenosine triphosphate[75] release also may influence urothelial integrity and cell-cell signaling.

Submucosa. Abnormalities also are present below the urothelium, although the histological features of Type I FIC[76] and IC[77] are somewhat unusual. Vasodilatation and vascular leakage in the general absence of any significant mononuclear or polymorphonuclear infiltrate is the most common finding, suggesting the presence of neurogenic inflammation.[78,79] Increased numbers of mast cells have been observed in biopsy specimens from about 20% of patients with Type I FIC[76] and IC,[28] and are thought by some to be involved in the pathophysiology of the syndrome.[80] The finding of mast cells in the bladder is by no means specific to these syndromes.[81] The role of mast cells in IC and comorbid disorders, especially those exacerbated by stress, was recently reviewed.[82] It was concluded that mast cell activation could be a neurally mediated byproduct of the stress response associated with the disorder. One beneficial action of the tricyclic antidepressant amitriptyline (if such exists[83]) could be through inhibition of mast cell activation.[84] In one recent report, however, no difference in the degree of lymphocyte and mast cell infiltration, or in neovascularization or staining for uroplakins, was found between bladders of cats with feline idiopathic cystitis and those with urolithiasis, and in this study urothelial GAG staining was *highest* in tissues from affected cats.[85]

Detrusor Muscle. In contrast to the many abnormalities found on the luminal side of the lamina propria, there is a paucity of data of etiopathogenic importance implicating the bladder muscle in the pathophysiology of FIC or IC.[86] In cats with FIC, nonspecific inflammatory changes in the detrusor,[87] as well as in vitro evidence to suggest that the muscle functions relatively normally,[79] have been reported.

Intrinsic Abnormalities—Summary. The etiopathogenic significance of local bladder abnormalities occurring in patients with FIC and IC remains to be established. Moreover, in chronic diseases, clinical signs often do not appear to correlate well with pathology in the bladder,[28] or elsewhere.[88] For example, bladder lesions characteristically associated with irritative voiding symptoms and pelvic pain in patients diagnosed with IC also have been observed in asymptomatic women undergoing tubal ligation.[89] Some patients treated with cyclophosphamide also develop a hemorrhagic cystitis and voiding dysfunction without the pain often associated with IC.[90] A similar situation also occurs in the bowel. In one study, rectal perception of distention was actually attenuated in patients with ulcerative colitis, whereas it was enhanced in patients with irritable bowel syndrome.[91] To paraphrase the conclusion of the authors of this study, low-grade mucosal inflammation alone is unlikely to be responsible for symptoms of functional disorders.

Most studies of FIC and IC also have failed to examine tissues from other organs for comparison, so one cannot determine whether the identified changes are restricted to the LUT, or whether they also occur elsewhere in the body of patients with the syndrome. Moreover, no temporal relationship has been established between these abnormalities and the onset of clinical signs. Finally, improvement in clinical signs has been reported to occur in the absence of cystoscopic or histological changes in cats[92] or human beings,[93] and cystectomy does not resolve symptoms in human beings with the Type-I form of the syndrome.[94] These findings suggest that important parts of the problem lie elsewhere.

Internal Abnormalities

Afferent Input. Sensory information is transmitted from the bladder to the spinal cord by afferent neurons. Mechanosensitive bladder afferent neurons were found to exhibit a small increase in sensitivity to distension with 154 mM saline in cats affected with FIC as compared with normal cats, albeit at higher than normal spontaneous micturition pressures.[95] The effect of increasing concentrations (80–300 mM) of potassium chloride

(KCl) on afferent firing also was examined, both because intravesical KCl has been used as a diagnostic probe for IC in human beings,[96] and because it has been speculated,[97] but never demonstrated, that the urine potassium concentration plays a role in the pathophysiology of IC. Increased afferent firing similar to that seen with saline was observed during filling with KCl at concentrations <150 mM; however, concentrations of 150–300 mM produced almost complete inhibition of afferent firing at pressures between 30 and 80 cm of water, suggesting that increased bladder permeability permits entry of sufficiently high concentrations of KCl into the submucosa to dampen neural activity. These data suggest that afferent nerves become more sensitive to stimuli in cats with FIC.

A modest increase in Substance P, an 11 amino acid sensory neurotransmitter peptide, immunoreactivity in unmyelinated neurons has been detected in bladder tissue from cats with FIC,[98] and in some,[99] but not all,[100] studies of bladder tissue from human beings with IC. Bladder Substance P receptor expression is significantly increased in cats with FIC,[101] and both increased[102] and decreased[103] in patients with IC. Clinical trials of the therapeutic properties of Substance P antagonists in human beings to date have been disappointing, however,[104,105] and recent evidence suggests that Substance P might limit the severity of inflammatory reactions,[106,107] opening the possibility that the changes observed in patients with these syndromes may reflect some protective response.

A variety of abnormalities have been identified in dorsal root ganglion cell bodies of bladder-identified neurons from cats with FIC. Cells from affected cats were ~30% larger, expressed altered neuropeptide profiles, and exhibited slowly desensitizing, capsaicin-induced currents related to increased protein kinase C-mediated phosphorylation of the transient receptor potential vanilloid 1 receptor.[108] Moreover, these abnormalities were not restricted to cells from bladder-identified neurons; similar findings were observed in dorsal root ganglion cells throughout the lumbosacral (L_4-S_3) spinal cord.[108]

Treatments targeting bladder sensory neurons have been tested, but without success to date.[109] Resiniferatoxin, a potent naturally occurring analog of capsaicin that activates transient receptor potential vanilloid 1 receptors on nociceptive sensory neurons, reduced bladder compliance and capacity in a pilot study of anesthetized cats with FIC.[110] Controlled trials of both capsaicin and resiniferatoxin in human beings with IC also have failed to find significant benefits over placebo.[111] As one expert recently concluded, "Intravesical instillation therapy has basically not changed during the last few years, although some studies have disconfirmed some regimens. Intensive research may hopefully result in more effective treatments in the future."[112]

Brain. Exacerbations of LUT signs in response to external environmental challenges have been reported both in laboratory studies[17] and in client-owned cats with FIC,[113–117] as well as in patients with IC.[118,119] In the brain, significant increases in tyrosine hydroxylase, the rate-limiting enzyme of catecholamine synthesis, immunoreactivity have been identified in the pontine locus coeruleus[120] and the paraventricular nucleus of the hypothalamus of cats with FIC.[121]

The locus coeruleus contains the largest number of noradrenergic neurons, and is the most important source of norepinephrine in the central nervous system. Afferent input, including bladder distention, stimulates neuronal activity in the locus coeruleus, which is the origin of the descending excitatory pathway to the bladder.[29] The locus coeruleus also is involved in such global brain functions as vigilance and arousal. Increased tyrosine hydroxylase activity in the locus coeruleus also can occur in response to chronic external stressors,[122] with accompanying increases in autonomic outflow.[123] Moreover, the locus coeruleus appears to mediate visceral responses to external as well as internal input.[124] The increased immunoreactivity found in these nuclei might thus provide clues to the observation that the signs in cats[117,125] and symptoms in human beings[126,127] follow a waxing and waning course that can be influenced by external as well as internal events.

External environmental events that activate the SRS are termed stressors.[128] Examples of these events include sudden movements, unknown or loud noises, novel and unfamiliar places and objects, and the approach of strangers. Inadequate perception of control and predictability also can activate the SRS in animals because of interference with attempts to cope with their environments.[129] Depending on the frequency, intensity, and duration, chronic activation of the SRS can overtax homeostatic regulatory systems, resulting in diminished welfare,[130] abnormal conduct, and sickness behaviors.[131,132]

The acoustic startle response has been used as a probe of sensitivity to external events in patients with FIC and IC. This response is a brainstem reflex that responds to unexpected, loud stimuli, which has been shown to be increased by both fear and anxiety mediated by higher brain structures.[133] The acoustic startle response in cats with FIC is greatest and most different from that of healthy cats during stressful situations, but is still greater in cats with FIC than in healthy cats even when adapted to enriched housing conditions.[134] Exaggerated acoustic startle responses also have been reported in women with IC.[135,136]

Efferent Output

Neural. Activation of the SRS by either internal or external stimuli can result in stimulation of peripheral neural, hormonal, and immune responses. In addition to increased activity in the locus coeruleus, plasma catecholamine concentrations are significantly ($P < .05$) higher in cats with FIC compared with healthy cats both at rest[125] as well as during exposure to a moderate stress protocol.[17] Furthermore, plasma catecholamine concentrations decreased in the healthy cats as they acclimated to the stress, whereas even higher concentrations of plasma norepinephrine and epinephrine were found in cats with idiopathic cystitis.[17]

A functional desensitization of α-2 adrenergic receptors in affected cats also has been identified by evaluating

their response to the selective α-2 adrenergic receptor agonist medetomidine in both in vivo[137] and in vitro studies.[79] In vivo, heart rate decreased and pupil diameter increased significantly in healthy cats compared with cats with idiopathic cystitis, which also had significantly lower respiratory rates than did healthy cats after intramuscular administration of 20 μg medetomidine/kg body weight. No significant differences in blood pressure or sedation level were observed. In vitro, electrical field stimulation of bladder strips from cats with FIC revealed that atipamezole, an α-2 adrenergic receptor antagonist, did not alter the relaxing effect of norepinephrine, further suggesting downregulation of α-2 adrenergic receptors.[79]

Abnormalities of efferent nerves also appear to be present. Bladder tissue from patients with FIC (A.J. Reche and C.A.T. Buffington, unpublished observations, 2001) and IC[99,100] contains increased tyrosine hydroxylase-immunoreactive neurons in both muscle and urothelium. There is increased nitric oxide[74] and norepinephrine (but not acetylcholine) release from bladder strips in cats with FIC.[79] In addition, tyrosine hydroxylase-containing nerves occur in or near the bladder mucosa, suggesting an interaction between noradrenergic nerves and the urothelium. Urothelial cells can express both α- and β-adrenergic receptors, and adrenergic agonist stimulation of these receptors leads to nitric oxide release. These data support the view that the urothelium can be influenced by both afferent and efferent nerves, which in turn can influence the function of a variety of cell types and ultimately bladder function.[138] Significant increases in local nerve growth factor concentrations also have been found in affected cats,[139] and human beings,[140,141] which too can affect bladder nerve function,[30] although the finding in humans was not specific to IC.[140] The specificity of the finding in cats is not known.

Activation of the SRS also can increase epithelial permeability by neural mechanisms, permitting environmental agents greater access to sensory neurons,[142] which could result both in increased afferent firing and local inflammation. Thus, the effects of the emotional state of the animal may modulate perceived sensations from peripheral organs, completing a loop that may be modulated by both central and peripheral neural activity.[143]

Hormonal. In addition to the sensory, central, and efferent neural abnormalities identified, an "uncoupling" of SRS output, with a relative predominance of sympathetic nervous system to hypothalamic-pituitary-adrenal activity,[144] appears to be present in patients with FIC and IC. Sympathoneural outflow normally is restrained by adrenocortical output.[145] In patients with FIC[20,146] and IC,[147,148] however, it increases without coactivation of the adrenal cortex. Additionally, the adrenocortical response to adrenocorticotropic hormone (ACTH) stimulation during stressful circumstances is reduced, and cats with FIC often have small adrenal glands.[25,146] Histopathological examination of these glands excluded the presence of hemorrhage, inflammation, infection, fibrosis or necrosis, and morphometric evaluation identified reduced size of the fasciculata and reticularis zones of the adrenal cortex.

These results, when combined with observations of increased concentrations of corticotrophin-releasing factor[121,149] and ACTH[146] in response to stress in the absence of a comparable increase in plasma adrenocortical hormone concentrations, suggest the presence of mild primary adrenocortical insufficiency or decreased adrenocortical reserve in cats with FIC. Inappropriately low plasma adrenocortical hormone concentrations also have been observed in human beings with IC and chronic idiopathic prostatic pain syndrome.[20,150] Potential mechanisms underlying the stress-related reductions in circulating adrenocortical steroid concentrations include endocrine,[151] neural,[152,153] and developmental influences on the adrenal gland.[20]

Immune. Studies of laboratory-housed[17,154] and zoo-confined cats[155] have found that activation of the SRS is associated with a variety of sickness behaviors.[18] Sickness behaviors refer to variable combinations of vomiting, diarrhea, anorexia or decreased food and water intake, fever, lethargy, somnolence, enhanced pain-like behaviors, as well as decreased general activity, body care activities (grooming), and social interactions.[156] Sickness behaviors are thought to reflect a change in motivation toward withdrawal to promote recovery by inhibiting metabolically expensive (eg, foraging) or dangerous (eg, exposure to predators) activities when the animal is in a relatively vulnerable state. Sickness behaviors are found across mammalian species, and their occurrence[157] has been linked to immune activation and proinflammatory cytokine release,[158] as well as to changes in mood and pathologic pain.[132,159] Sickness behaviors can result both from peripheral (bottom-up) and central (top-down) activation of immune responses. In a recent study of healthy cats and cats with FIC,[18] (infra vide) unusual environmental events, but not disease status, resulted in a significant increase in total sickness behaviors when the results were controlled for other factors.

Recent studies have begun to map the pathways that transduce activation of the SRS into cellular dysfunction. Induction of the transcription factor nuclear factor-κB in peripheral blood mononuclear cells was observed after environmental activation of the SRS.[160] Only norepinephrine induced this response, which was reduced by both α(1)- and β-adrenergic inhibitors. The authors concluded that norepinephrine-mediated activation of nuclear factor-κB represented a downstream effector of the response to stressful psychosocial events, linking changes in the activity of the SRS to a bewildering array of cellular responses via cell surface receptors.[161] Cytokines and a variety of other inflammatory and metabolic signals also can activate nuclear factor-κB by binding to different cell surface receptors, further complicating interpretation of the source(s) of generation of cellular responses. Adrenocortical steroids tend to inhibit activation of nuclear factor-κB.[162,163] This and other adrenocortical steroid-related protective mechanisms[164–166] might be less efficient in hypoadrenocortical states such as FIC and IC.

Comorbid Disorders. The possibility of an internal cause in some patients with FIC and IC also is suggested by the presence of multiple comorbid disorders in many

patients, the absence of this pattern of comorbidity in patients with other LUT diseases, and the unpredictable order of appearance of the comorbidities. Cats with FIC can have variable combinations of comorbid disorders, including behavioral, cardiovascular, endocrine, and gastrointestinal problems in addition to their LUT signs.[15,16,20,115,167] Most human beings with IC also suffer from variable combinations of comorbid disorders that affect a variety of other body systems.[20,168–170] That patients with FIC and IC have variable combinations of other comorbid disorders raises the question of the extent to which a different etiology affects each organ versus the extent to which some common disorder affects all organs, which then respond in their own characteristic ways.

External, intrinsic, or both, bladder abnormalities could lead to development of these other disorders. Patients with extrinsic (eg, chronic UTI) or intrinsic (eg, bladder cancer or "overactive bladder") urological disorders, however, have not been reported to be at comparable increased risk for development of the many comorbid disorders that afflict patients with IC. Moreover, appearance of FIC (C.A.T. Buffington, unpublished observation) or IC[21,22] does not predictably precede development of other syndromes, further suggesting that they are not a consequence but rather independent events or separate manifestations of a common underlying disorder.

Internal Abnormalities—Summary. In addition to the variety of local bladder abnormalities identified in patients with FIC and IC, examination of other tissues for comparison has revealed that many of the identified changes are not restricted to the bladder, but also occur elsewhere in the body of patients with the syndrome. Moreover, comorbid disorders apparently are as likely to precede as to follow the onset of the syndrome. The number, order of onset, and extent of abnormalities identified outside the LUT in cats with FIC were unexpected, and it seems likely that more will be identified in the future. Moreover, many of the changes seem to be "functional," waxing and waning with disease activity, rather than structural. Disease activity also was found to change with environmental circumstances, worsening during exposure to challenging (stressful) circumstances.

Although a variety of internal abnormalities in tissues or systems distant to the bladder occur in patients with FIC and IC, their etiopathologic significance has not been established. Evidence also supports the observation that both external (environmental) as well as internal (visceral) events can activate the SRS, leading to activation of variable combinations of neural, hormonal, and immune responses. These responses might help explain the number, location, and variability of subsequent health problems.[171]

Early Life Events

The findings of increased corticotrophin-releasing factor, ACTH, and sympathoneural activity in the presence of reduced adrenocortical response and small adrenal fasciculata and reticularis zones without other apparent abnormalities suggest a genetic or familial susceptibility, a developmental accident, or some combination of these.[20,26] When a pregnant female is exposed to a sufficiently harsh stressor, or is unusually sensitive to environmental stressors herself, the hormonal products of the ensuing stress response may cross the placenta and affect the course of fetal development.[172] The biological "purpose" of transmitting this response to the fetus might be to program the development of the fetal SRS and associated behaviors toward enhanced vigilance to increase the probability of survival.[173]

The effects of maternal hormones on the fetus seem to depend on the timing and magnitude of exposure in relation to the developmental "programs" that determine the maturation of the various body systems during gestation and early postnatal development.[172] For example, if the fetus is exposed before initiation of a developmental program, there might be no effect on adrenal development. Adrenal development might be reduced, however, if exposure occurs during the critical period when the adrenocortical maturation program is running,[20] or increased if exposure occurs after the period of adrenocortical development.[173]

Postnatal stressors also can result in persistently increased central corticotrophin-releasing factor activity in animals.[174] Behavioral abnormalities in adult rats can result from adverse events during the neonatal period.[175] These effects were mediated by epigenetic modification of glucocorticoid receptor gene expression in the hippocampus by DNA methylation and histone acetylation.[176] Adult mice subjected to chronic social stress have stress-induced epigenetic modulation of hippocampal gene expression that is not restricted to the neonatal period.[177] In addition, other studies of early environmental effects on rat pups have found alterations in autonomic emotional motor circuits,[178] as well as in monoamine, γ-amino butyric acid, and glutaminergic circuits in adulthood.[179]

Studies in rodents also have shown that neonatal inflammation of the bladder can result in impaired bladder function in adults when the bladder is rechallenged.[180] Similar results also have been reported in the colon after neonatal manipulation[181] or maternal deprivation.[182] These results support the hypothesis that events experienced during development may permanently affect visceral sensory systems, representing an additional potential cause of chronic idiopathic disorders. Unfortunately, other organs were not evaluated in these studies, so the full extent of the changes resulting from early adverse experiences remains to be determined.

Recent studies in human beings also have demonstrated that early adverse experience can result in durable alterations in endocrine and autonomic responses to stress similar to those identified in IC.[147,183] Although the dramatic adverse effects of abuse on the SRS of human beings are well known,[184] less extreme parenting behaviors such as neglect, rejection, and hostility[185] as well as a host of environmental events[186] also might play important mediating roles in the neuroendocrine abnormalities observed.[187,188]

Early life events also can confer resilience to adverse experience. Both genetic and environmental resilience

factors have been identified,[189–191] and the effect of external events on these factors on the developing nervous system might depend on the timing of exposure to them.[192] Thus, research has demonstrated that early life experience can have a multitude of effects on the exposed individual, from conferring susceptibility to reinforcing resilience. Moreover, these effects can confer a susceptibility that might or might not eventually be unmasked by later events,[193,194] further complicating the story.

Additional Findings

The idea that a ''Pandora'' syndrome might be present in some cats with chronic idiopathic LUT signs developed from a number of clinical and laboratory studies. In the late 1990s, a prospective, multicenter, double-blinded, placebo-controlled, randomized clinical trial designed to evaluate the efficacy of pentosan polysulfate for improving LUT signs in cats with FIC was conducted.[60] Cats with at least 2 episodes of LUT signs within the past 6 months, cystoscopic findings of diffuse glomerulations present in at least 2 quadrants of the bladder, and the absence of an alternative diagnosis after appropriate clinical investigations were randomly assigned to receive either 0.0 (vehicle placebo), 2.0, 8.0, or 16.0 mg/kg pentosan polysulfate twice daily for 26 weeks. Owners evaluated the cats weekly by rating hematuria, stranguria, pollakiuria, periuria, and vocalization during voiding attempts on a scale of 0–3 (none, mild, moderate, severe), and additional cystoscopic examination was performed at the end of the study. All treatments were well tolerated by the cats; adverse events were rare and no consistent treatment-related pattern was evident. Average owner-recorded scores of signs of LUT dysfunction decreased by approximately 75% in all groups, although recurrent episodes occurred on some 35% of cats. While these results suggest that nonspecific therapeutic responses might occur in cats with FIC, possibly by altering their perception of their surroundings, lack of a ''usual care'' control group require that the study be interpreted with caution.

The hypothesis that LUT signs might be responsive to environmental influences, while not novel,[113,114] led to additional investigations. Laboratory studies revealed that environmental enrichment was associated not only with reduction in LUT signs, but also with normalization of circulating catecholamine concentrations, bladder permeability, and cardiac function,[17,137] and reduced responses to acoustic startle.[134] Based on these findings, environmental enrichment was evaluated in a 10-month prospective observational study of client-owned cats with moderate to severe feline idiopathic cystitis.[15] In addition to their usual care, clients were offered individualized recommendations for multimodal environmental modification based on a detailed environmental history. In addition to significant reductions in LUT signs, decreased fearfulness, nervousness, signs referable to the respiratory tract, and a trend toward reduced aggressive behaviors were identified.[15]

Most recently, a clinical study of pharmacologic therapy, extrusion, inspection, and gentle massage of the distal penis to attempt to dislodge any obstructions, decompressive cystocentesis, and a darkened, low stress environment that did not house any dogs resulted in resolution of urethral obstruction, defined as spontaneous urination within 72 hours and subsequent discharge from the hospital, without the need for urethral catheterization in 11/15 (73%) of male cats with urethral obstruction.[195] And in a laboratory study, sickness behaviors were observed both in healthy cats and in cats with FIC in response to unusual external events for 77 weeks after environmental enrichment.[18] Increasing age and weeks when unusual external events occurred, but not disease status, resulted in a significant increase in total sickness behaviors when controlled for other factors. A protective effect of male sex on food intake in healthy cats was observed, as well as a small increased risk of age for upper gastrointestinal (1.2) and avoidance behaviors (1.7). In contrast, unusual external events were associated with significantly increased risks for decreases in food intake (9.3) and elimination (6.4), and increases in defecation (9.8) and urination (1.6) outside the litter box. These results suggest that some of the most commonly observed abnormalities in client-owned cats occurred after unusual external events in both groups. Because all cats were comparably affected by unusual external events, clinicians may need to consider the possibility of exposure to unusual external events in the differential diagnosis of cats presented for care for these signs.

Clinical Implications

Based on the evidence available to date, some cats evaluated for chronic signs of LUT dysfunction might instead have a ''Pandora'' syndrome. Given the comorbid disorders sometimes found in cats with some other chronic disorders, other presentations of the syndrome seem likely. Based on these observations, and on the current limited understanding of the many factors potentially involved, a reasonable diagnostic strategy for cats with chronic clinical signs referable to a particular organ system might be to conduct a comprehensive investigation of the animal's history, environment, and other organ system function. Additional supportive data might include evidence of early adverse experience (orphaned, abandoned, etc.), presence of related signs in family members, waxing and waning of signs related to environmental threat, and the absence of evidence for an alternative cause. Evidence for the presence of these additional factors would support diagnosis of ''Pandora'' syndrome, whereas evidence of absence of these factors would argue for an organ-specific disorder.

With regard to treatment, significant recovery from signs referable to the LUT and other systems has been reported in cats with LUT-predominant ''Pandora'' syndrome using tailored multimodal environmental modification.[15] The effectiveness of environmental enrichment also suggests that pharmacological or other therapeutic interventions face an important barrier to demonstrate efficacy in the presence of the large therapeutic response to this approach in cats with the syndrome. Moreover, pharmacological approaches that

require force, such as pilling, also might result in activation of the SRS. Given the lack of evidence for effectiveness of most currently available pharmaceutical treatments for cats with chronic idiopathic LUT signs at least, these approaches should be undertaken with caution.

The prognosis for recovery of cats with LUT-predominant "Pandora" syndrome appears to depend on the commitment of the owner, the modifiability of the environment, and the severity of the disorder in the cat. Additionally, cats seem to retain the underlying vulnerability, however, even after long periods of time without expressing clinical signs, if exposed to sufficiently severe stressors.

Summary and Perspective

Currently available evidence suggests that many cases of chronic idiopathic LUT signs presently diagnosed as having FIC actually may have a "Pandora" syndrome. The syndrome might result from early adverse experiences that sensitize the neuraxis to sensory input, increasing the frequency and duration of activation of the SRS when the individual is housed in a provocative environment. The chronic "wear and tear" of persistent activation of the SRS, when superimposed on the (possibly familial) variability of organ involvement, possibly explains the inconsistency of comorbid disorder presentation.[171]

The available data only suggest this scenario, however, and permit generation of the hypothesis. Many of the findings are based on data obtained from small numbers of severely affected animals recruited because of the severity of their disease, and have not been independently replicated. One might imagine a number of additional complementary or alternative "systemic" hypotheses related to variable combinations of genetic, epigenetic, and environmental influences; these remain to be explored.

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