

Interstitial Cystitis and the CNS/WH Center

The establishment of the CNS/WH Center provides a golden opportunity to increase our knowledge about causes and treatments for IC. Since it might seem strange that a veterinarian is involved with this research, I want to introduce myself and share my perspective on IC. Then I'll try to answer some questions that have been asked about our studies, and tell you what we hope to accomplish.

I am a professor of veterinary clinical sciences at The Ohio State University. I have been studying IC since 1992, when a chance occurrence brought IC to my attention. I had been studying cats with bladder disease for nearly 20 years. I am a nutritionist by training, because the prevailing thought when I did my graduate work was that bladder problems in cats were caused by stones that resulted from improperly formulated diets. I was searching the literature one evening for more information about a urinary protein (Tamm-Horsfall protein) I was studying, and came across a paper that had measured this protein in the urine of women with IC. Since I'd never heard of IC, I read the paper, and was struck by the similarities between the description of this disease in women and what I was seeing in cats.

At nearly the same time, the National Institutes of Health (NIH) had just released a request for proposals to study IC as a result of patient efforts led by Dr. Vicki Ratner, founder of the Interstitial Cystitis Association. I was awarded one of these grants, and during the past 10 years our studies have found that most cats brought to veterinarians for treatment of signs of bladder disease meet the criteria for diagnosis of IC established by the NIH to ensure that research studies of IC include reasonably comparable groups of patients.¹ Cats with IC meet all the inclusion, and the 18 exclusion, criteria for diagnosis of IC that can be applied to animals.² IC in cats and humans is remarkably similar; patients of both species have abnormalities of local bladder factors, the sensory, central (CNS), and sympathetic nervous systems (SNS – the “fight-or-flight” system), and the hypothalamic-pituitary-adrenal (HPA – the system that restrains the “fight-or-flight” system) axis. Table 1 compares results of studies in humans with our findings to date in cats:

Table 1. Some IC-related comparisons between humans and cats with the syndrome.

Parameter	Human beings	Cats
<i>Patient features</i>		
Gender	Females and males	Females and males
Bladder symptoms	Frequency, urgency, pain	Frequency, urgency, pain
Non-bladder symptoms	Yes	Yes
Clinical course	Waxes and wanes	Waxes and wanes
Meet NIDDK diagnostic criteria	Most	Most
<i>Local bladder abnormalities</i>		
Petechial hemorrhages (cystoscopy)	Present	Present
Urothelial Permeability	Increased	Increased
Urothelial cell abnormalities	Yes	Yes
Mast cells	±Increased	±Increased
Total glycosaminoglycan excretion	±Decreased	Decreased
Glycosaminoglycan GP-51 expression	Decreased	Decreased
Vasodilatation and edema without inflammatory infiltrate	Present	Present
<i>Sensory abnormalities</i>		
Bladder substance P-immunoreactivity (SPIR)	Increased in some, but not all studies	±Increase
Sensory neuron abnormalities	Not Determined (ND)	Yes
Dorsal root ganglia abnormalities	ND	Yes
Sacral cord SPIR	ND	Increased
Bladder SP receptors	ND	Increased
<i>Central abnormalities</i>		
Response to stress	Exacerbation of signs	Exacerbation of signs
Locus coeruleus tyrosine hydroxylase IR	ND	Increased
<i>Efferent abnormalities</i>		
Bladder neuropeptide Y-IR	Increased	ND
Bladder norepinephrine content	ND	Increased
Plasma catecholamine concentrations	ND	Increased
Urine norepinephrine excretion	Increased	ND
Cortisol responses	± Decreased	± Decreased
<i>Response to treatment</i>		
Amitriptyline	Beneficial	Beneficial
Stress reduction	“	“

During the course of my studies of feline IC as a naturally occurring model of interstitial cystitis (IC) in humans, I had the good fortune to become acquainted with Dr. Emeran Mayer, a gastroenterologist and neuroscientist at UCLA. Dr. Mayer and his colleagues are leaders in the study of irritable bowel syndrome (IBS). As you may know, both IBS and IC can occur in the same patient. Both syndromes sometimes are classified as “functional” visceral disorders, since current tests cannot identify any obvious source of the symptoms of pain and organ dysfunction the patients suffer. I sought out Dr. Mayer because of his investigation of the hypothesis that IBS might be a “neurovisceral” disease, that is, one with central nervous system pathology that might not be apparent using conventionally available diagnostic methods. My own clinical observations and research had led me to similar speculations. Our mutual interests led Dr. Mayer to invite me to participate in a Center grant proposal to be prepared in collaboration with Dr. Lin Chang, another gastroenterologist at UCLA, and Dr. Yvette Taché, a neuroscientist expert in the neurophysiology of stress. We were fortunate to have our proposal funded resulting in the establishment of the CNS: Center for Neurovisceral Sciences and Women’s Health. This new multidisciplinary center has provided me the opportunity to collaborate more formally with this outstanding group. To help ensure rapid and effective interaction with the urology

community, Dr. Philip Hanno, professor of Urology at the University of Pennsylvania has agreed to work together with me as an external advisor to the CNS.

What is IC?

We don't know, yet. Based on the currently available evidence, it seems most honest to classify IC as a syndrome, a collection of symptoms for which no causes currently are recognized. We already know that IC is not a single disease because of the differences between the ulcer and non-ulcer forms. It is easy to imagine that more than one cause of the "IC Syndrome" will be found, which may respond to different forms of therapy. I believe this because symptoms of IC extend beyond the bladder, affecting all the body systems. Table 2 summarizes extra-bladder symptoms reported in four separate studies of patients with IC.³⁻⁶ Numbers in bold type indicate problems that were statistically significantly more common in IC patients than in controls. Numbers in regular type indicate parameters for which no difference was identified, although the sample size may not have been large enough to detect differences for some parameters. In addition to IBS, IC can occur with a wide variety of other physical chronic ailments, including other chronic pelvic pain syndromes, chronic fatigue syndrome (CFS) and fibromyalgia (FM).

There also is another group of stress-related syndromes that sometimes co-occur with symptoms of IBS and IC. These include panic disorder and post-traumatic stress disorder (PTSD).⁷ Moreover, there also is overlap between PTSD and IBS, FM, CFS and other chronic disorders.⁸⁻¹⁰ Weissman, et al.,¹¹ recently identified a potential genetic linkage between panic disorder and kidney, bladder, migraine, thyroid, and mitral valve disorders. The bladder problems turned out to be IC.¹² Since these disorders also are poorly understood syndromes, one's "diagnosis" may sometimes depend on the specialist one seeks out for care of the most troublesome symptoms.

Table 2. Body systems affected by IC. These studies were somewhat different in design and approach, so the number of IC patients was divided by the number of controls with each problem. For example, Koziol⁵ found that 2.5 times as many IC patients as controls had undergone a hysterectomy, while the empty blocks indicate that no data about that abnormality were collected in the other studies. Numbers in bold type indicate problems that were statistically significantly more common in IC patients than in controls. The data suggest that many IC patients have problems affecting many body systems other than the bladder.

Study	1 ³	2 ⁴	3 ⁵	4 ⁶	Study	1 ³	2 ⁴	3 ⁵	4 ⁶
	IC Cases/ Controls	565/ 171	30/ 30	2682/ varied	35/ 35				
<i>Abnormality</i>									
Genitourinary					Cardiopulmonary				
Hysterectomy	2.5				Sinusitis	2.3			
Vaginal pain		7.7			Asthma	1.7		1.6	
PMS		1.2			Frequent upper resp. inf.	3.6			
Menstrual pain		1.9			Heart palpitations		4.3		
Endometriosis			0.7		Shortness of breath when hurrying		5.2		
Incontinence			0.7		Chest pain*		4.7		26/0
Other pelvic discomfort				8.5	Shortness of breath when walking		11.0		
Musculoskeletal					Increased heart rate				
Arthritis	1.5				Shortness of breath		3.3		
Muscle spasms		4.6			Shortness of breath when dressing		1.4		
Morning stiffness		2.9			Stop for breath when walking		4.3		
Muscle pain		3.4			Heart pounding				6
Swollen joints		3.9			Nasal congestion				1.3
Fibromyalgia			5.8		Coughing				2
Backache				3.3	Suffocation				3/0
Aches in joints				2.2	Allergic/Immune				
Swollen ankles				3.3	Drug allergy	2.7			
Dermatological					Hay fever				
Sensitive skin			2.3		Food allergies	2.9			
Neurological					Epstein-Barr virus				
Numbness	1.9	6.7		3.2	Swollen lymph nodes		3.9		
Memory problems		3.3			Recurrent fever		7.7		
Concentration problems		5.1			Allergies			1.9	
Dizziness		9.0		31/0	SLE			40	
Tension headache		1.8			Flu				6/0
Migraine headache		3.1	1.1		Endocrine				
Headache				2.4	Hypothyroid	2.3			
Vision problems				4.5	Hyperthyroid	1.7			
Ringing in ears				2.3	Diabetes	0.7			
Gastrointestinal					Other				
Abdominal (Abd.) cramps	3.4			38/0	Family history of IC	0.9			
IBS	3.4		10.3		Fatigue		5.9		
Frequent stools	8.3				Dry mouth		3.6		
Spastic colon	6.1				Dry eyes		3.6		
Diverticulitis	3.3				Cold-sensitive fingers		3.3		
Bloating		3.0			Balance problems		3.9		
Changes in stool consistency		6.1			Sinus pain		2.4		
Changes in stool form		3.6			Ear pain		4.6		
Changes in passing of stool		4.7			Ear blockage or fullness		13.3		
Abd. Pain relieved by defecation		3.1			Hearing loss		7.7		
Abd pain with change in stool		5.0			Hands turn white in cold		11.0		
Nausea or vomiting		2.7		9.0	Chronic fatigue syndrome			1.2	
Mucus in feces		36/0							
Colitis/Crohn's disease				110.7					

The terms “stress” and “stress responses,” which mean different things to different people. A “stress” or “stressor” is a quality events of the external (and internal) environment, whereas the “stress response” is how our bodies respond to these events. The brain constantly receives massive amounts of information about the environment from the senses via the nervous system on an instantaneous basis, and must decide what it all means, and what to do about it, just as quickly. These responses range from approach (for food or company) to withdrawal (from threats). The system is millions of years old, and probably developed to enhance our probability of survival. Moreover, individuals with more sensitive stress response systems may well be at an advantage in some environments. A diagram of this system is presented in figure 1.

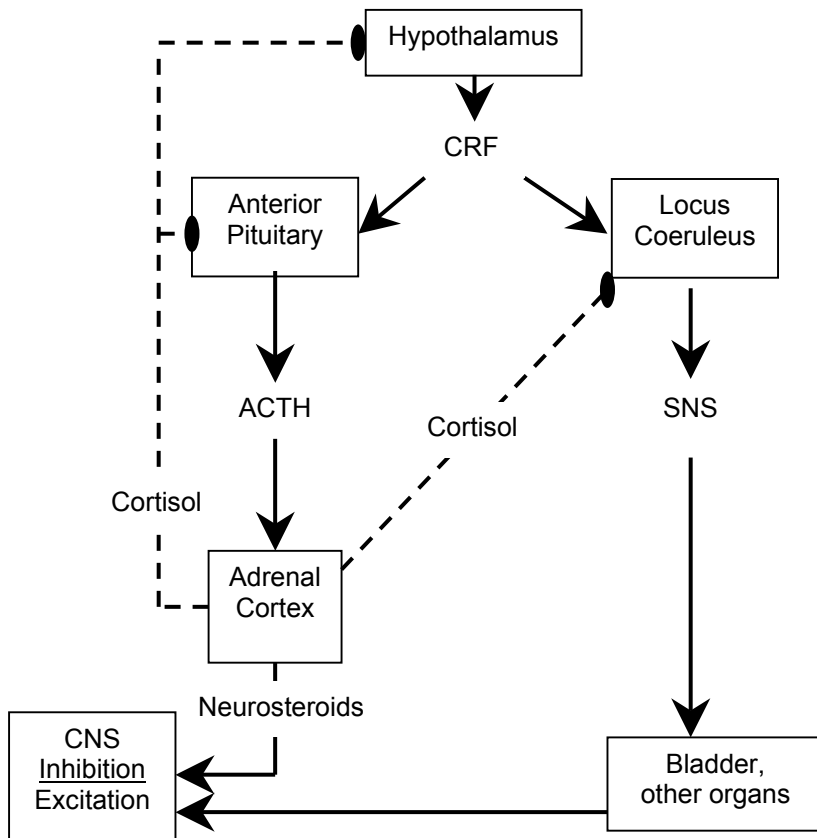


Figure 1. Normal balance of the CRF response system to stressors. In this case, excitatory SNS outflow from the locus coeruleus is restrained by cortisol. Cortisol also restrains the system by feedback inhibition at the level of the anterior pituitary and hypothalamus. The solid lines indicate stimulation, the dotted lines indicate inhibition. Both are of equal size

Evidence from our own studies and a variety of separate lines of research, including stress,¹³ psychiatric,^{14, 15} and medical^{16, 17} appear to be converging on the hypothesis that enhanced responsiveness of stress response systems in the brain play an important role in the pathophysiology of all these disorders. The stress response systems can be acutely activated by internal “threats”, like bladder pain, as well as external ones.^{18, 19} Activation of the stress response systems results in a complex cascade of events, one of which is release of a hormone and neurotransmitter called corticotrophin-releasing hormone (CRF). CRF can activate both the HPA axis and SNS arms of the stress response system. During chronic stress, SNS activity appears to be persistently enhanced. But for as-yet unknown reasons, the HPA system, which interacts with the SNS in complex ways,²⁰ does not appear to be comparably activated. These relationships are shown in Figure 2.

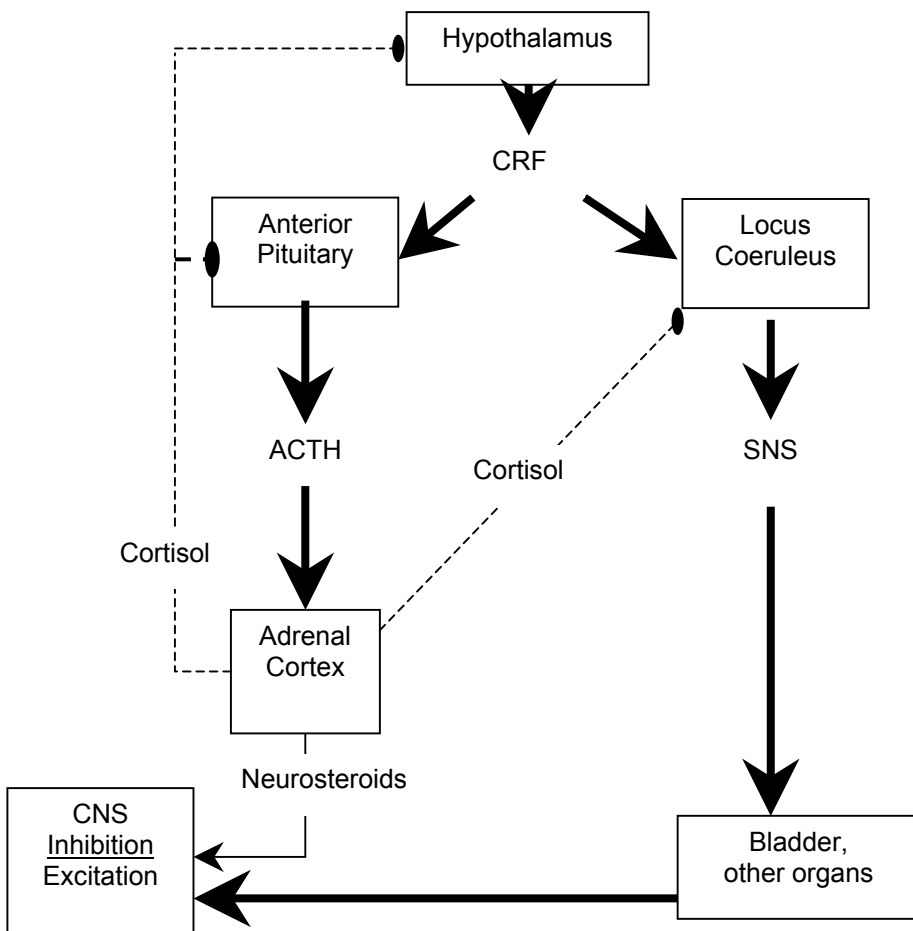


Figure 2. Imbalanced system of IC. In this case, excitatory SNS outflow from the locus coeruleus is inadequately restrained by cortisol. This enhanced activity can increase tissue permeability, resulting in increased sensory afferent activity. Feedback inhibition at the level of the anterior pituitary and hypothalamus also is reduced, which tends to perpetuate CRF output. Neurosteroid production by the adrenal cortex, which generally enhances CNS inhibitory tone during chronic stress, also may be reduced.

The results of investigations of the stress response systems, although extensive,^{10,21} are not consistent. These inconsistencies may result from the uncertainties in diagnosis of these syndromes,²² the number of co-morbid conditions,²³ and differences in disease severity and relative activation of different aspects of the stress response systems among the subjects at the time of the study.²⁴

We recognize a pattern of abnormalities in cats with FIC that is quite comparable to those observed in humans with IC. Stressed cats with FIC have significant increases in SNS activity without increased HPA activity, whereas in healthy cats, both increase together.²⁵ Similar to humans, anxiety also is commonly associated with bladder problems in cats.²⁶ We found in one study that 60% of cats with no clinical signs other than urinating outside the litter box (a sign of anxiety in cats) had glomerulations at cystoscopy.²⁷ Also, we have documented panic-related respiratory abnormalities in cats with FIC,²⁸ that cats restricted to indoor living are some five times more likely to develop urinary problems than cats allowed outdoors,²⁹ and that cats with FIC have exaggerated sensitivity to sound, suggesting increased sensory responsiveness.³⁰ Thus, a roughly comparable combination of physiological and behavioral abnormalities seems to affect cats with FIC as well as humans with IC and related syndromes. To me, one of the most important consequences of identification of comparable abnormalities in another species is the implication that some underlying disorder must exist to explain the findings.

The preceding discussion only sketches the outlines of a huge area of science as it relates to IC. I describe IC to cat owners as a syndrome that may result when a susceptible individual enters a provocative environment. We currently don't understand the causes, but we can use medical, behavioral and environmental approaches to treatment that may not cure the disease, but can effectively resolve much of the patient's suffering, and reduce the severity of their disease (if you're interested, some of our recommendations are at <http://www.nssvet.org/ici>). I hope association with colleagues at UCLA will help us find better approaches to therapy based on a better understanding of the role of the brain in the causes of, and cures for, the IC syndrome.

To summarize, extensive evidence supports the hypothesis of enhanced stress responsiveness as a factor in both human and feline IC, and to other related syndromes, including IBS. While undoubtedly not the only factor, understanding the role of this system may help take the "waxing" out of "waxing and waning signs."

Since the Center has been announced, I've gotten a number of important questions about our plans; I'll try to answer some of the more common ones:

Q. Do you think that IC is caused by how patients deal emotionally and physically with stress, that we initiated it ourselves? Are you trying to prove that IC is all in our heads?

A. Absolutely not! We do think that the brain plays an important role in IC, but patients clearly do not "cause" this syndrome themselves. Determining the relative importance of the many systems - bladder, sensory nerve, brain, sympathetic, endocrine, and others - involved in the syndrome is one of the major overall goals of the Center. I specifically want to comment on the "all in your heads" phrase. First, to the extent that the brain is involved, the statement only localizes one of the sites of abnormalities. Second, to the extent that it means "it's in your mind," which sometimes seems to insinuate that "it's your fault," I point out that cats have the

IC-related problems humans do, and yet they probably do not have a “mind” in the sense that most people think of mind.

Q. Will you be studying men?

A. Since the focus of the Center is women’s’ health, we won’t be studying men with urinary disorders, at least initially. This does not mean that men don’t have problems comparable to the IC syndrome, however. As Drs. John Kusek and Lee Nyberg (a urologist and champion of IC-related studies at NIH) recently observed, “Evidence suggests men with the IC symptom complex are often misdiagnosed by physicians and identified as having chronic prostatitis (also called the chronic pelvic pain syndrome) or benign prostatic hyperplasia.”³¹

Q. What treatments will you be studying?

A. We will initially focus on abnormalities that differentiate IC from normal, and make comparisons between patients with IC and IBS. We will be testing compounds that block the activity of corticotrophin releasing factor in both rats and cats in anticipation of using them in patients. Based on these studies, I imagine we also will develop ideas for other potential approaches to therapy.

A health outcomes research arm of the Center will explore quality of care and evaluate patient-centered outcomes, including health-related quality of life, patient satisfaction with care, and costs in this patient population.

Q. Isn’t IC likely to be caused by some bacteria scientists just haven’t found yet? Ulcers used to be thought to be caused by stress, until the helicobacter organism was found.

A. It could be, at least in some cases. When working with any syndrome, it is essential to keep an open mind. We also have to be careful to separate “causes” from “associations.” Using the helicobacter- gastric ulcer example, we know that many people, and cats, have the organism in their gastrointestinal tracts and don’t develop gastric ulcers, and that patients with gastric ulcers don’t always have the organism present (also people have looked for this, and many other organisms, in the bladder of IC patients without success). So even if (when) an organism is found in patients with IC, we still will need to understand its relative importance; is it present in all patients? How does it cause the many non-bladder problems documented in patients with the syndrome? What role does it play in waxing and waning of signs? These and many more questions will need to be answered for any “bug” associated with IC.

Summary

We are embarking on a large and complex endeavor, investigating two common, seemingly related, yet perplexing syndromes. Despite this, I have complete confidence in Dr. Mayer’s leadership, and believe that the whole of the Center’s efforts will be much greater than the sum of the talents of each individual investigator. I hope to engage the IC patient community’s support for our work, and will keep you updated on our progress with periodic updates.

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