REVIEW

The role of the bladder surface in interstitial cystitis/painful bladder syndrome

Joel M. H. Teichman, MD,[1] Robert Moldwin, MD[2]

[1]Division of Urology, St. Paul's Hospital, Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada
[2]Pelvic Pain Center, The Arthur Smith Institute for Urology, Long Island Jewish Medical Center, New Hyde Park, New York, USA

TEICHMAN JMH, MOLDWIN R. The role of the bladder surface in interstitial cystitis/painful bladder syndrome. The Canadian Journal of Urology. 2007;14(4):3599-3607.

Introduction: *Interstitial cystitis (IC) is a potentially severe and debilitating condition of the bladder. Numerous factors have been implicated in its pathogenesis.*
Materials and methods: *A literature review was conducted on the following topics: urothelium, mucosal lining, interstitial cystitis, bladder, and glycosaminoglycans.*
Results: *A commonly proposed cause for IC is a defect or alteration in the bladder surface leading to increased permeability to noxious urinary solutes and ultimately to tissue inflammation and neurogenic upregulation. Support for this concept is drawn from studies of the structure, function, and composition of the bladder surface. The cause(s) of this alteration is not known, although recent research has implicated changes in the levels of growth factors and/or compounds that protect against irritants and potentially "toxic" factors. The etiology of IC is likely multifactorial.*
Conclusions: *Alterations of the bladder surface are observed in IC, and may play an important role in the etiology of this condition.*

Key Words: interstitial cystitis, bladder, urothelium, mucosal lining, glycosaminoglycan

Introduction

Interstitial cystitis (IC) is a potentially severe and debilitating bladder disorder that is characterized by the symptoms of pelvic pain; urinary urgency and frequency; nocturia; and, frequently, dyspareunia.[1] In one of the earliest reports of IC, in 1836, Joseph Parrish described the condition as *tic doloureux* of the bladder.[2] Later, in 1907, Nitze was probably the first to codify the symptomatic features of IC and named it cystitis parenchymatosa.[3] Hunner popularized the concept in 1914, calling it the 'elusive ulcer.'[4] Increasing awareness of IC in recent years has led to more frequent diagnosis of this condition.[5,6] Also, the nomenclature has evolved to include painful bladder syndrome (PBS) along with IC—IC/PBS—to describe the condition.[7-9]

The pathogenesis of IC/PBS is likely multifactorial.[3,10-12] Causal factors that have been suggested include increased permeability of the bladder epithelium to noxious urinary substances, neurogenic upregulation, mast cell activation, autoimmune disorders, ischemia, chronic infection, and decreased levels of urinary growth factor.[3,10-12] These factors may be interrelated. One theory regarding the pathogenesis of IC/PBS that has gained considerable acceptance is that defects in the mucosal lining of the bladder epithelium lead to abnormally

Accepted for publication July 2007

Acknowledgement
Dr. Teichman has served as a consultant for Ortho-McNeil Pharmaceutical and Urigen. Dr. Moldwin is a member of the speakers bureau for Ortho-McNeil Pharmaceutical.
This publication is supported by Ortho-McNeil Janssen Scientific Affairs, LLC.

Address correspondence to Dr. Joel M. H. Teichman, Division of Urology, St. Paul's Hospital, 1081 Burrard Street, #C307 - Burrard Building, Vancouver, BC V6Z 1Y6 Canada

enhanced permeability.[10] Although the concept of enhanced bladder permeability in IC/PBS is not without controversy, consistent evidence suggests that increased permeability, or bladder urothelial dysfunction, is a feature of IC, and may initiate the cascade of events that produce the typical symptoms of IC/PBS.[13,14]

Normal bladder epithelium

Urothelial structure

The bladder is lined with a transitional cell epithelium that is highly impermeable to water and solutes (other than active transport of necessary substances), and serves to maintain the composition of urine during bladder filling.[15] The normal bladder urothelium is three to seven cells thick, and consists of three distinct cell layers: a basal cell layer that is mitotically active, one or more intermediate cell layers, and a superficial layer of terminally differentiated "umbrella cells."[15-17]

The umbrella cells are large, polygonal, multinucleate cells that are interconnected with tight junctions.[15] Specialized apical membranes allow the bladder to stretch during filling and then contract upon emptying. The outer luminal leaflet of the umbrella cells contains plaques of proteins called uroplakins, interspersed with hingelike regions that form ridges on the surface of the bladder epithelium.[15] It is thought that these hinges flatten out as the bladder fills, and then submembrane vesicles containing uroplakins fuse with the apical membrane, further expanding the bladder surface area. After the bladder empties, the hinges refold and endocytosis removes excess membrane from the apical region.[15]

Permeability barrier function

Movement of substances between the urine and plasma compartments is restricted by tight junctions between the umbrella cells of the bladder epithelium that, along with ion pumps, play an important role in decreasing epithelial permeability.[15] Tight junctions are composed of a complex protein scaffold linking adjoining cell membranes with the intracellular cytoskeleton. Transmembrane proteins include the tetraspan proteins occludin and members of the claudin family, which are responsible for the unique ion selectivity and permeability in different tissues.[18,19] The cytoplasmic protein zonula occludens-1 (ZO-1) link the junction with the actin cytoskeleton. In mammalian bladder epithelium, actin and ZO-1 colocalize at the apicolateral boundary around the periphery of the umbrella cells, demonstrating the presence of tight junctions in this area.[18] Bladder epithelium tight junctions also contain claudins-4, -8, and -12, which may confer the high-resistance and low permeability properties of this tissue.[18]

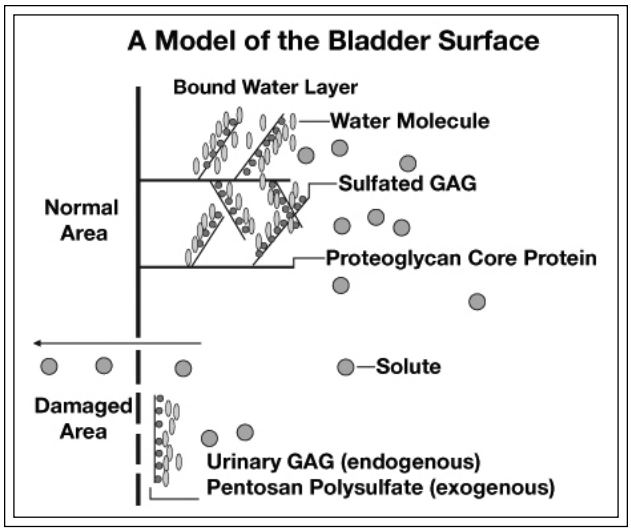

Figure 1. Schematic of the bladder urothelium. GAG = glycosaminoglycan. (Reproduced, with permission, from Hurst RE. Structure, function, and pathology of proteoglycans and glycosaminoglycans in the urinary tract. *World J Urol* 1994;12(1):3-10. ©Springer-Verlag 1994.)

In addition to the permeability barrier established by apical cell tight junctions, the mucous layer covering the surface of the epithelium also plays a role in maintaining the impermeability of the bladder epithelium.[20-23] In the bladder mucosal lining, highly anionic glycosaminoglycans (GAGs) with a marked avidity for water are present at high densities.[20,21] These GAGs are likely produced by the bladder urothelium itself,[24] but there is also evidence to suggest that GAGs may be produced from cells lining the renal tubule and other locations along the urinary tract, as well as in the glomeruli.[25] The GAGs bind tightly to water, creating a mucous biofilm that essentially functions as an impermeable barrier to solutes, Figure 1.[20,21,26]

Structure and composition of the bladder mucosal lining

Ultrastructural and biochemical studies have shown the presence of a bladder mucosal lining composed of GAGs, proteoglycans, and glycoproteins.[21,22,27,28] Table 1 shows the GAG composition of normal bladders taken at autopsy from patients less than 40 years of age.[29] The composition of GAGs in the mucosal layer changes with age and hormone status.[25,30,31] In the bladder mucosal lining, GAGs are linked to core proteins that, in turn,

TABLE 1. **Glycosaminoglycan composition of normal bladder**

	Epithelium/ submucosa	Muscle	Full thickness bladder
Hyaluronic acid, %	32.4 ± 3.2	16.9 ± 6.8	22.6 ± 14.5
Heparan sulfate, %	14.2 ± 3.6	35.4 ± 5.5	32.8 ± 6.8
Dermatan sulfate, %	46.0 ± 3.9	38.7 ± 2.4	36.1 ± 1.2
Chondroitin sulfate, %	7.5 ± 1.8	9.0 ± 1.5	8.5 ± 1.3
Total dry weight of purified GAGs, μg/mg	6.9 ± 2.5	3.3 ± 1.1	4.0 ± 1.9

GAGs = glycosaminoglycans.
Adapted with permission of Elsevier, from De Klerk DP. The glycosaminoglycans of human bladder cancers of varying grade and stage. J Urol. 1985;134(5):978-981.

are perpendicularly attached to the surface of the transitional epithelium.[21,26] Glycosaminoglycans bound to proteoglycans are held apart by their highly anionic charge, with water trapped between their spaces and held in place by electrical attraction.[21,26] Formation of a tightly bound impermeable water layer requires that GAGs be distributed at a high density in the space throughout the glycocalyx.[16,21] Current calculations suggest that stacks of GAG molecules 5 to 60 deep must be present in the area covered by a single chain on the surface of normal bladder epithelium.[16,21] The presence of both proteoglycans and glycoproteins is required to maintain the impermeability properties of bladder epithelium.[16]

Neurosensory properties of bladder urothelium

The bladder urothelium has traditionally been considered a passive barrier. However, recent research shows that the urothelium exhibits neurosensory-like properties and may have an active role in regulating bladder function, Figure 2.[32] Bladder urothelial cells express several receptors and ion channels found on sensory neurons, including receptors for bradykinin, purines, norepinephrine, and acetylcholine, as well as the receptor for capsaicin: transient receptor potential vanilloid subtype 1 (TRPV1).[32-34] These receptors are functional and active.[34] For example, urothelial cells in culture respond to exogenously applied capsaicin with a rise in intracellular Ca levels and release of the neurotransmitter nitric oxide (NO), whereas these responses were not present in TRPV1 null mice.[32,35]

The bladder urothelium actively communicates with bladder afferent nerves as well as neighboring cells. Upon bladder stretching, urothelial cells release adenosine triphosphate (ATP), which activates a subpopulation of bladder afferents expressing the purinergic $P2X_3$ receptors, signaling bladder fullness and pain.[36,37] Mice that lack the $P2X_3$ gene exhibit bladder hyporeflexia, suggesting that this epithelial-neural signaling is necessary for bladder function.[38] The urothelium also expresses P2X and P2Y receptors, and autocrine signaling via stretch-induced ATP may trigger the vesicle exocytosis that contributes to bladder expansion during filling.[39] Multiple putative mediators (e.g. ATP) and peptides have been identified in the afferent pathways of the bladder, including substance P, neurokinin A, calcitonin gene–related peptide (CGRP), vasoactive intestinal peptide (VIP), and enkephalins.[40-42] In particular, substance P

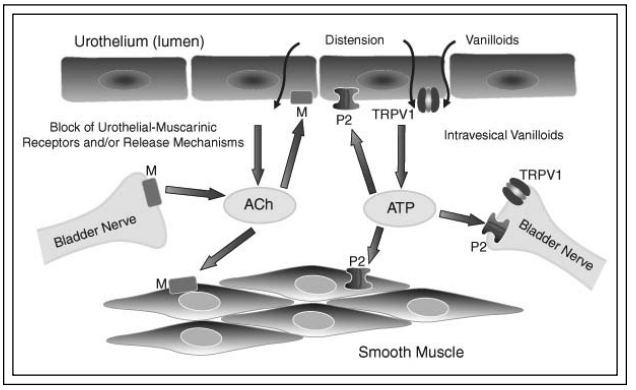

Figure 2. Schematic of neurosensory function of bladder epithelium.
TRPV1 = transient receptor potential vanilloid subtype 1; ACh = acetylcholine; ATP = adenosine triphosphate; M = muscarinic receptor; P = purinergic receptor. (Reproduced, with permission, from Birder LA. More than just a barrier: urothelium as a drug target for urinary bladder pain. *Am J Physiol Renal Physiol* 2005;289(3):F489-F495. ©American Physiological Society 2005.)

and CGRP can function as neurotransmitters in sensory nerves.[41] It is, therefore, possible that urothelial cells are capable of sensing and responding to their environment, and signaling in both an autocrine and paracrine manner.

Role of the bladder surface in IC/PBS

Increased permeability in IC/PBS

Abnormally enhanced permeability across the urothelium, or bladder urothelial dysfunction, has been proposed as a major cause of the typical symptoms of IC/PBS: urgency, frequency, and pelvic pain.[14,16,43,44] One of the first studies to provide evidence for an association between bladder urothelial dysfunction and IC compared absorption of concentrated urea instilled in the bladder of 56 patients with IC and 31 normal subjects.[14] Forty-five minutes after instillation, patients with IC had absorbed significantly more urea from the urine compared with normal subjects (25% versus 4.3%, $p < .005$, Figure 3).[14] In a study using a mouse model of IC, an increase in urothelial permeability was shown to accompany development of features similar to human IC.[45] An increase in bidirectional urothelial permeability was suggested by the findings of Erickson et al, who used a highly sensitive radiometric assay to show an increase in urinary hyaluronic acid (HA) among patients with IC compared with normal controls.[46] Mean urinary HA concentrations (normalized to urinary creatinine) were 674 ± 220 ng/mg creatinine in the IC group (n = 17) and 446 ± 220 ng/mg creatinine ($p = .0019$) in the control group (n = 17).[46] As HA is normally localized in the subepithelial connective tissue, increased concentrations of HA in the urine suggest increased leakage across the epithelium in patients with IC.[46] Additional studies comparing patients with IC to controls demonstrated urinary hyaluronic acid levels elevated 3- to 4-fold.[12] Moreover, the urinary uronate profile demonstrated alterations, with controls exhibiting more high-molecular-weight sulfated GAGs and patients with IC exhibiting more small oligosaccharides. The concept that the bladder epithelium is abnormally permeable in IC/PBS is not universally supported, however. One study often cited as evidence that permeability is unaltered in IC measured serum concentrations of the radioactive tracer ^{99m}technetium-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) following intravesical instillation in patients with IC (n = 10) and in age-matched controls (n = 9).[47] This study reported no significant difference in absorption between patients with IC and control subjects, although the mean DTPA absorption was 83% greater in patients with IC. Given the low (33%) statistical power of this study due to the small number of subjects, results are open to interpretation.[48]

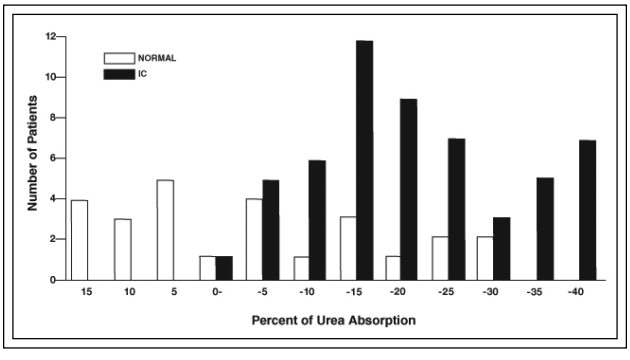

Figure 3. Urea absorption in patients with IC versus normal subjects. IC = interstitial cystitis. (Adapted, with permission, from Parsons CL, Lilly JD, Stein P: Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). *J Urol*. 1991;145(4):732-735. ©Elsevier 1991.)

Anatomic changes that can be viewed microscopically have been evaluated to determine if there is a visible change in the bladder surface. The exact location of the defect allowing increased permeability in IC/PBS has not been established. It may lie in the tight junctions of the epithelium, the overlying mucosal layer, or both.[15] In a feline model of IC, scanning laser and electron microscopy of urothelial biopsies show areas of denuded epithelium, in which the umbrella cells are missing and the underlying intermediate layer, which lacks tight junctions, is exposed.[49] The same pattern has been observed in bladder biopsies from patients with IC.[50] The expression of tight junction proteins is altered in bladder epithelial cells cultured from biopsies from patients with IC.[51] Although visual changes have been described, it is the physiological changes that are often reported as demonstrating the permeability abnormality.[52]

Changes in the structure or composition of the bladder mucosal lining may play a key role in the increased epithelial permeability associated with IC.[14,20,26] Urinary GAG excretion is reduced in patients with IC. In one study, urinary GAG levels in patients with IC were half that of normal subjects, and only slightly lower than that of spinal cord injury patients.[16] In bladder biopsies, GAGs have a well-ordered arrangement in normal bladder epithelium, but are disrupted in IC epithelium.[53]

Studies using electron microscopy to image the mucosal layer have produced equivocal results. Using transmission electron microscopy (TEM), Dixon et al

found no significant differences in the appearance, thickness, or distribution of the bladder mucosal lining between patients with IC and normal subjects.[54] Similar findings were reported by Nickel et al using a technique in which the polysaccharide component of the mucosal lining is stabilized by specific antibodies prior to TEM.[55] In another study, Anderstrom et al compared transurethral resection biopsies from patients with IC and those with stress incontinence, using scanning electron microscopy.[50] In this study, although specimens from both patient cohorts showed defects in the bladder mucosal lining, the areas with a disrupted or absent mucosal layer were larger in specimens from patients with IC than in those with stress incontinence.[50] Scanning electron microscopy allows for the examination of a larger surface area than TEM.

It has been theorized that once epithelial permeability is enhanced, potassium and other irritants diffuse into the bladder epithelium at toxic levels, causing depolarization of the sensory nerves and muscles and ultimately tissue injury and destruction.[56-60] The role of potassium in the pathogenesis of IC was examined in a study comparing 24-hour urine potassium levels in 30 newly diagnosed patients with IC who had not yet received treatment and 47 normal subjects.[61] Twenty four–hour urine potassium levels in the patients with IC were significantly lower than those in patients without IC (31.0 mEq/l versus 46.2 mEq/l, $p = .01$).[61] These findings are consistent with increased potassium absorption and enhanced epithelial permeability in the bladders of patients with IC.[61]

Studies have examined the effects of replacing a damaged mucosal layer with GAG substitutes. Normal rabbit bladders treated with protamine, a protein that binds to GAGs and interferes with their function, exhibited increased movement of urea and calcium across the bladder epithelium. This effect was reversed by administration of pentosan polysulfate sodium (PPS), a semisynthetic heparinlike compound that chemically and structurally resembles GAGs.[20,62] A study on humans produced similar results.[63] In this study, 27 normal volunteers had urea instilled in their bladders before and after treatment with protamine sulfate. Urea loss from the bladder was significantly increased following treatment with protamine (5% before versus 22% after; $p < .02$), but this effect was significantly reversed following treatment with the exogenous GAG substitute heparin (10%; $p = .04$).[63] Intravesical instillation of protamine provoked the symptoms of urgency and pain, which were exacerbated by urea instillation and relieved by heparin.

In a randomized, double-blind, placebo-controlled study that evaluated the effects of PPS in 148 patients with severe IC refractory to conventional treatment, 32% of patients who received the drug over a 3-month period experienced significant overall symptom improvement (as measured by the patient's global assessment of at least a 50% decrease in symptoms), compared with only 16% of those who received placebo ($p = .01$).[44] In a 32-week, randomized, double-blind study, patient response increased steadily over the duration of therapy. Among patients who received 300 mg/day PPS ($n = 128$), the percentage of responders (≥ 50% improvement on Patient's Overall Rating of Symptoms Index [PORIS]) increased from 34% at 8 weeks to 50% at 32 weeks.[64] Intravesical instillation of heparin also resulted in symptom relief for patients with IC. In an open-label study, more than half (56%) of the 48 patients studied achieved a 50% or greater improvement in symptoms after 3 months of therapy with intravesical heparin (10,000 units in 10 ml sterile water 3 times per week).[65] In a small trial, intravesical instillation of chondroitin sulfate also produced some symptom relief.[66] One interpretation of these clinical studies is that GAG-replacement therapy with PPS or heparin helps to repair and heal the permeability defect in the bladder of patients with IC/PBS.

It is unclear whether abnormally enhanced permeability across the bladder epithelium is a cause or an effect of IC.[3] In IC, the bladder epithelium either fails to establish an impermeable water layer or is structurally compromised.[14,20] Abnormally enhanced permeability across the bladder epithelium may be due to several factors, such as genetics, downregulation of proteoglycan biosynthesis by either viral infection or urine mediators, or chronic neutralization of the surface charge by cationic proteins.[16] Failure of the stroma to provide the proper peptide signal for growth and differentiation may also contribute to enhanced permeability in the bladder epithelium.[16]

Role of GP51

Reduction in levels of a glycoprotein known as GP51 (previously termed GP1) has been observed in patients with IC. Immunohistochemical staining of bladder epithelial tissue from patients with IC versus controls showed decreased or absent staining reactions for GP51 among biopsies of patients with IC (61% and 35%, respectively).[67] In another study, levels of GP51 were significantly decreased in the urine of patients with IC compared with normal controls ($p = .008$).[68] These results indicate that levels of GP51 may be a useful clinical marker for the diagnosis of IC.

Role of Tamm-Horsfall protein in IC/PBS

A potential factor contributing to the loss of epithelial impermeability in IC is the chronic neutralization of the anionic bladder mucosal lining by cationic toxic factors in the urine.[16,69] Normal human urine contains cationic factors that are toxic to both bladder epithelial cells and smooth muscle cells. Unregulated, these factors could, potentially, interact with the anionic bladder mucosal lining and impede its ability to bind water to the bladder surface, increasing epithelial permeability and permitting urinary solutes to leak into the subepithelial space.[69] Healthy individuals may possess urinary defense mechanisms that prevent cationic toxic factors from interacting with the bladder mucosal lining, thereby preserving the impermeability of the bladder epithelium.[69]

Tamm-Horsfall protein (THP), a protein found in normal urine, may form a complex with cationic toxic factors, capturing potentially injurious factors before they can damage the bladder mucosal lining.[69,70] The potential protective role of THP was demonstrated in a study that compared cytotoxic activity in low molecular weight urine fractions pretreated with THP versus that in untreated urine.[69] Tamm-Horsfall protein–treated urine fractions had significantly lower cytotoxicity levels compared with untreated urine fractions in both epithelial cells (7% versus 89%, $p < .001$) and smooth muscle cells (8% versus 70%, $p < .01$). These findings suggest that THP may play a key role in regulating the balance between cationic toxic factors in the urine and defense mechanisms in the bladder. Impairment of the cytoprotective capacity of THP may disrupt this balance by allowing cationic toxic factors to interact with the bladder mucosal lining, thereby contributing to the development of IC.[69,70] A recent study showed that PPS can neutralize the effect of toxic urine factors in a similar fashion to THP.[71]

Role of antiproliferative factor

Antiproliferative factor (APF), a modified frizzled 8–related sialoglycopeptide, is a peptide in the urine of patients with IC.[72,73] It is produced specifically by bladder epithelial cells in patients with IC, and has been shown to inhibit bladder epithelial cell proliferation.[73,74] Cultured bladder epithelial cells from subjects with IC exhibit significantly reduced rates of proliferation compared with cells from control subjects ($p = .02$ by Day 2 after serum starvation and $p < .0005$ by Day 3).[75] Although its mechanism of action has not been fully elucidated, evidence suggests that APF may induce distinct changes in the cell cycle and cause a G2/M phase blockade.[72] Antiproliferative factor has also been shown to decrease levels of urinary heparin-binding epidermal growth factor–like growth factor (HB-EGF) and to increase levels of epidermal growth factor (EGF), reflecting the altered levels of these growth factors seen in patients with IC.[72,74] When APF is applied to normal bladder epithelial cells in culture, changes occur that are similar to those seen in cells from patients with IC, including increased paracellular permeability, decreased expression of tight junction proteins, and changes in the expression of other proteins involved in cell adhesion.[51] These results support a causal role for APF in the etiology of IC, by contributing to abnormal permeability. In the future, a test to detect urine biomarkers, such as APF, HB-EGF, and EGF, might be developed for use in the clinical setting to diagnose and monitor IC.[74]

Role of surface sensitization

The recent discovery that the bladder urothelium exhibits neurosensory properties has led to the suggestion that abnormalities in urothelial signaling may contribute to the development of IC/PBS. Urine from patients with IC contains significantly more ATP than urine from non-IC patients.[76] Furthermore, ATP release during stretch is augmented in cultured bladder epithelial cells from patients with IC, and these cells exhibit more robust responses to exogenous ATP.[76,77] Urothelial cells also exhibit upregulated P2X receptors, which are involved in signaling bladder fullness and pain.[78,79] In sensory neurons, ATP can potentiate the responsiveness of capsaicin receptors. Some investigators have proposed that ATP release upon tissue injury may trigger sensitization and hyperalgesia, along with increased sensations of urgency and pain.[80]

Other theories of IC pathogenesis

The pathogenesis of IC/PBS is likely multifactorial, and a number of factors other than bladder urothelial dysfunction, such as autoimmunity, neurogenic inflammation, and mast cell activation, may be involved.[3,10-12] The concept that IC/PBS may be an autoimmune disorder largely stems from its predominance in women; noninfectious inflammatory changes, concomitance with other autoimmune disorders, such as systemic lupus erythematosus, rheumatoid arthritis, and ulcerative colitis; and other similarities to immunologically mediated diseases.[11,81] However, numerous serologic and histologic studies have failed to provide evidence that IC is an autoimmune disorder, and the lack of specificity of immunologic bladder responses in IC suggests that immune responses may be secondary to bladder inflammatory damage rather than the primary cause of the condition.[11,81]

The theory that IC/PBS is caused by neurogenic inflammation is based on observations of neuroproliferation and chronic perineuritis in the bladder wall as well as on the symptom complex of pain, frequency, and urgency that typically accompanies the condition.[11,82] Treatments that are effective for patients with neuropathic pain disorders (such as amitriptyline and gabapentin) have also been shown to provide symptom relief in patients with IC, although these agents are not approved for this indication.[83,84] It has been speculated that neurogenic inflammation may be a primary pathogenic factor in the development of the condition, leading to the production of neuropeptides and mast cell mediators that can cause inflammation, tissue damage, and fibrosis.[11]

Another explanation for the data is that neurogenic inflammation represents a protective response to noxious stimuli. In the normal response to injury, edema and the recruitment of local defense cells help to combat and dilute toxins and bacteria.[40] In IC/PBS, neurogenic inflammation can become maladaptive. Nerve growth factor (NGF) levels are elevated in patients with IC, and NGF is one of the early genes upregulated in IC.[85,86] The increase in NGF expression in cystitis may explain the neuroplasticity and long-term effects of pain after the original inciting agent and inflammation have abated.[87-89]

Compelling evidence suggests that mast cells play an important role in the pathogenesis of IC.[11] Multiple studies have shown that mast cells occur in increased numbers in the bladder mucosa and epithelium and in the detrusor muscle bundles of the bladder in patients with IC, suggesting that mast cells may be a key mediator of the inflammatory processes responsible for the condition.[90-95] In addition, bladder biopsies from patients with IC had a significantly elevated histamine content compared with the control group.[94] In an analysis of biopsy samples from patients in the Interstitial Cystitis Database, Tomaszewski et al found that an increased mast cell count in the lamina propria was significantly associated with nocturia in a predictive model.[96] These findings were most notable in patients with Hunner's ulcers. Although these studies implicate mast cells in the pathogenesis of IC, there is no evidence that IC is the manifestation of a primary mast cell disorder.[11]

Conclusions

Defects in the bladder surface and abnormally enhanced permeability are common features of IC. There is strong evidence that these defects in the bladder mucosa may increase epithelial permeability, initiating the cascade of events that results in the symptoms of IC/PBS. The underlying factors that cause abnormalities in the bladders of patients with IC have not yet been fully elucidated, but emerging research focusing on THP, APF, and bladder surface sensitization as causal factors appears promising. The large amount of data demonstrating an abnormal increase in urothelial permeability suggests the bladder epithelium as a therapeutic target. Further investigation is needed to enhance our understanding of this common and potentially debilitating condition. □

References

1. Hanno PM. Interstitial cystitis and related disorders. In: Walsh PC, Retik AB, Vaughan ED Jr, et al, eds. Campbell's Urology. Vol 1. 8th ed. Philadelphia, Pa: Saunders; 2002:631-670.
2. Teichman JMH, Thompson IM, Taichman NS. Joseph Parrish, tic doloureux of the bladder and interstitial cystitis. *J Urol* 2000;164(5):1473-1475.
3. Ratliff TL, Klutke CG, McDougall EM. The etiology of interstitial cystitis. *Urol Clin North Am* 1994;21(1):21-30.
4. Messing EM, Stamey TA. Interstitial cystitis: early diagnosis, pathology, and treatment. *Urology* 1978;12(4):381-392.
5. Parsons CL, Tatsis V. Prevalence of interstitial cystitis in young women. *Urology* 2004;64(5):866-870.
6. Rosenberg MT, Hazzard M. Prevalence of interstitial cystitis symptoms in women: a population based study in the primary care office. *J Urol* 2005;174(6):2231-2234.
7. Hanno P, Keay S, Moldwin R, van Ophoven A. International Consultation on IC - Rome, September 2004/Forging an International Consensus: Progress in Painful Bladder Syndrome/Interstitial Cystitis. Report and abstracts. *Int Urogynecol J Pelvic Floor Dysfunct* 2005;16(suppl 1):S2-S34.
8. National Institute of Diabetes and Digestive and Kidney Diseases. National Institute of Diabetes and Digestive and Kidney Diseases. Interstitial Cystitis/Painful Bladder Syndrome. NIH Publication 05-3220. http://kidney.niddk.nih.gov/kudiseases/pubs/interstitialcystitis. Published June 2005. Accessed June 15, 2006.
9. Warren JW, Meyer WA, Greenberg P et al. Using the International Continence Society's definition of painful bladder syndrome. *Urology* 2006;67(6):1138-1143.
10. Parsons CL, Parsons JK. Interstitial cystitis. In: Raz S, ed. Female Urology. 2nd ed. Philadelphia, Pa: WB Saunders Company; 1996:167-182.
11. Elbadawi A. Interstitial cystitis: a critique of current concepts with a new proposal for pathologic diagnosis and pathogenesis. *Urology* 1997;49(suppl 5A):14-40.
12. Lokeshwar VB, Selzer MG, Cerwinka WH et al. Urinary uronate and sulfated glycosaminoglycan levels: markers for interstitial cystitis severity. *J Urol* 2005;174:344-349.
13. Slobodov G, Feloney M, Gran C et al. Abnormal expression of molecular markers for bladder impermeability and differentiation in the urothelium of patients with interstitial cystitis. *J Urol* 2004;171(4):1554-1558.
14. Parsons CL, Lilly JD, Stein P. Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). *J Urol* 1991;145(4):732-735.

15. Lewis SA. Everything you wanted to know about the bladder epithelium but were afraid to ask. *Am J Physiol Renal Physiol* 2000;278(6):F867-F874.
16. Hurst RE. Structure, function, and pathology of proteoglycans and glycosaminoglycans in the urinary tract. *World J Urol* 1994;12(1):3-10.
17. Jost SP, Gosling JA, Dixon JS. The morphology of normal human bladder urothelium. *J Anat* 1989;167:103-115.
18. Acharya P, Beckel J, Ruiz WG et al. Distribution of the tight junction proteins ZO-1, occludin, and claudin-4, -8, and -12 in bladder epithelium. *Am J Physiol Renal Physiol* 2004;287(2):F305-F318.
19. Balkovetz DF. Claudins at the gate: determinants of renal epithelial tight junction paracellular permeability. *Am J Physiol Renal Physiol* 2006;290(3):F572-F579.
20. Parsons CL, Boychuk D, Jones S et al. Bladder surface glycosaminoglycans: an epithelial permeability barrier. *J Urol* 1990;143(1):139-142.
21. Hurst RE, Zebrowski R. Identification of proteoglycans present at high density on bovine and human bladder luminal surface. *J Urol* 1994;152(5, pt 1):1641-1645.
22. Hurst RE, Rhodes SW, Adamson PB et al. Functional and structural characteristics of the glycosaminoglycans of the bladder luminal surface. *J Urol* 1987;138(2):433-437.
23. Grist M, Chakraborty J. Identification of a mucin layer in the urinary bladder. *Urology* 1994;44(1):26-33.
24. Parsons CL, Greenspan C, Moore SW et al. Role of surface mucin in primary antibacterial defense of bladder. *Urology* 1977;9(1):48-52.
25. Lee E-Y, Kim S-H, Whang S-K et al. Isolation, identification, and quantitation of urinary glycosaminoglycans. *Am J Nephrol* 2003;23(3):152-157.
26. Russell AL. Glycoaminoglycan (GAG) deficiency in protective barrier as an underlying, primary cause of ulcerative colitis, Crohn's disease interstitial cystitis and possibly Reiter's syndrome. *Med Hypotheses* 1999;52(4):297-301.
27. Cornish J, Nickel JC, Vanderwee M et al. Ultrastructural visualization of human bladder mucous. *Urol Res* 1990;18(4):263-266.
28. Nickel JC, Cornish J. Ultrastructural study of an antibody-stabilized bladder surface: a new perspective on the elusive glycosaminoglycan layer. *World J Urol* 1994;12(1):11-14.
29. De Klerk DP. The glycosaminoglycans of human bladder cancers of varying grade and stage. *J Urol* 1985;134(5):978-981.
30. Cabral CAP, Sampaio FJB, Cardoso LEM. Analysis of the modifications in the composition of bladder glycosaminoglycan and collagen as a consequence of changes in sex hormones associated with puberty or oophorectomy in female rats. *J Urol* 2003;170(6, pt 1):2512-2516.
31. de Deus JM, Girão MJBC, Sartori MGF et al. Glycosaminoglycan profile in bladder and urethra of castrated rats treated with estrogen, progestogen, and raloxifene. *Am J Obstet Gynecol* 2003;189(6):1654-1659.
32. Birder LA. More than just a barrier: urothelium as a drug target for urinary bladder pain. *Am J Physiol Renal Physiol* 2005;289(3):F489-F495.
33. Beckel JM, Kanai A, Lee S-J et al. Expression of functional nicotinic acetylcholine receptors in rat urinary bladder epithelial cells. *Am J Physiol Renal Physiol* 2006;290(1):F103-F110.
34. Chopra B, Barrick SR, Meyers S et al. Expression and function of bradykinin B1 and B2 receptors in normal and inflamed rat urinary bladder urothelium. *J Physiol* 2005;562(pt 3):859-871.
35. Birder LA, Apodaca G, de Groat WC et al. Adrenergic- and capsaicin-evoked nitric oxide release from urothelium and afferent nerves in urinary bladder. *Am J Physiol* 1998;275(2, pt 2):F226-F229.
36. Burnstock G. Purine-mediated signalling in pain and visceral perception. *Trends Pharmacol Sci* 2001;22(4):182-188.
37. Ferguson DR, Kennedy I, Burton TJ. ATP is released from rabbit urinary bladder epithelial cells by hydrostatic pressure changes–a possible sensory mechanism? *J Physiol* 1997;505:503-511.
38. Cockayne DA, Hamilton SG, Zhu Q-M et al. Urinary bladder hyporeflexia and reduced pain-related behaviour in $P2X_3$-deficient mice [letter]. *Nature* 2000;407(6807):1011-1015.
39. Wang ECY, Lee J-M, Ruiz WG et al. ATP and purinergic receptor–dependent membrane traffic in bladder umbrella cells. *J Clin Invest* 2005;115(9):2412-2422.
40. Wesselmann U. Neurogenic inflammation and chronic pelvic pain. *World J Urol* 2001;19(3):180-185.
41. Maggi CA. Tachykinins and calcitonin gene-related peptide (CGRP) as co-transmitters released from peripheral endings of sensory nerves. *Prog Neurobiol* 1995;45(1):1-98.
42. Li MZ, Masuko S. Target specific organization and neuron types of the dog pelvic ganglia: a retrograde-tracing and immunohistochemical study. *Arch Histol Cytol*.2001;64(3):267-280.
43. Evans RJ. Treatment approaches for interstitial cystitis: multimodality therapy. *Rev Urol* 2002;4(suppl 1):S16-S20.
44. Parsons CL, Benson G, Childs SJ et al. A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosanpolysulfate. *J Urol* 1993;150(3):845-848.
45. Bullock AD, Becich MJ, Klutke CG et al. Experimental autoimmune cystitis: a potential murine model for ulcerative interstitial cystitis. *J Urol* 1992;148(6):1951-1956.
46. Erickson DR, Sheykhnazari M, Ordille S et al. Increased urinary hyaluronic acid and interstitial cystitis. *J Urol* 1998;160(4):1282-1284.
47. Chelsky MJ, Rosen SI, Knight LC et al. Bladder permeability in interstitial cystitis is similar to that of normal volunteers: direct measurement by transvesical absorption of ^{99m}technetium-diethylenetriaminepentaacetic acid. *J Urol* 1994;151(2):346-349.
48. Teichman JMH, Nielsen-Omeis BJ. Potassium leak test predicts outcome in interstitial cystitis. *J Urol* 1999;161(6):1791-1796.
49. Lavelle JP, Meyers SA, Ruiz WG et al. Urothelial pathophysiological changes in feline interstitial cystitis: a human model. *Am J Physiol Renal Physiol* 2000;278(4):F540-F553.
50. Anderström CRK, Fall M, Johansson SL. Scanning electron microscopic findings in interstitial cystitis. *Br J Urol* 1989;63(3):270-275.
51. Zhang C-O, Wang J-Y, Koch KR et al. Regulation of tight junction proteins and bladder epithelial paracellular permeability by an antiproliferative factor from patients with interstitial cystitis. *J Urol* 2005;174(6):2382-2387.
52. Parsons CL. The role of the urinary epithelium in the pathogenesis of interstitial cystitis/prostatitis/urethritis. *Urology* 2007;69(Suppl 4A):9-16.
53. Davis JA, Hauser P, Kyker KD et al. Urothelial proteoglycans of the normal human and interstitial cystitis bladder. *J Urol* 2006;175(suppl 4):93. Abstract 280.
54. Dixon JS, Holm-Bentzen M, Gilpin CJ, Gosling JA, Bostofte E, Hald T et al. Electron microscopic investigation of the bladder urothelium and glycocalyx in patients with interstitial cystitis. *J Urol* 1986;135(3):621-625.
55. Nickel JC, Emerson L, Cornish J. The bladder mucus (glycosaminoglycan) layer in interstitial cystitis. *J Urol* 1993;149(4):716-718.
56. Parsons CL. Prostatitis, interstitial cystitis, chronic pelvic pain, and urethral syndrome share a common pathophysiology: lower urinary dysfunctional epithelium and potassium recycling. *Urology* 2003;62(6):976-982.
57. Hohlbrugger G. The vesical blood-urine barrier: a relevant and dynamic interface between renal function and nervous bladder control. *J Urol* 1995;154(1):6-15.
58. Parsons CL, Greenberger M, Gabal L et al. The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. *J Urol* 1998;159(6):1862-1867.

59. Parsons CL, Stein PC, Bidair M et al. Abnormal sensitivity to intravesical potassium in interstitial cystitis and radiation cystitis. *Neurourol Urodyn* 1994;13(5):515-520.
60. Hohlbrugger G, Lentsch P. Intravesical ions, osmolality and pH influence the volume pressure response in the normal rat bladder, and this is more pronounced after DMSO exposure. *Eur Urol* 1985;11(2):127-130.
61. Parsons CL, Greene RA, Chung M et al. Abnormal urinary potassium metabolism in patients with interstitial cystitis. *J Urol* 2005;173(4):1182-1185.
62. ELMIRON® (pentosan polysulfate sodium) 100 mg capsules prescribing information. Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc; September 2006.
63. Lilly JD, Parsons CL. Bladder surface glycosaminoglycans is a human epithelial permeability barrier. *Surg Gynecol Obstet* 1990;171(6):493-496.
64. Nickel JC, Barkin J, Forrest J et al. Randomized, double-blind, dose-ranging study of pentosan polysulfate sodium for interstitial cystitis. *Urology* 2005;65(4):654-658.
65. Parsons CL, Housley T, Schmidt JD et al. Treatment of interstitial cystitis with intravesical heparin. *Br J Urol* 1994;73(5):504-507.
66. Steinhoff G, Ittah B, Rowan S. The efficacy of intravesicular sterile sodium chondroitin sulfate 0.2% in potassium tested positive patients with interstitial cystitis. *Adv Exp Med Biol* 2003;539(pt B):731-739.
67. Moskowitz MO, Byrne DS, Callahan HJ et al. Decreased expression of a glycoprotein component of bladder surface mucin (GP1) in interstitial cystitis. *J Urol* 1994;151(2):343-345.
68. Byrne DS, Sedor JF, Estojak J, et al. The urinary glycoprotein GP51 as a clinical marker for interstitial cystitis. *J Urol* 1999;161(6):1786-1790.
69. Parsons CL, Bautista SL, Stein PC et al. Cyto-injury factors in urine: a possible mechanism for the development of interstitial cystitis. *J Urol* 2000;164(4):1381-1384.
70. Akiyama A, Stein PC, Houshiar A et al. Urothelial cytoprotective activity of Tamm-Horsfall protein isolated from the urine of healthy subjects and patients with interstitial cystitis. *Int J Urol* 2000;7(5):176-183.
71. Rajasekaran M, Stein P, Parsons CL. Toxic factors in human urine that injure urothelium. *Int J Urol* 2006;13(4):409-414.
72. Rashid HH, Reeder JE, O'Connell MJ et al. Interstitial cystitis antiproliferative factor (APF) as a cell-cycle modulator. *BMC Urol* [serial online]. 2004;4. Available at: http://www.biomedcentral.com/content/pdf/1471-2490-4-3.pdf. Accessed July 17, 2006.
73. Keay SK, Szekely Z, Conrads TP et al. An antiproliferative factor from interstitial cystitis patients is a frizzled 8 protein-related sialoglycopeptide. *Proc Natl Acad Sci USA* 2004;101(32):11803-11808.
74. Keay SK, Zhang C-O, Shoenfelt J et al. Sensitivity and specificity of antiproliferative factor, heparin-binding epidermal growth factor–like growth factor, and epidermal growth factor as urine markers for interstitial cystitis. *Urology* 2001;57(suppl 6A):9-14.
75. Keay S, Zhang C-O, Shoenfelt JL et al. Decreased in vitro proliferation of bladder epithelial cells from patients with interstitial cystitis. *Urology* 2003;61(6):1278-1284.
76. Sun Y, Keay S, De Deyne PG et al. Augmented stretch activated adenosine triphosphate release from bladder uroepithelial cells in patients with interstitial cystitis. *J Urol* 2001;166(5):1951-1956.
77. Sun Y, Chai TC. Augmented extracellular ATP signaling in bladder urothelial cells from patients with interstitial cystitis. *Am J Physiol Cell Physiol*.2006;290(1):C27-C34.
78. Birder LA, Ruan HZ, Chopra B et al. Alterations in P2X and P2Y purinergic receptor expression in urinary bladder from normal cats and cats with interstitial cystitis. *Am J Physiol Renal Physiol* 2004;287(5):F1084-F1091.
79. Tempest HV, Dixon AK, Turner WH et al. $P2X_2$ and $P2X_3$ receptor expression in human bladder urothelium and changes in interstitial cystitis. *BJU Int* 2004;93(9):1344-1348.
80. Kanai A, de Groat W, Birder L et al. Symposium report on urothelial dysfunction: pathophysiology and novel therapies. *J Urol* 2006;175(5):1624-1629.
81. Anderson JB, Parivar F, Lee G, et al. The enigma of interstitial cystitis—an autoimmune disease? *Br J Urol* 1989;63(1):58-63.
82. Christmas TJ, Rode J. Characteristics of mast cells in normal bladder, bacterial cystitis and interstitial cystitis. *Br J Urol* 1991;68(5):473-478.
83. van Ophoven A, Pokupic S, Heinecke A et al. A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. *J Urol* 2004;172(2):533-536.
84. Hansen HC. Interstitial cystitis and the potential role of gabapentin. *South Med J* 2000;93(2):238-242.
85. Lowe EM, Anand P, Terenghi G et al. Increased nerve growth factor levels in the urinary bladder of women with idiopathic sensory urgency and interstitial cystitis. *Br J Urol* 1997;79(4):572-577.
86. Saban MR, Hellmich H, Nguyen N-B et al. Time course of LPS-induced gene expression in a mouse model of genitourinary inflammation. *Physiol Genomics* 2001;5(3):147-160.
87. Oddiah D, Anand P, McMahon SB et al. Rapid increase of NGF, BDNF and NT-3 mRNAs in inflamed bladder. *Neuroreport* 1998;9(7):1455-1458.
88. Vizzard MA. Changes in urinary bladder neurotrophic factor mRNA and NGF protein following urinary bladder dysfunction. *Exp Neurol* 2000;161(1):273-284.
89. Dupont MC, Spitsbergen JM, Kim KB, et al. Histological and neurotrophic changes triggered by varying models of bladder inflammation. *J Urol* 2001;166(3):1111-1118.
90. Feltis JT, Perez-Marrero R, Emerson LE. Increased mast cells of the bladder in suspected cases of interstitial cystitis: a possible disease marker. *J Urol* 1987;138(1):42-43.
91. Lynes WL, Flynn SD, Shortliffe LD et al. Mast cell involvement in interstitial cystitis. *J Urol* 1987;138(4):746-752.
92. Peeker R, Enerbäck L, Fall M et al. Recruitment, distribution and phenotypes of mast cells in interstitial cystitis. *J Urol* 2000;163(3):1009-1015.
93. Larsen S, Thompson SA, Hald T et al. Mast cells in interstitial cystitis. *Br J Urol* 1982;54(3):283-286.
94. Kastrup J, Hald T, Larsen S et al. Histamine content and mast cell count of detrusor muscle in patients with interstitial cystitis and other types of chronic cystitis. *Br J Urol* 1983;55(5):495-500.
95. Aldenborg F, Fall M, Enerbäck L. Proliferation and transepithelial migration of mucosal mast cells in interstitial cystitis. *Immunology* 1986;58(3):411-416.
96. Tomaszewski JE, Landis JR, Russack V et al. Biopsy features are associated with primary symptoms in interstitial cystitis: results from the Interstitial Cystitis Database Study. *Urology* 2001;57(suppl 6A):67-81.