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Interstitial Cystitis: New Concepts in Pathogenesis, Diagnosis, and Management

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FACULTY

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INTERSTITIAL CYSTITIS

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INTRODUCTION

Perhaps one of the main problem areas in working with the syndrome interstitial cystitis (IC) is attempting to recognize the patient population that actually has the disease complex. Historically the diagnosis was limited to only those patients with severe symptom complex of urinary urgency, frequency, pelvic and perineal pain. However, this traditional concept basically recognizes only those patients with end-stage disease and probably only represents 5% or less of the people who are actually afflicted with IC. This disease has been misdiagnosed as recurrent bladder infections, urethral syndrome, perhaps even prostatitis in men. In the gynecological realm it is probably misdiagnosed as pelvic pain and confused with endometriosis, various types of vaginitis or vulvodynia. The disease is often confused with bladder outlet obstruction due to prostate enlargement or prostatitis. This review, in part, will attempt to define better the patient population that actually has IC. This disease traditionally thought to be quite rare may, in fact, be quite common with recurrent bacterial cystitis being a rare event. Part of the confusion in recognizing patients with this disease in the early phases is that frequently the complaints are intermittent and confused with other bladder disorders such as bacterial cystitis. It seems to progress slowly and until the symptoms become more continuous, it is likely that the patient will not be diagnosed as having IC.

Other areas where much progress has been made in understanding IC has been in new concepts of pathogenesis as well as new methods to successfully treat and manage patients with this disease. These shall also be reviewed.

DEFINITION

This may be one of the most confusing parts of IC because the definition is changing drastically as we understand better the patient population that has the disease, how it progresses, and what factors provoke it. Not much progress was made in defining this patient population until 1987 when a group of interested researchers met at the National Institutes of Health to establish clinical criteria for characterizing the IC syndrome patient for research studies.[80] While these criteria were never meant to be diagnostic for IC, it was agreed they represented patients with sufficiently advanced and persistent disease that, when one was doing research and incorporating these patients, they should have sufficient pathologic changes to study relative to possible pathogenesis and therapy. These criteria were never meant to be used for defining or diagnosing the patient population since the researchers had agreed it really represented very advanced patients. In fact, more recent studies have shown that they only represent a small part of the patients with the disease. Most patients who were diagnosed in an NIH-sponsored IC Data Base met less than 25% of the criteria but were recognized by the investigators as having. We will attempt to define the patient population here which will probably also lead to substantial changes in the future as we understand more about the manner in which the disease presents itself and what causes it.

For practical purposes we believe that the most important parts of defining IC are relative to the fact that it is still a clinical syndrome with no distinct pathologic tissue or serum changes that would define someone as having IC. It is to be emphasized that it depends upon the state of the disease, whether it is an early phase, milder version of the symptom complex,

or a more advanced later stage seen in an older patient as to what symptoms may actually be present. In general, the disease is best defined by the clinical symptoms of urinary urgency, frequency and/or pelvic pain that are present in a patient with no other definable pathology such as urinary infection, carcinoma, radiation or medication induced cystitis. It may well be that the syndrome encompasses a number of different etiologies but with a bladder insult that ultimately results in urinary frequency and urgency or pain which is essentially its only clinical response to noxious stimuli. It should also be emphasized that the pain may be the only principle component of the syndrome and may have associated with it very little urgency or frequency and it is perhaps this patient population that would most likely present to the gynecologist and not to the urologist.

We will present some data to look at the clinical parameters that help define the disease. The clinician should bear in mind that there may be some significant variance depending upon how severe the patient symptoms are when you see them and how early or late it is in the disease and how mild or severe the disease is in any particular individual. Perhaps the most important thing for the clinician to keep in mind is that by utilizing a broad definition of the syndrome and recognizing the disease is significantly under diagnosed[98] then many patients with milder forms of the disease could readily benefit from therapy if the diagnosis is considered and treatment initiated. This is of significance today as many of the patients will respond readily to therapy and hopefully prevent patients from advancing to the more severe end-stage disease.

PATHOGENESIS

There has been substantial progress in understanding the etiology of interstitial cystitis. It is best to approach it with the concept that there are probably a number of mechanisms that lead to the production of symptoms in the individual patient. Another difficult part in trying to understand the disease is that in most people it starts out with mild, intermittent flares of disease which make them difficult to quantify and study and historically we have been looking mostly to the end-stage patient who has very severe and advanced disease. Consequently, since there are fewer of them, it has been difficult for any patient studies to be obtained due to the limited access to large numbers of patients for research. There are many suggested etiologies including lymphatic, chronic infection, neurologic, psychologic, autoimmune disorders and vasculitis.[3-10] Most of the proposed etiologies are still hypothetical in nature with not much data to define the role of these mechanisms. For example, Oravisto[9] had suggested there were increased antinuclear antibodies in patients with IC which appears to be true. But, it is difficult to know what this means because mild elevations in autoimmune antibodies may be present in many chronic diseases. Also, there is no obvious association of the IC syndrome in most patients with autoimmune phenomenon. In many respects, the mild elevation of antibodies may represent an epiphenomenon.

There have been a number of discoveries which have helped to put some of the IC puzzle pieces in place. One of the more widely accepted theories is that there is a defective bladder epithelium with loss of the "blood urine barrier" resulting in a leaky membrane.[11,12] An epithelium permeable to small molecules could then explain the induction of symptoms associated with a complex, especially if the diffusing substances stimulate the depolarization of sensory nerves.[13,14] In particular, it has been shown that diffusion of potassium across the bladder epithelium could trigger the sensory nerve endings resulting in not only symptoms, but even in disease progression due to tissue injury.[15] While other factors seem to play a role such as mast cells and their degranulation, vascular problems such as reflex sympathetic dystrophy, and probably neuroinflammation from upregulation of the sensory nerves.

INFLAMMATION and IC

It has been long present in the literature that IC is primarily an inflammatory disease, but this is probably not true or substantiated by any data. In fact, what few studies have been done, little inflammation has been reported in IC biopsies. In addition, neither inflammatory mediators nor white blood cells are present in IC urine.

Mast cells, on the other hand, are a prominent feature in perhaps ⅓ of patients and may be important in the provocation of symptoms, especially in atopic people.[18,20-24] In addition, animal models of mast cell stimulation also suggest that these cells may provoke abnormalities in both smooth muscle activity and epithelial permeability.[25,26] In our experience, it is certainly is important to control allergies in patients with IC as they can be very provocative to the induction of significant symptom flares. Consequently, mast cell aggravation may be very relevant and important to recognize for therapy and suggests that combinations of treatment will be necessary to control the disease.

VASCULAR INSUFFICIENCY

Reduction of vascular perfusion may negatively effect mucosal, muscle and nerve nutrition and initiate a cascade of events that causes symptoms. Radiation is known to impair blood supply by injuring the microvasculature of organs and certainly, in the case of urinary bladder, leads to a syndrome that is basically IC with urgency, frequency, and altered epithelial permeability.[28] Other profusion abnormalities such as reflex, sympathetic dystrophy[27] may result in secondary decrease in blood flow that also triggers events leading to symptoms in the IC syndrome. Vascular intrigue could be even augmented by reduced epithelial permeability regulation with potassium leak into the bladder interstitial space that may be directly toxic to the small blood supply of the subepithelial tissues leading to further bladder impairment.

EPITHELIAL LEAK

A widely held theory concerning pathogenesis today is that of an epithelial leak. The hypothesis is that the permeability regulatory mechanism of the superficial epithelial cells is impaired resulting in solute migration across the epithelium. There had been little data to support the concept that such a leak existed[11] and a subsequent study was unable to confirm the initial observation that both normals and IC patients had findings in their tight junctions relative to ruthenium red penetration. However, the initial study only involved three patients and was anatomic and more hypothesis than actual data to support it. The hypothesis essentially had no data to support it.

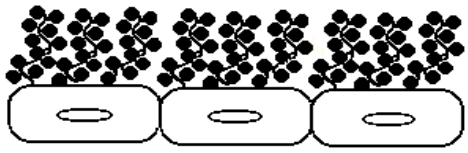
However, a well controlled study in 56 patients provided data to support the hypothesis that the bladder surface in many IC patients may indeed leak solute.[12] This data has been supported by subsequent investigations which employed an even more sensitive "leak assay" to screen individual patients for potential permeability aberrations. From these studies it was estimated that about 70% of the patients could be detected to have a leaky epithelium while 30% may not.[28,102] The caveat here being that there are false negatives to the test (probably not false positives) and a slightly skewed population with the patients who have a non-leaky epithelium being more difficult to treat and presenting to the tertiary care center.

This latter concept is supported by the fact that other investigators have found similar responses to the potassium test,[103,104] but find that up to 90% of them have a leaky epithelium. These studies also suggest that there is a small part of this patient population that does not have a detectable epithelial leak (by current technologies) and may represent some other problem such as neurological inflammation. These studies also suggest that perhaps there is now a method to at least stratify the IC patients into two groups, those who appear to be epithelial leakers from those who are non-leakers.

GLYCOSAMINOGLYCANS: THE BLOOD-URINE BARRIER

The transitional epithelium has been long known to be relatively impermeable and one of the most impermeable epitheliums in the body. The regulation of this permeability has traditionally been ascribed to tight junctions that are unique to bladder epithelium and ion pumps as well as the actual membranes.[11,29-34] Many of these concepts are still somewhat hypothetical and not completely validated physiologically. More recently it has been discovered that the surface mucus which contains proteoglycans and glycoproteins may actually be another critical component by which the epithelium maintains a barrier between the bladder wall and urine and an important part of the so-called "blood-urine" barrier.[12-14] These studies suggest that perhaps the tight junctions which are present in most epithelium, the lipid membranes and the ion pumps which are present in most interfaces are important in the process of permeability regulation, but the initial contact for the solute is the mucus and it may be the one barrier that excludes most solute from ever reaching the membrane and the other secondary controllers of permeability.

This mucus (GAG, proteoglycans) appears to have multiple protective roles in the bladder including antiadherence (relative to bacteria and crystaloid) and regulation of transepithelial solute movement.[14,35-37] The transitional cell's external surface polysacharrides are capable of preventing the adherence of bacteria, crystals, proteins and ions, a function that is lost when this layer is removed with a dilute acid or detergent,[35-38] but restored when mucus is replaced by exogenous polysacharrides such as heparin or pentosanpolysulfate (PPS).[35,39,40] The oxygen atom present on the sulfated polysaccharides in the mucus is negatively charged and has a high affinity to bond ionically with water. This results in exclusion of urinary ionic solutes by a Donnan effect.[41] When glycosaminoglycans are present at a surface (the bladder), it will in effect bind water molecules tightly to the oxygen of the sulfate groups in these molecules in preference to calcium, barium and even hydrogen ions.[42-44] Water molecules become trapped and interposed at the boundary between the cell surface (bladder) and the environment (urine). (See figure below). This bound molecular layer of water acts as a physical barrier such that urinary solutes, including urea and calcium,[14,35] are not able to reach the underlying cell membrane, adhere to it, nor move across it.



Biofilm at bladder surface drawn to demonstrate location of trapped water at surface. Circles represent bound water and wavy lines are protein backbone.

Quaternary amines, on the other hand, have a high affinity for sulfated polysaccharides and will displace the water bound to the oxygen groups and form a salt.[41,45,46] This concept is supported by the fact that when GAG chemically reacts with quaternary amines, it results in an increased entropy reflecting the loss of water ordering around the sulfate groups.[41,47] This interaction is the basis of the clinical use of protamine sulfate (a highly charged proteinaeous group of amines with quaternary amines) to precipitate and inactivate the anticoagulant effects of heparin. It has been demonstrated both in animal and human models that protamine sulfate will inactivate native cell surface polysaccharides and result in increased epithelial permeability. Such damage to the transitional cells can be reversed by the addition of exogenous GAG such as heparin or PPS.[13,14]

Based on these concepts, Parsons et al.[12] hypothesized that the surface polysaccharide is functionally defective (not absent) in some patients with IC. The cause for the deficiency could be for a variety of reasons which could include reduced sulfation of the polysaccharides, diminished density or thickness of the material, or the presence of a compound such as a urinary quaternary amine which could bind to it and inactivate it. It has been demonstrated

that normal individuals who have their bladder surface challenged by protamine lose the impermeability of the epithelium. The permeability to urea in normal individuals will increase from 5% to 25%.[13] When the blood-urine barrier is lost because of protamine treatment, all normal subjects experience urgency, frequency and in some, bladder pain (the same symptoms of IC). These symptoms were reversed with a subsequent treatment with heparin.

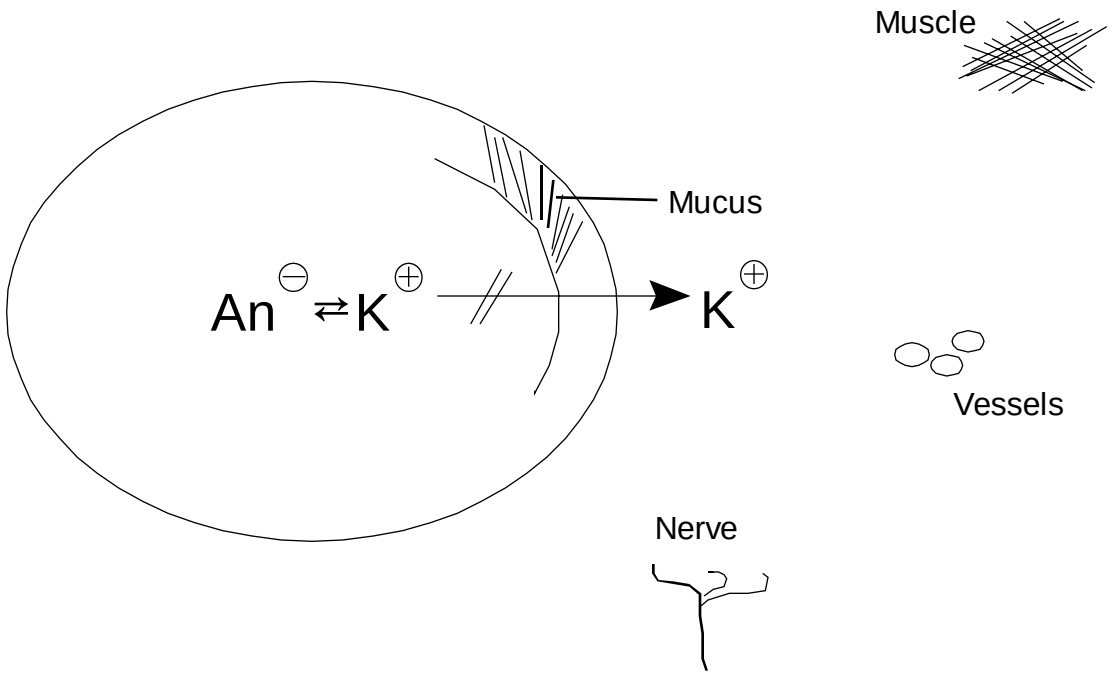
This data is additionally supported by the fact that a semi-synthetic polysaccharide similar to heparin is effective in ameliorating the symptoms of IC.[48-51] To test the hypothesis that some patients with IC have a permeable transitional cell layer, Parsons et al. measured the permeability of the normal bladder epithelium to a concentrated solution of urea and compared it to IC patients.[12] Twenty-nine normals absorbed approximately 5% of the urea whereas 56 patients with IC absorbed 25% (these differences were statistically significant, $p<.01$). Recent evidence from Buffington et al.[105] adds additional support to the epithelial permeability dysfunction in IC. They showed that in subjects with oral fluorescein, IC patients maintained significantly higher serum levels and took longer to clear the fluorescein from their blood than did normal controls. They concluded that patients were "reabsorbing" the fluorescein from their bladder resulting in recycling and prolonged clearance from the blood stream. It is then the resulting leak of urinary solutes in IC that results in the symptoms of urgency, frequency and pain.

Additionally, there was a study in which authors looked at a small group patients[10] where there was a 80% increase in DPTA absorption in IC patients vs normals, however there weren't sufficient numbers with a difference between normals and controls that was approaching statistical significance with a p value of .07. The number of subjects was too small to give any more meaningful significance to the differences. Nonetheless, these data also supported the concept of epithelial dysfunction in IC patients.

ROLE OF URINARY POTASSIUM IN THE PATHOGENESIS AND DIAGNOSIS OF IC

One of the most important pieces of the interstitial cystitis puzzle has been identifying the toxic substance in urine that was leaking across the epithelium provoking the symptoms of IC. It has been proposed by Parsons et al.[28] that the principle toxic substance in urine is potassium. In essence, it is rather an obvious toxin in that the urine levels range between 30 and 150 mEq/L with an average of about 75 mEq/L. It has been long known that this concentration of potassium is toxic to all mammalian cells. In addition, it has been known for many years that levels of potassium in the level of 15 mEq/L will depolarize sensory nerves and muscle. Since the kidneys are the main route of excretion of the dietary potassium, bladder theoretically had to be adapted to handle these very toxic levels of potassium and it may well be that the most important role of the relatively impermeable bladder epithelium is to prevent potassium from diffusing into the bladder interstitium and destroying the tissue.

The role of the transitional epithelium in regulating potassium metabolism is depicted in the Figure on the following page. If urinary potassium should excessively leak into the bladder interstitium, there could be another secondary defense mechanism. The rich supply of subepithelial lymphatic and blood vessels could resorb this cation and restore the normal equilibrium.[106]



As shown above, the high levels of urinary potassium are more than sufficient to depolarize sensory nerves if they present themselves to the subepithelial area. Once in the subepithelial space, they can depolarize muscle or nerves or be carried away by an intact vascular supply restoring tissue levels of potassium to normal.

Toxic levels of interstitial potassium could also induce other neurologically active agents, such as substance P, and also lead to upregulation of pain fibers which may be an important feature of IC.[111] The potassium hypothesis also explains the lack of any significant inflammatory response in most patients with IC, either in the urine or bladder interstitium.[21]

Based on the above concepts, there may be several important components in the paradigm of IC pathogenesis. One, the regulatory role of mucus in reducing permeability is impaired (for reasons unknown) and two, once impaired, the high levels of urinary potassium will result in increased interstitial levels in the bladder that induce sensory nerves (and muscle) to depolarize resulting in pain and urgency and may destroy tissue causing progression of the disease. Incorporated into the progression may be the upregulation of nerve fibers, mast cells and an ever increasing neurogenic inflammation which may become an important and perhaps driving force of the disease and one that also has to be dealt with in terms of therapy.

To test the hypothesis that potassium induces symptoms in IC, Parsons et al. tested normals and a variety of bladder sensory disorders for sensitivity to a solution of intravesical potassium as noted in the Table below.

Results of Stimulation of Sensory Urgency or Pain in Various Groups Using KCl				
Group	N	% Positive[A] to KCl	P Value[D]	% Positive to H_2O
Normals	41	4	–	0
IC (meeting NIH criteria)	92	74	<0.001[E]	10
IC (not cystoscoped)	139	76	<0.001[E]	10
Radiation Cystitis[F]	5	100	0.001	0
BPH	29	3	1.0	3
UTI Acute[B]	4	100	0.01	0
UTI Uninfected[C]	5	0	1.0	0
Detrusor Instability	26	6/26		0

(A) At least >2 point change in visual analogue scale
(B) Test performed when infected
(C) Test performed when uninfected
(D) Fisher's exact test employed to compare group to controls
(E) Chi square analysis
(F) Parsons CL et al.: Abnormal sensitivity to intravesical potassium in interstitial cystitis and radiation cystitis. *Neurourol Urody* 13: 515, 1994.

As can be seen, IC patients reacted strongly to the potassium solution but normals did not. Patients with acute urinary tract infection and radiation cystitis were also found to be potassium sensitive whereas BPH patients and most detrusor instability patients were not provoked. Lastly, to test the hypothesis we compared sodium (which should not depolarize nerves) to potassium and sodium chloride did not cause symptoms in the normal subjects who were evaluated. See the Table below. These concepts have been supported in part by experimental data from Hohlbrugger.[15,97]

Sodium Versus Potassium Provocation in IC Subjects			
Treatment Arm	% Urgency Na	% Urgency K	P Value
Control	0/10 (0%)	0/11 (0%)	–
Protamine	1.10 (10%)	10/11 (90%)	<0.001
Heparin	1/10 (10%)	5/11 (54%)	0.035*
*Compares KCl after protamine to KCl after heparin			

MAST CELLS and NERVE FIBERS

The role of mast cells in IC seems to be significant. Mast cells have been reported by a number of investigators to be present in IC bladders while other data suggests that they are also present in non-IC bladders.[8,10,17,18,52,53,107] The central point of confusion is whether or not mast cells play a causative or secondary role. Causative in that they may be degranulating and

producing the symptoms, or, on the other hand, that they represent a response to whatever is causing IC (e.g. an epithelial leak) and be a type of defense mechanism that may ultimately become part of the problem by degranulating and causing a "leak".

Regardless of how one views the data, most clinical IC researchers believe mast cells play an important role in IC. Clinical impressions are supported by research data in animal models. Saban and co-workers have shown quite well that mast cell activation in guinea pig bladders results in an increase in epithelial permeability.[25] Add to this our observations, as well as others, the fact that active allergies will significantly flare IC and the mast cell takes on added significance, especially when one embarks on therapy.

Mast cells interact with sensory nerves and release transmitters that activate pain. Sant and others have obtained data to show up regulation of nerves and neurotransmitters.[52,107-112] This is to be remembered when therapy is reviewed because suppression of mast cells seems important.

NOTES:

INFLAMMATION and IC

The role of inflammation and inflammatory mediators in IC is not known. Traditionally, there has been a concept that inflammation is present in IC while this is probably not the case in most patients. Several points can be made which support the notion that inflammation plays little role in most IC patients. First, biopsy specimens show almost no inflammation. Second, no systemic signs are found (e.g. no leucocytosis).[16] And third, no inflammatory mediators are found in the urine of more than 90% of these patients.[54] Patients with IC do not suffer from other generalized inflammatory diseases such as collagen vascular diseases.[3,7] On the other hand, there may be significant interplay between mast and inflammatory cells (their mediators) which is yet to be determined in subsets of patients. Perhaps it is best to consider IC as a long-term chronic disease with gradual destruction of bladder tissue over time, so slow that minimal or no inflammation occurs.

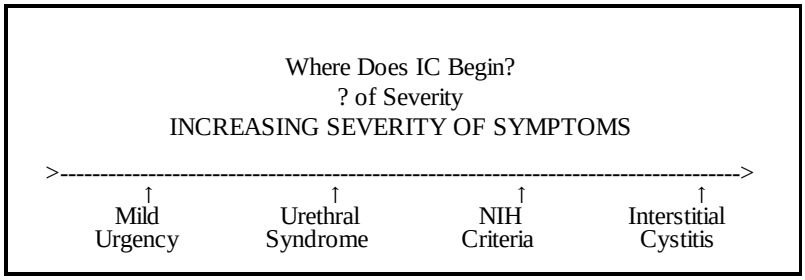
PYSCHOSOMATIC FACTORS:

It has been suggested that psychosomatic factors initiate IC, but this is rarely true. Most patients (especially those with chronic pain) are secondarily affected by their disease and as a result may show signs of mild or moderate chronic depression. Those suffering from severe nocturia will exhibit even more profound depression due to sleep deprivation. In the author's experience, essentially no one has been cured of IC by psychotherapy. Earlier researchers reported similar findings.[4] It is important to emphasize that treating depression can improve overall sense of well-being for a patient and help them cope with their disease, but it will not cure the IC or reduce the number of daily voids. It is true that acute stress will flare IC symptoms and stress reduction will improve them, but the patient still has IC. Stress factors could be physical such as viral infections, exercise, surgery, travel in a car or plane, or jobbing. They could also be emotional. It is important to the rapport between physician and patient for the physician to make it clear that IC is not a psychological disorder.

INCIDENCE - EPIDEMIOLOGY

Although IC was first identified in 1907 by Nitze, few epidemiological studies have been reported.[55] Oravisto, in a Finnish study of 103 people with IC, estimated an annual incidence of 1.2 cases per 100,000 and a prevalence of about 10-11 per 100,000.[56]

The incidence in the United States has been estimated from two sources. Held et al.[57] estimated about 44,000 cases in the U.S.; the author's estimate extrapolated from San Diego County is placed at 40-60,000. Held also estimated a worst case scenario in the U.S. at 450,000.[58] These are the traditional reported incidences of IC. However these are probably not even close to the true mark of how many individuals may have this disease. More recently Jones and Nyberg[98] reported an incidence of 500,000 to 1,000,000 people in the U.S. with IC. Consider further that it was estimated in 1966 that 4-6% of pre-menopausal females in the United States have bladder infections every year. However, this is not documented by any clinical experience or data reported in the literature. In fact, in a large study in England, of 1,000 successive patients presenting to outpatient centers for a clinical trial, 50% of the patients with signs and symptoms of urinary tract infection (urgency/frequency) had negative cultures. Their conclusions were that these patients had "the urethral syndrome" which they defined as having signs and symptoms of infection but negative cultures. It is likely that these patients have a mild form of IC which very gradually escalates over the years and when symptoms become severe enough, they are defined as having IC.



Most likely there is some type of time-line (see Figure above) for the younger patient with mild urgency/ frequency being diagnosed with bladder infections. After persistent negative cultures and symptoms, they are diagnosed perhaps with urethral syndrome. As their disease progresses and they become very symptomatic, they may reach the so-called NIH criteria for IC and ultimately develop a more advanced form of the disease in later years which we have classically called IC. In all likelihood, all patients represent the same disease process but are early or late in this time-line in terms of having mild or severe disease. Generally the disease appears to incubate slowly over the years and with progressive increase in symptomatology and decrease in bladder function as the disease takes its toll.

Demographic factors: The studies mentioned above reveal several risk factors. Sex, of course, with a female:male ratio of about 9:1[57,59-61] in all reports. Age is also a risk factor with incidence generally limited to those over 18 years of age but there are reported cases in younger people.[62-65]

Median age of diagnosis is between 40-46 in most series with disease appearing several years earlier.[57,59,66] Race and ethnicity appeared to be a risk factor occurring mostly in Caucasians,[67-69] but also reported in African-Americans.[70] Here too these numbers probably do not reflect an accurate picture since many patients with milder forms are misdiagnosed.

In a review of 300 cases at the University of California, San Diego, it was also observed that those without diabetes (no diabetes seen) seem to be at a greater risk.[66] Finally, there was a 400% increased incidence seen in Jewish people. All these findings are similar to those seen in inflammatory bowel diseases.[59,71-75] The bottom line - IC is not rare, but common, maybe as high as 1-2% of females but is misdiagnosed. Male incidence may also be grossly underestimated, with patients lost in the prostatitis or BPH diagnoses.

PATHOLOGY

One should keep in mind this concept that IC is a disease in a continuum. The 19 year-old with early disease has significant sensory nerve activation, but no real damage to the bladder. But, as the disease progresses over 10-20 years, at age 40 she may have some significant secondary changes to her bladder. For example, altered epithelial mucus, adhesion molecules, basement membrane changes, muscle loss, nerve up regulation, but no translational clinical pathology changes. consequently, routine pathologic processing of tissue yields to pathonomic changes in IC. As new methods develop to identify proteins, GAG, etc., methods may develop to aid the clinician in diagnosis. But remember, in early disease no substantial anatomic changes may be present - in early phases (perhaps represent 75% of IC patients). The physiological changes may be dramatic (e.g., epithelial leak of potassium) and functional tests of nerve function (not anatomic) may be more important in diagnosis. Various descriptions have been proposed, but unfortunately there is nothing pathognomonic of IC in bladder biopsy specimens. The mast cell controversy has already been reviewed; approximately one-third of these patients will have increased mast cell infiltration of their bladder wall and mucosa, significance unknown. Light microscopy will generally reveal a urothelium which is thinned, readily detached and nearly absent in many areas.

Unlike the normal six or seven layer thick epithelium, the mucosa is frequently only 2-4 cell layers thick. These changes are consistent with a dysfunctional epithelium.[12] A generalized pan cystitis[53,70,76,77] with infiltration of the lamina propria by mononuclear and chronic inflammatory cells is seen. However, these changes are also consistent with the effects of hydrodilation. Most physicians will biopsy after the distention and perhaps many of these changes are artifacts.

The distribution of collagen within the bladder wall is controversial.[78] One hypothesis suggests that as the disorder progresses, a fibrotic small end-stage type bladder develops. There is little or no data to support this theory. The author believes that this is untrue and instead that frequent low volume voiding coupled with possible epithelial solute leaks leads to a thinned epithelium with destruction of smooth muscle bundles and the net result is a small bladder. Furthermore the only scarring present in the bladder wall is probably iatrogenic, stemming from prior biopsies since many of these patients undergo multiple biopsies over years which causes it.[78] As the entire bladder shrinks from frequent low volume voiding, this scar tissue takes on a disproportionate and artifactually enlarged total volume of the bladder wall. In the author's experience (over 500 biopsies) scarring, in fact, is not identified when biopsies are obtained from an area of the bladder not previously biopsied. At this institution, 27 patients have had cystectomy performed for IC. Seventy per cent of these patients have only epithelium and a few blood vessels and muscle bundles left representing the urinary bladder. There is also severe wasting of perivesical fat. Perhaps the urinary solutes leak through the thin (perhaps 3-4mm) bladder wall and the perivesical fat atrophies. This may help explain the increasingly diffuse lower abdominal pain these patients experience. The medial thigh pain may represent provocation of the obturator nerves from this process.

Bladder biopsy is useless in IC since it is not diagnostic. There is no way to rule in or out this disorder by pathological examination of bladder tissue. Some of the changes as mentioned above, however, are associated with IC. While it is rare that these patients are confused with those having carcinoma in situ of the bladder, the biopsy may be necessary to rule out cancer (reviewed by Burford).[79] A combination of cytological evaluation of the urine and bladder washings plus the biopsy is necessary to exclude malignancy. In over 2,000 patients evaluated by the author, no cancers have been diagnosed at presentation but one male developed a transitional cell tumor 8 years after the initial diagnosis of IC. An additional male with suspicious cytologies at presentation after 6 months had a second bladder biopsy positive for cancer. So,

it is necessary to monitor at risk patients, males over 40, females over 45, and people with hematuria.

SIGNS and SYMPTOMS

The primary symptom of IC is the presence of abnormal sensory urgency. From sensory urgency derives urinary frequency. In addition, most patients will have associated bladder pain. One study of over 200 patients[66] showed that of patients presenting with IC, approx. 15% will have little or no bladder pain while 85% of patients present with significant pain. It is important to determine whether the pain is of bladder origin. Ask the patient if the pain (despite being constantly present) worsens if the bladder is not emptied and improves (not disappears) with voiding. Bladder pain of IC is experienced suprapubically, in the perineum, vaginally or in the low back or even medial in the thighs.[4] Two-thirds of patients do not experience dysuria.

URINARY SYMPTOMS

Symptoms reported in 225 pts including frequency distributions for symptom severity.

NOCTURIA			
	Mean	4.7	
	90% cut-off level*	1.5	(1-2 voidings)
	Range	0-13	
	1-2	41	18%
	2-4	90	40%
	4.5-8	63	28%
DAYTIME FREQUENCY			
	Mean	16.0	
	90% cut-off level	7	
	Range	5.5-40	
URGENCY			
	Mild	8	3.5%
	Moderate	63	28%
	Moderate-Severe	35	15.5%
	Severe	119	53%
PAIN			
	None	41	18%
	Mild	16	7%
	Moderate	82	36%

Nocturia is variable, but in general, 90% of patients will complain of voiding at least 1-2 times per night.[66] Nocturia increases with the severity and duration of the disease. The average patient voids approximately 16 times/day; a minimum for diagnostic purposes is considered to be 8 voids per day.[80] The average voided volume is 75 ml. Between 85-90% of individuals with IC are female. Of those who are sexually active, the majority (75%) will complain of exacerbation of the symptom complex associated with sexual intercourse.[66] The increase in symptoms may be felt during sexual activity, immediately after, or within 24 hours. In addition, most women who are still menstruating will complain of a flare of symptoms several days before the onset of the menstrual cycle.[4,66]

The median age of diagnosis of IC is between 42-46 years and at the time of presentation to the urologist with an average duration of symptoms for 3-4 years.[4,66]

EVALUATION

The physician has struggled to establish a diagnosis of IC primarily because no objective "blood test" exists. Evaluation of large numbers of patients with the urgency-frequency syndrome reveals historical and clinical findings that help establish the diagnosis.

In August 1987, a group of investigators and patients interested in IC met at the National Institutes of Health and defined the NIDDKD (National Institute of Diabetes and Digestive and Kidney Diseases) criteria to establish the diagnosis for research purposes.[80] These criteria are a practical attempt to quantitate findings in IC. In part they were based on a study reported by Parsons et al.[66] where the symptoms of over 200 IC patients were measured and analyzed. From Parsons' data each variable was examined; the point which included 90% of the patients was the number taken for the NIDDKD criteria. For example, 90% of IC patients were found to void at least 1-2 times at night, complained of 8 or more voidings during the day and had moderate urinary urgency, but the presence of bladder pain was optional. The data upon which these criteria were based are reported in the Urinary Symptoms Table on the previous page. It is important to note that these criteria were developed to provide uniform criteria for

researchers investigating IC. They were never meant to be a gold standard for diagnosis. Patients meeting this criteria have advanced disease. There are many patients with IC (perhaps most) who do not meet this criteria but have the disease and will benefit from therapy.

Changes Associated with Duration of IC

	Avg at 1 yr*	Avg at >7 yrs**
# of pts	34	42
Voidings	15.2	17.3
Voided volume (ml)	128	105
Anesthetic cap. (ml)	711	518

** Patients with 1-year symptoms*
*** Patients with >7 yrs of symptoms*

Duration of symptoms helps to define patients with IC versus those with urgency-frequency syndrome. The diagnosis of IC is more likely if the individual has had the presence of continuous symptoms for at least six months. Clinically to separate IC from the UFS is worthwhile since the UFS may need little or no therapy and the prognosis for the patient is good.

NOTES:

VOIDING LOG

The more accurate assessment of number of daily voidings and average volume is determined from a 3-day voiding log where each voiding is measured and recorded by the patient at home. From these data it was found that the average patient voids 16 times per day with a capacity of 73 cc. The voiding profile is a useful method to help establish the diagnosis of IC, and may be used subsequently to create a therapeutic plan and to determine progress in therapy. It is recommended that the clinician obtain one initially and at subsequent visits. As might be anticipated, patients with a longer disease history have a smaller functional bladder capacity as reflected in the average voided volume and number of daily voidings (see Table below).

PHYSICAL EXAMINATION

There is one important part of the examination that helps confirm the diagnosis of IC. On physical examination, over 95% of patients will complain of a tender bladder base during the pelvic examination. This discomfort is easily demonstrated by palpation of the anterior vaginal wall.

Urine analysis on

VOIDING PROFILES OF 145 PTS WITH IC

	# of Voidings*	Voided Vol (ml)	Nocturia
Average	16.4	73	4.7
90% confidence limit **	9	125	
Range	6-39	26-235	

** Per day*
*** 90% of subjects had at least this level*

VOIDING PROFILES OF 48 NORMALS

	# of Voidings*	Voided Vol (ml)
Average	6.5	270
90% confidence limit **	7**	150***
Range	3-13	100-600

** Per day*
*** 90% of subjects had at least this level*
**** 90% of patients above this level*

voided specimens is not useful in these patients since their low voided volumes make midstream collection impossible. One sees only vaginal secretions unless a catheterized specimen is obtained. A catheterized specimen examined under the microscope should show no bacteria, and most will show no red or white blood cells. Urine should be sent for cytological evaluation to rule out the possibility of carcinoma but in actuality, there has never been a positive cytology at our center, but perhaps this is because the patients are usually seen first by other urologists. Patients presenting with hematuria are rare, and when present require a full GU work-up to exclude malignancy.

URODYNAMICS

The cystometrogram (CMG) is a valuable study to perform in patients with this syndrome since a normal study essentially excludes the diagnosis of IC. Recent published data by the NIH ICDB Study Group demonstrated that the urodynamics could be substituted for cystoscopy in diagnosis.[101] This study helps substantially to both include and exclude patients in diagnosing IC. Together with the voiding log, the potassium test is quite helpful in diagnosing IC. Since all patients complain of significant urinary urgency, this can usually be documented with cystometry. If gas is employed, they will have a sensation of significant urgency at less than 125 cc and with water <150 ml. If this portion of the CMG is normal, they may not have IC or only a mild form. In 75 patients with cystometrograms reported by Parsons,[66] the average bladder capacity was 220 cc with over 90% of patients having a functional volume of less than 350 cc. Patients should have the bladder discomfort they experience provoked by the CMG. However, there is an important caveat relative to maximum bladder capacity. A small group of patients with significant IC will develop detrusor myopathy (about 5%).[66,81] Individuals with this complication will have large atonic bladders with little muscle present. They have moderate to severe sensory urgency, large bladder capacities (>1000 cc), and usually carry residual urines (>100 cc). Detrusor function is poor or absent. In fact, many patients with IC have poor muscle function in their bladder and empty only with difficulty. Since most of the patients are females, they are able to void but primarily with a valsalva maneuver. This subgroup represents approximately 5% of patients with IC.[66] Males with detrusor myopathy may require a program of intermittent catheterization (ICP) as part of their treatment. In fact, due to the generalized atrophy of bladder muscle with this disease, males with low voiding pressure may require ICP.

CYSTOSCOPIC EVALUATION

Cystoscopic evaluation of the bladder under anesthesia is primarily important as a therapeutic maneuver. It is not necessary for diagnosis[101] unless cancer is suspected (e.g. hematuria, older male). Examination under local anesthesia is to be discouraged since it offers little help in diagnosis and causes the patient severe discomfort, but may be used when ruling out cancer is the primary reason for the procedure. It is recommended that when a cystoscopy is to be performed for therapy, that it be done under anesthesia. Not all patients need cystoscopy. In fact, most patients do not need this unless severe symptoms are present. It is best to omit cystoscopy on milder patients and proceed with other therapies listed below.

The cystoscopy under anesthesia is performed in a manner to both diagnose and treat. The diagnosis depends on discovering one of two findings, a Hunner's ulcer or the presence of glomerulations or petechial hemorrhages. However, not all patients show these changes, so there absence does not exclude the diagnosis.

POTASSIUM TEST

A simple method has been devised by Parsons (the Parsons Test) to measure epithelial permeability. The test is based on the hypothesis that if a solution of KCl is placed into a normal bladder, it provokes no symptoms of urgency or pain. On the other hand, if placed into

a bladder which has an impaired mechanism to maintain the impermeable epithelium, the potassium diffuses across the transitional cells to stimulate sensory nerves and cause urgency or pain. (See attached POTASSIUM PROTOCOL)

Use of Potassium Sensitivity Test as a Guide to Therapy

Potassium positive patients respond best to:*
- -dilation
- -DMSO
- -heparin
- -pentosanpolysulfate
- -polycitrate

Potassium negative patients respond best to:
- -antidepressants
- -possibly pentosanpolysulfate

**add hydroxyzine if allergies are present*

CYSTOSCOPY

The report by Bumpus in 1930 of bladder hydrodistention improving the symptoms of IC, has resulted in this procedure being a mainstay of therapy.[82] Few would question the activity of hydrodistention in ameliorating the symptoms in 60% of IC patients. The procedure must be performed under anesthesia since it is not possible to dilate a painful bladder without anesthesia. The procedure for hydrodistention has been described under diagnosis. Pressure dilatation of the bladder using a syringe should not be done since it can result in bladder rupture; a maximum of 80-100 cm H_2O pressure is recommended.

The cystoscopy should be performed in two phases. Phase one is the initial inspection. Here the physician should obtain specimens for cytology and urine for regular and tuberculosis culture (optional since almost never diagnosed). Visual examination of the bladder may reveal a true Hunner's ulcer (patch). The patch is a velvety red patch present in only 6-8% of patients[66] and is very similar in appearance to carcinoma in-situ. However, it is not actually a true ulcer, only a red patch. Do not biopsy at this part of the cystoscopy. Prior biopsy site scars which are frequently mistaken for ulcers may also be seen.[78] Bladders with IC appear to heal poorly, and biopsy scars are frequently large but are recognized by the spoke wheel blood vessels that radiate from the central scarred portion. These scars frequently tear and bleed after distention and account for most so-called epithelial disruptions. Parsons reported as many as 75% of ulcers described at previous cystoscopy by other urologists to actually be biopsy site scars.[66]

The second phase of the cystoscopic procedure is the hydrodistention to demonstrate glomerulations. Hydrodistention will also induce a disease remission in 60% of patients. Hydrodistention is performed by filling the bladder slowly up to 80-100 cm of water pressure maximum. The urethra of the female should be manually compressed over the cystoscope to prevent leakage of fluid. After several minutes, the bladder is emptied, the volume measured and recorded. The last part of the effluent is usually bloody if glomerulations or ulcers are present. When the bladder is re-examined the glomerulations should be demonstrated. They are diffusely located around the bladder, at least 10-20 per field of vision. Hemorrhages on the trigone or posterior bladder wall are irrelevant and do not constitute a positive finding since they probably represent cystoscope trauma.

What constitutes an abnormal bladder capacity under anesthesia may be surprising to many physicians. A normal female bladder holds well over 1000 ml while the IC bladder usually holds less than 850 ml. The average anesthetic capacity for IC patients is between 550-650 ml. Patients with a longer history of symptoms have smaller bladder capacities suggesting the disease is slowly progressive.[66] This is also supported by the fact that patients with Hunner's ulcers have the worst symptoms and also have the smallest bladder capacities and the greatest problem with loss of epithelial impermeability.[12,66]

The mechanism by which hydrodistention improves symptoms is unknown; several theories have been postulated. Neuropraxis induced by mechanical trauma may occur in some individuals. However, few patients awaken with decreased pain which would support the

neuropraxis concept. Rather, most (90%) awaken from anesthesia with significantly worse pain that slowly improves over 2-3 weeks. This pain usually requires narcotic analgesia. Remission will occur over several weeks.

As a result of the increased pain, it is recommended that all patients receive belladonna and opium rectal suppositories immediately in the recovery room or better yet, instill 10 ml of 2% viscous xylocaine into the bladder at the end of hydrodistention. In addition, they should be discharged with medication (narcotic) to control the increased pain.

Since most patient's symptoms are exacerbated by hydrodistention, we believe that this is due to epithelial damage from the mechanical trauma. The disruption in the integrity of the mucosal cells increases the epithelial leak, causing symptoms to flare. Healing may occur over the next several weeks which correlates with the time of clinical remission. Perhaps the epithelium regenerates and for a period of time is "healthy" and impermeable. Then, whatever events initiate the disease continue and relapse occurs.

Remission may persist between 4-12 months, hydrodistention may be repeated as needed. If no remission is obtained, repeat the dilation at least two more times since frequently in our experience patients respond to a subsequent dilation.

BIOPSY

The last part of the cystoscopic procedure should be the biopsy. One should never biopsy before hydrodistention since the bladder could tear at the biopsy site and may lead to a significant bladder rupture. If one is employing a caustic agent for therapy, never biopsy before the solution is placed in the bladder. Should the solution extravasate through the biopsy site, severe tissue damage may occur.

The biopsy itself is not diagnostic for IC but can rule out other diseases such as carcinoma in-situ. The findings on pathologic examination include the presence of mast cells (demonstrated by toluidine blue staining),[52,53] inflammatory cells and a thinned mucosa. A normal biopsy does not exclude IC and should not be so utilized in diagnosis. Conversely, no pathologic findings specifically make a diagnosis of IC.

While diagnosis of IC depends in part on abnormal cystoscopic findings, one cannot arbitrarily rule out the disease purely by the endoscopic findings. There are many patients who have IC without such findings who will benefit from therapy. The physician needs to remember this disease complex is still primarily manifested by significant urinary urgency or frequency and perhaps few or no other findings.

At the end of the cystoscopy, place 10 ml of 2% viscous xylocaine jelly into the bladder. This aids in pain control during the anesthesia recovery period.

THERAPY

Therapy is continuing to evolve for IC with better and better treatments emerging. The most important considerations are multiple therapies (polytherapy) and time. There are a number of drugs that have been employed for treatment of IC. Most have been used empirically and only a few have been tested in controlled trials. Basically therapy for IC can be divided into three major categories:

1) Drugs that alter nerve function directly or indirectly such as narcotics, anti-depressants, antihistamines, anti-inflammatories, anticholinergics, antispasmodics, analgesics.

2) Cytodestructive techniques. These methods destroy the umbrella cells of the bladder which cause a regeneration, a new bladder surface and a period of remission. In general, they cause symptoms to flare substantially before the repair process is completed and symptoms resolve. These techniques include DMSO, hydrodistention, chlorpactin, silver nitrate and more recently BCG.

3) Cytoprotective techniques. There are medications, primarily polysaccharides, which

can "coat" the bladder and help re-establish or protect the bladder surface mucus. These include heparin, pentosanpolysulfate and possibly hyaluronic acid.

When discussing therapy with the individual patient, it is important for the physician to emphasize to the patient that if the symptoms have been present for more than a year, no particular therapy is likely to be curative. In this case, this is a chronic disease which requires chronic therapy. While he or she may have a significant remission of symptoms, in all probability, relapse will occur. If patients are prepared for this eventuality, they are much less distressed when symptoms return and cope better with their disease. The physician-patient relationship is strengthened in terms of credibility if this area is addressed prior to initiating treatment. Patients readily accept this explanation and overall appear to adjust to their disorder when their outlook is realistic and persist with their treatment regimen, otherwise many stop therapy too quickly even though they would benefit.

THERAPY RECOMMENDATIONS

Mild Patients:
DMSO for 3 months may induce long remission.•
If unsuccessful, try heparin.

Moderate-Severe Patients:
Elavil, Elmiron and/or daily intravesical heparin.
(When improved, slowly taper off heparin).•°

Severe Patients:
Daily intravesical heparin, Elavil, Elmiron.•°

• *add hydroxyzine if food or pollen allergies*
° *add polycitrate*

ANTIDEPRESSANT THERAPY

Chronic pain and sleep loss cause depression. Thus, it is valuable to place most IC patients with moderate or worse symptoms on antidepressant medications. Tricyclic antidepressants have several modes of action that are beneficial. They have side effects of drowsiness (aids sleep), increased pain thresholds and elevation of mood. If tricyclic anti-depressants are used, start with low doses and warn patients they will be tired (for 12-15 hours per day) for the first 2-3 weeks of therapy. Once they become tolerant to this side effect, increase dose, if needed. Amitriptyline[84], or imipramine can be prescribed in doses of 25 mg (or even 10 mg) one hour before bedtime.

In an uncontrolled trial, amitriptyline was reported by Hanno et al.[84] to ameliorate the symptoms of IC. Patients were treated with 25 mg of amitriptyline one hour before bedtime for one week; the dose was then increased weekly by 25 mg to 75 mg. Fifty per cent of patients responded to this medication.

The exact mechanism of action of amitriptyline is unknown, although it may block H_1 histamine receptors and perhaps mast cell degranulation. More likely the drug raises pain tolerance due to its antidepressant activity.

If fluoxetine (Prozac®) is selected, use 20 mg per day and increase if needed to 40 mg. Sertraline (Zoloft®) is another well- tolerated antidepressant. It can be used at 50 mg per day and increased to 100 mg if needed.

Antidepressant therapy is an important adjunct to treatment. It does not cure IC, but patients function much better with their disabling symptoms if not depressed. In essence, they "feel better" even if they still void 20 times per day.

Surprisingly, many patients (about 25-30%) improve dramatically only with antidepressant therapy. No matter what other therapy has been initiated we place all moderately (or worse) symptomatic patients on anti-depressants and remove them if they improve and are being successfully managed with some other treatment (e.g., heparin or pentosanpolysulfate).

NOTES:

DIMETHYLSULFOXIDE

Dimethylsulfoxide (DMSO) was approved for use in IC in 1977 based on uncontrolled trials.[83] Morales did one small controlled clinical trial with DMSO, and it does appear to induce remission in 34-40% of the patients. The difficulty with DMSO is that it may induce an excellent remission in the first one to three cycles of therapy, but as an individual relapses and requires subsequent treatment, progressive resistance to its beneficial effects is seen in almost all patients for reasons unknown.

For treatment, instill 50 cc of 50% dimethylsulfoxide into the bladder for 5-10 minutes. Longer periods are unnecessary since DMSO rapidly absorbs into the bloodstream. Instillations are performed on an out-patient basis or the patient can be taught to perform it themselves. The author recommends that patients receive 6-8 weekly treatments to determine whether a therapeutic response is achieved. If the patient has moderate or worse symptoms, continue the therapy for an additional 4-6 months once every other week. Remember, once you stop DMSO therapy, the patient is likely to become resistant to its use. Some patients will experience a flare of symptoms when DMSO is placed into the bladder. This phenomenon may be related to DMSO's ability to degranulate mast cells and may occur primarily in patients who have significant bladder mastocytosis. Nonetheless, DMSO may be very effective at treating these patients. Should the patient experience pain with DMSO, it is recommended that he or she receive intravesically 10 ml. of 2% viscous xylocaine jelly 15 minutes before placing DMSO. If this is not successful, then use an injectable narcotic or Toradol® 60 mgm IM before the intravesical instillation. The flare of symptoms associated with DMSO usually disappears over 24 hours. As these patients receive subsequent treatments, the pain tends to diminish.

Patients may also receive indefinite therapy using DMSO. As originally reported by Stewart,[83] patients have used DMSO weekly for several years without problems. DMSO has been reported to be associated with cataracts in animals, however this complication has not been reported in humans. Therefore, if your patient is on chronic therapy, it is recommended that he or she have a slit lamp evaluation at 3-6 month intervals.

ANTIHISTAMINES

Antihistamines are critical to managing IC in people with hay fever, sinusitis or food allergies. Patients in good control of their symptoms will breakthrough in allergy season. Antihistamines have been tried in IC but without controlled studies. Antihistamines were chosen because of the possible role of mast cells.[53,70,85,86] While most patients may not respond to antihistamines, subsets of patients seem to have major benefit, especially when combined with other therapy. Allergic people in particular will benefit from hydroxyzine 25-50 mgm H-S.[87] This is an extremely effective way to manage allergies when the medication is used chronically. Beneficial effects appear 2-3 months after start of treatment and patients are urged to stay on medication for at least 3 months to determine effectiveness.

STEROIDS

Because of the assumption that inflammation plays a role in this disorder, patients have received steroids. Badenoch[88] found significant improvement in 19 of 25 patients treated with prednisone. However, all were treated following hydrodistention under anesthesia which may have been responsible for most of the benefit. In the author's experience, steroids do not ameliorate the symptoms of this complex. As with most drugs, there have been no controlled clinical trials conducted on the efficacy of steroids in the treatment of IC.

INTRAVESICAL SILVER NITRATE

Intravesical silver nitrate was first reported in 1926 by Dodson.[89] Pool[67] fashioned a treatment regimen in which bladder irrigations were begun under anesthesia with 1:5,000 concentration. This was followed subsequently by gradually increasing the concentrations on a daily basis, ultimately employing a 1% solution. Again, this was done in an uncontrolled setting on patients who had had dilatation of the bladder under anesthesia. Pool reported good results in 89% of patients. There have been other uncontrolled studies reporting that this compound is helpful; nevertheless, it is not very widely used today. One caution in the use of silver nitrate: never instill into the bladder after biopsy. If there is a perforation and this solution is placed into the bladder, intra- and extraperitoneal extravasation could occur resulting in major tissue damage.

NOTES:

INTRAVESICAL SODIUM OXYCHLOROSENE (Clorpactin WCS-90®)

Clorpactin is a highly reactive chemical compound that is a modified derivative of hypochlorous acid in a buffered base. Its activity is dependent on the liberation of hypochlorous acid and its resulting oxidizing effects and detergency.[90] It was reported by Wishard who treated 20 patients with 5 weekly instillations of 0.2% clorpactin WCS-90 under local anesthesia. Improvement was reported in 14 of the 20 patients, and follow-up was brief. Messing and Stamey, treating 38 patients with 0.4% Clorpactin, reported significant improvement in 72%. Ureteral reflux is a contraindication to the use of Clorpactin. It is recommended that the compound usually be used under anesthesia.

URINARY ALKALINIZERS

Polycitrate is a dilation agent that not only alkalinizes the urine, but also binds potassium. Both effects may be beneficial in IC and it is recommended that patients receive a trial of therapy for 3-6 months. Employing 2 doses a day of medication appears to be sufficient. In general, this drug should be combined with other treatments such as heparin, Elmiron or Elavil to obtain the best effect. The best tolerated salt of polycitrate is potassium, not to worry about this small amount of potassium. When polycitrate is absorbed and excreted in the urine, here it will help chelate potassium so the original salt is not a problem for the bladder.

BCG THERAPY

In a recent study on employing BCG therapy for IC, efficacy was demonstrated. BCG causes intense desquamation of the mucosa and theoretically should be active. Its desquamating ability puts it into the class of cytodestructive techniques, similar to DMSO and dilation. Because of its infectious side-effects, it is recommended DMSO be employed first and BCG therapy used later.

L. ARGININE

Smith and associates reported the use of L. Arginine for patients with IC. It was used in a limited open phase study and its true activity is unknown. But it is non-toxic it can certainly be tried.

HEPARINOID THERAPY

A major breakthrough in therapy is the use of heparin-like drugs (heparin, PPS-Elmiron®) which, when effective, reverse the course of the disease. Patients rarely become resistant to their use.

HEPARINOID THERAPY

DRUG	DOSE	ROUTE
Heparin	20-40,000 units daily	Intravesical and self-administered
Pentosanpolysulfate*	100-200 mg TID	Oral

NOTE: Drugs work best after 6-12 months of chronic use.
** Males and severe females should receive 200 mg TID*

HEPARIN

Heparin, when given by injection, has been reported to alleviate the symptoms of IC.[91] Again this was not in a controlled study. Chronic systemic heparin therapy cannot be employed in most individuals since it results in osteoporosis in 100% of patients who use it for 26 weeks. In our experience, intravesical heparin has significant activity in approximately 50% of patients.[92] Here too the data were obtained in an uncontrolled investigation.

Previous controlled studies by the author demonstrated a placebo effect of approximately 20% suggesting possible activity for heparin.[48] The technique uses 20,000 units of heparin in 20 cc of saline, and this solution is instilled intravesically initially daily, then after 3-4 months reduce to 3-4 times per week. If there is no effect after 3 months, increase to daily instillation of 40,000 units. This treatment can be carried on indefinitely. It takes 2-4 months to begin to see improvements but encourage therapy and urge for at least 6 months before abandoning it. The best improvements are noted after 1-2 years. Long-term therapy is recommended for patients with moderate or worse disease who respond to its use. Serum PT and PTT are monitored for several weeks after therapy begins to rule out the formation of an unusual antibody to heparin or systemic absorption (heparin should not be absorbed across the bladder mucosa). Patients are instructed in self-catheterization so this therapy can be performed at home.

PENTOSANPOLYSULFATE

Parsons et al.[48,49] first reported pentosanpolysulfate as active at ameliorating the symptoms of IC. Since pentosanpolysulfate (Elmiron®) is a sulfated polysaccharide, theoretically it may augment the bladder surface defense mechanism or detoxify in urine agents which have a capacity to attack the bladder surface, e.g., quaternary amines.

In a controlled clinical study 42% of patients were shown to have their symptoms controlled versus 20% for placebo.[48] This has been borne out in several subsequent studies including a 5-center trial where 28% of patients versus 13% on placebo improved[49] and in a 7-center study of 150 patients there was a 32% patient improvement on drug versus 15% on placebo.[93]

Additionally, an English-Danish study also found a significant reduction of pain in patients on drug compared to placebo.[18] It is employed in an oral dose of 100 mg three times per day. In patients with moderate disease, it appears to have about 40-50% activity. In the controlled clinical trials which were done on patients with severe disease, its activity was lower. Continued use of Elmiron® for several years leads to long-term disease control in most of the

drug responders.[113] and an efficacy rate of up to 74% was reported when used for 6 months or longer. This has not been previously found in any other therapy except Heparin. Response to therapy is first seen after 6-10 weeks, but may take 6-12 months to work.

Male and female patients with more severe disease may need 200 mg TID to control their disease. It takes 3-12 months to get a good response and so the medication should be used at least 9-12 months before abandoning its use. We currently see about a 60% efficacy rate when using it longer and at a bigger dose. The primary side effects are GI and can frequently be reduced by taking the medication with a small snack or taking it out of the capsule and dissolving it in one ounce of water. Hair loss is reported in about 3-4% of people, but it is completely reversible even when continuing to take the medication.

NOTES:

SURGERY

Approximately 2% of patients presenting with IC to the University of California, San Diego Medical Center have ultimately undergone some type of surgery for disease that is severe and refractory to all treatment. The question is the type of surgery to be performed.

CYSTOLYSIS

Attempts at surgical ablation of the bladder innervation by cystolysis are to be discouraged since most patients will fail this and develop a neurogenic bladder with significant urinary pain, frequency and perhaps require intermittent catheterization.

BLADDER AUGMENTATION

A concept exists that these patients have small bladders and thus, void frequently. Actually the reverse is true. They have sensory urgency, void frequently and subsequently develop a small bladder. Hence, attempts to augment the bladder with a patch of bowel are likely to fail. Patients will then have a capacity that is perhaps large, have more difficulty emptying (usually requiring intermittent catheterization), but still retain all their sensory urgency and pain.[94]

URINARY DIVERSION ALONE

There are no controlled studies evaluating diversion alone, but studies suggest it is not effective.[95] However the author has taken out two bladders in patients who had urinary diversions alone with persistent pelvic pain. The pain was eliminated by removal of the bladder. In counseling, one should tell patients that diversion alone may not be sufficient to control their pain and they may subsequently require a cystectomy. The patient can then decide whether or not they want a risk of more than one surgery. It is the author's experience that almost no one elects for the potential of two surgeries.

CYSTECTOMY and DIVERSION

This is the mainstay of therapy for patients with "end-stage bladder". It is successful,

especially in today's environment of performing continent diversions. Pelvic pain will present after the procedure in 5% of patients. In general, if the patients have classic bladder pain associated with filling and relieved or partially relieved by emptying and have urinary frequency and urgency and the usual stigmata of IC under anesthesia, they are likely to have relief of their symptoms by cystectomy. Those individuals with severe pelvic pain, not associated with classic parameters of IC and particularly not exacerbated by bladder filling, will be unlikely to have their pain alleviated.

When continent diversion is performed 20-30% of patients will develop pouch pain 6-36 months after surgery. This can be managed successfully by having the patient instill 10,000 units of heparin in 10 ml water into the pouch after each catheterization.

BLADDER TRAINING

Whatever therapy is successful at alleviating the pain and sensory urgency of IC, the individual afflicted with the chronic form of the disorder will have a small capacity bladder that is in part based on sensory urgency and in part on frequent low volume voiding. In controlled clinical trials, it has been reported that even with good remission of pain and urgency, there is almost no change in urinary frequency over a 12-week period.[48,49,93] This issue must be addressed in order to obtain a functional recovery of the bladder.

Persistent urinary frequency from a small bladder can be reversed after therapy has controlled urgency and pain. This is accomplished by training the patients to undergo a program of progressively holding their urine to increase their bladder capacity.[96] This therapy can be directed by a urological nurse. To begin this treatment, obtain a 3-day voiding profile from the patient (to include time of voiding and a measurement of volume). Determine the average time interval between voids, and gradually increase this interval monthly. For example, if the patient voids every hour, it is recommended that he or she attempt to void every hour and a quarter and at the end of one month increase that to an hour and a half.

The patient should never progress too quickly because they will become discouraged and quit. It takes 3-5 months of this protocol to see results. At the end of 3-4 months, the bladder capacity will increase approximately 2½ times and there will be a corresponding reduction in urgency and the number of voids per day.

We also discovered that in patients who have minimal or no pain associated with their urinary frequency, bladder training may be the only therapy required to improve them and in fact the only therapy that is effective. For more details concerning the employment of this protocol, the reader is referred elsewhere.[96]

In summary, IC is a syndrome in a state of rapid change in regard to the understanding of the pathogenesis and the development of therapy due to a significant increase in research activity. These investigations will help the clinician quantitate the symptoms and clinical findings to better diagnose the syndrome and will simultaneously lead to new therapies which will result in symptom reduction (hydrodistention, DMSO, Elmiron®, or heparin). In addition, bladder training methods can further rehabilitate the patient with the IC bladder. As reviewed herein, perhaps 75-85% of patients with moderate to severe IC can experience significant indefinite remissions with conservative therapy and avoid the need for extirpative surgery.

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POTASSIUM PROTOCOL

A simple method has been devised by Parsons (the Parsons Test) to measure epithelial permeability. The test is based on the hypothesis that if one places a solution of KCl into a normal bladder, it provokes no symptoms of urgency or pain. On the other hand, if placed into a bladder which has an impaired mechanism to maintain the impermeable epithelium, then the potassium diffuses across the transitional cells to stimulate sensory nerves and cause urgency or pain.

To perform the test, 2 syringes labeled solution 1 and solution 2 are prepared with 40cc in each. The amount used is only 40cc to reduce stimulation due to volume. Solution 1 is sterile water and solution 2 is made by adding KCl to sterile water at a 400 mEq/L or 40 mEq per 100cc ratio. Catheterize the patient preferably with a small lumen catheter. Instill solution 1. Then after 5 minutes ask the patient to rate any increase or decrease in pain and urgency. Drain the bladder completely. Then instill solution 2. After 5 minutes have the patient rate any change in pain and/or urgency. Use the scale below to rate the changes. In severe cases of interstitial cystitis the patient may not be able to hold solution 2 for the full 5 minutes. If the patient does not respond to solution 1 and states solution 2 caused their pain and/or urgency to increase by 2 or more points on the scale, this is considered a positive test. In a recent study, 70% of IC patients had provocation of symptoms while only 4% of the normal group responded. This test is useful in detecting those patients who may have a defective mucous layer in their bladder.

NOTE: In the past few years, we have noticed that there are a group of IC patients who have a mucous epithelial layer dysfunction, but do not respond to the KCl. These patients typically had undergone hydrodistention or DMSO treatments within the past 6 months. The tip off was the difference in the perception of coldness during the instillation. Both solutions are kept at room temperature. The patients with mucous epithelial layer dysfunction felt a colder sensation with the KCl than with the H_2O. These are usually patients with mild to moderate disease.

GRADING SCALE FOR SYMPTOMS

```
          None       Mild              Moderate             Severe
PAIN       |__________|__________|__________|__________|__________|

          None       Mild              Moderate             Severe
URGENCY    |__________|__________|__________|__________|__________|
```

Questions:

1. Which solution is worse? ___Solution 1 ___Solution 2 ___Neither

2. Is the difference between solutions: ___None ___Mild ___ Moderate ___Severe

NOTE: Each subject was told to consider their symptoms at the start as baseline of 0. When a solution was added, they were asked if it provoked symptoms (pain or urgency) on a scale of 0-5.

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PERMEABILITY STUDY

Name:_____ UCSD Unit #:_____
Date:_____ Age:_____ IC_____ NL_____

URGENCY today: 0 1 2 3 4 5 **PAIN today**: 0 1 2 3 4 5

Drug therapy or treatment received today:_____

SOLUTION A:

Coldness: Mild Moderate Severe

1. How much urgency to urinate do you have now compared to before the solution was placed? (Choose from -5 to 5)

less				no change					severe		ONSET Grad	Immed
-5	-4	-3	-2	-1	0	1	2	3	4	5	☐	☐

2. How much pain in the bladder do you have now compared to before the solution was placed? (Choose from -5 to 5)

less				no change					severe		ONSET Grad	Immed
-5	-4	-3	-2	-1	0	1	2	3	4	5	☐	☐

SOLUTION B:

Coldness: Mild Moderate Severe

1. How much urgency to urinate do you have now compared to before the solution was placed? (Choose from -5 to 5)

less				no change					severe		ONSET Grad	Immed
-5	-4	-3	-2	-1	0	1	2	3	4	5	☐	☐

2. How much pain in the bladder do you have now compared to before the solution was placed? (Choose from -5 to 5)

less				no change					severe		ONSET Grad	Immed
-5	-4	-3	-2	-1	0	1	2	3	4	5	☐	☐

Which solution felt worse? _____A _____B or _____Neither
Is A or B: Mild Moderate Severe

Pre-volume:_____ Post-volume:_____ KCl in:_____ KCl out:_____