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2006 NIDDK International Symposium: Frontiers in Painful Bladder Syndrome and Interstitial Cystitis

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Welcome and Introductions

Deborah Erickson, M.D., Professor, Department of Surgery/Urology, University of Kentucky College of Medicine, Lexington, KY, Robert Star, M.D. Acting Director, Division of Kidney, Urologic, and Hematologic Diseases, NIDDK, NIH, Bethesda, MD, and Debuene Chang, M.D., Director, Women's Urology, Division of Kidney, Urologic, and Hematologic Diseases, NIDDK, NIH, Bethesda, MD

Dr. Erickson, Dr. Star, and Dr. Chang welcomed speakers and attendees to this important symposium. Dr. Erickson provided a statement on the goal of the symposium, which was to address the current state of research and clinical treatments, both in the United States and internationally, of painful bladder syndrome and interstitial cystitis. In addition, the symposium was intended to expand scientific awareness of interstitial cystitis and its treatments, to provide a forum for discussion of the definition and etiology of interstitial cystitis and painful bladder syndrome, and to exchange information and ideas on current and contemplated research and treatments of the disease and its symptoms.

SESSION 1: BLADDER AND PAINFUL BLADDER SYNDROME/INTERSTITIAL CYSTITIS (PBS/IC)

Overview: The Urothelium: Role in PBS/IC

Lori Birder, Ph.D., University of Pittsburgh School of Medicine, Pittsburgh, PA

The urothelium is a multilayered structure composed of apical or umbrella cells, intermediate cells, and the basal epithelium. The primary role of urothelium is to form a barrier, which is highly dependent on tight junctions, specialized membrane domains between the apical cells. Barrier function can be disrupted in a number of pathologies and following a number of treatments. In humans with interstitial cystitis (IC), dysfunctions in the mucosal barrier and disruption of barrier function have been observed. Direct insults to the bladder, such as those that occur in the cyclophosphamide model of IC, disrupt barrier function, but a model of acute spinal cord injury also shows that the apical surface of the urothelium is disrupted with 2 hours of transection of the spinal cord. Other irritants, such as protamine sulfate, radiation cystitis,

inflammation, overdistension, and ischemia, can impact urothelial integrity, changing the permeability, ultrastructure, and function of the urothelium.
Because bladder afferents and efferents are located in close proximity to the urothelium, any disruption of the barrier can impact nervous functions. Transient receptor potential vanilloid 1 (TRPV1)+ fibers are in close contact with basal epithelial cells and are found in a region of overlap between urothelial cells and nerve fibers. Following changes to the barrier, sensitization of afferents can occur, leading to alterations in neural transmission that could result in urgency and frequency. A number of laboratories are interested in the changes that occur in the nervous system after barrier function changes. Toxic factors can affect the barrier and also impact nervous and smooth muscle function. Intervesical substances, such as adenosine triphosphate (ATP), also may have an effect on underlying nerves if the urothelial barrier is disrupted. Neurotrophins released from the urothelium after exposure to a toxin or other irritant also may impact nervous function.

Urothelium sensor function is modulated by expression of receptors and proteins that have transducer properties. Urothelial cells can sense temperature and mechanical changes, and respond to a number of chemical factors. The cells express proteins to sense ATP, a number of TRPV channels, bradykinin, and acetylcholine. The capsaicin receptor, TRPV1, which is altered in some pathologies, was of interest initially because of its history in studies of urinary bladder function and pain. TRPV1 is expressed throughout the afferent limb and micturition reflex pathway, and also is expressed by the urothelial cells. TRPV1 urothelial receptors are activated by vanilloids, such as capsaicin, and by distension or stretch. This induces the release of substances such as ATP, activating receptors on nearby afferents, and leading to changes in sensory events such as fullness or pain or activation of bladder reflexes. In neurons, TRPV1 can integrate or amplify response to painful or nociceptive stimuli; a similar effect may occur in urothelial cells following detection of an irritating stimulus or with infection or inflammation. Urothelial cells also secrete mediators that can affect bladder nerves, myofibroglasts, immune cells, and smooth muscle cells.

There is evidence that urothelial cells exhibit plasticity, and inflammation and injury can alter the properties of the cells, which could contribute to hypersensitivity and pain. TRPV1 is increased in patients with bladder overactivity in nerves and in the urothelium. Intervesical use of vanilloids such as capsaicin or resiniferatoxin (RTX) has long been long used to treat neurogenic bladder and reduce pain in patients with hypersensitivity disorders. Intervesical RTX has been demonstrated to reduce nerve density staining of TRPV1 and urothelial staining, suggesting that vanilloid actions are not just neuronal-selective. Many treatments used intervesically to treat these disorders may therefore impact urothelial targets or their release mechanisms.

Besides TRPV1, a number of other signaling pathways may be altered in IC, such as the purinergic pathway and ATP release upon stretching; ATP has been implicated in distension-evoked activation of afferents. When urothelial cells are stretched after filling, they can release ATP, which can impact nearby purinergic receptors on afferents, signaling changes about bladder pain or distension. In addition to the purinergic system, nitric oxide (NO) signaling pathways are altered in IC. Cats with IC have increased inducible NO synthase expression and basal release of NO. Concentrations of NO in the urine of patients with IC are increased. Although the role of NO in IC is unclear, it could involve increasing the permeability of the

urothelial barrier. Any changes in the barrier can result or lead to increased activity of afferent nerves located in close proximity.
A number of pathologies can alter the transducer and sensor functions of urothelial cells by increasing the release of a number of mediators from urothelial and other cell types, leading to changes in the response of urothelial cells to a variety of stimuli as well as ultimately influencing afferent function. These cells exhibit plasticity—they can react to changes in the environment, leading to changes in a variety of sensor molecules. Increased stress of urothelial cells can increase cyclooxygenase activity, which may play a role in inflammation and injury. Alterations in the expression or sensitization of a number of urothelial targets, and in urothelial sensor and transducer properties, could be one reason for the many symptoms of IC and other bladder pathologies.

The Uroepithelial-Associated "Sensory Web": Role of Epidermal Growth Factor Receptor in Regulating Exocytosis in Umbrella Cells
Jerry Apodaca, Ph.D., University of Pittsburgh, Pittsburgh, PA

The urothelium is an important barrier, and is part of a sensory web that includes the urothelium, afferent and efferent nerve processes, smooth muscle cell, mast cells, macrophages, and many other cell types. Umbrella cells and underlying basal and intermediate cells can express different channels, transporters, and receptor molecules that modulate urothelium response to different sensory input. Mechanical stimuli, which can lead to distension and affect bladder function, are mediated by these molecules.

Sensory input results in stimulation of input pathways that involve membrane turnover, or exocytosis and endocytosis. This can occur at the apical membrane of the umbrella cells, and at the basolateral surface and membranes of other cells in the urothelium. Another consequence of stimulating input pathways is the release of mediators such as ATP, NO, and prostaglandins as sensory outputs. Production of these sensory outputs permits interaction with nerves and muscle cells and can cause changes in function. Thus, as the bladder responds to stimuli in the extracellular environment, such as bladder filling, changes can be communicated from the urothelium to underlying tissues and vice versa. Modulating exocytosis and endocytosis modulates the input and output pathway; altering these pathways may result in changes associated with pathologies such as IC.

Filling or stretching the bladder results in exocytosis in the vesicals of surface umbrella cells in a normally functioning bladder. A rabbit bladder model showed that stretch, rather than pressure, is important in affecting exocytosis in the urothelium. Without stretch, there is no change in capacitance, which reflects changes in the apical surface area. When stretch is applied, the response occurs in 2 phases. During the early phase, surface area is increased by 25 percent within the first 30 minutes of response; subsequently, another 25 percent increase occurs over a longer time period. Stretch results in a 50 percent change in capacitance; in the presence of the protein synthesis inhibitor, cyclohexamide, this change in capacitance does not occur, implying a need for protein synthesis.

Tyrosine kinases have important regulatory roles in a number of mechanically sensitive mechanisms. AG1478, a specific inhibitor of the epidermal growth factor receptor (EGFR)

erbB1, blocked late-phase stretch. EGFR receptors also were found in rabbit epithelium, further implying a role for this receptor in the stretch response. EGFR can be visualized in the apical membranes of umbrella cells; significant amounts of epidermal growth factor (EGF) itself bind at the apical surface of the cells and slight amounts of binding also are observed in the underlying cell layers. EGF applied to either the mucosal or serosal surfaces induces a significant rise in capacitance, even in the absence of stretch; however, this occurs at lower doses of EGF on the apical pole than at the basolateral surface.

Stretch activates EGFR by inducing tyrosine phosphorylation on a tyrosine residue in the cytoplasmic domain of the receptor. Adding a function-blocking antibody that binds to the ligand binding site, thus preventing receptor activation, results in blockage of the late-phase response if the antibody is applied to the mucosal surface, consistent with an apical channeling response in epithelium. All ligands are synthesized as transmembrane precursors, which are activated by cleavage by metalloproteinases. Treating urothelial tissue with a broad-spectrum metalloproteinase inhibitor blocks receptor activation and late-phase response, thus confirming the role of ligand activation of the receptor in the stretch response. Activation of the metalloproteinases may involve upstream G-protein coupled receptors such as adenosine receptors, P2Y receptors, or channels that import calcium into the cytoplasm of cells.

Heparin-binding EGF (HB-EGF) is the key ligand in this system. Activation of the receptor activates mitogen-activated protein (MAP) kinases; use of inhibitors specific for the MAP kinases p38, mek, or erk blocks the late phase-response. Thus, the EGF signaling pathway, in addition to growth effects that regulate the recovery of epithelium in response to injury, also may play a significant role in the sensory web by affecting the receptor content and the ability to secrete and exocytose in the urothelium.

Urothelial Dysregulation in Disease States
Jenny Southgate, Ph.D., University of York, York, UK

Understanding the function and regulation of normal urothelium is essential for understanding the role this tissue may have in IC. The urothelium is composed of highly specialized superficial cells, intermediate cells, and basal cells, all resting on a basement membrane. Terminally differentiated superficial cells are in contact with the urine and provide a physical barrier by means of tight junctions between the cells that prevent ingress of urine by the paracellular route, and specialized plaques of asymmetric unit membrane, constituted of uroplakin proteins, over the surface of the cells. The claudin proteins are constituents of the tight junctions and are responsible for the "tightness" of the epithelial barrier. The urothelium is mitotically quiescent, but has a high regenerative capacity, meaning that the urothelium responds to damage by proliferation and differentiation to reinstate barrier function. The urothelium also is involved in the micturition reflex: it has a sensory function and expresses mechano- and chemo-sensitive receptors. The urothelium releases neuroactive substances that can signal the afferent nervous system and also expresses the receptors needed to respond to these neurotransmitters. The urothelium also has a role in pathogen defense, responding with innate immune mechanisms, release of and response to immune mediators, and recruitment of adaptive immunity. Cell culture systems have been developed that involve isolation of normal human urothelial cells and growth of these cells in culture; such cells acquire a regenerative phenotype and are highly

proliferative. This represents a model system to study mechanisms involved in regulating human urothelial cell proliferation and differentiation, and forms a platform for research to understand the physiology and function of the urothelium, and how it may interact with the immune, neurological, smooth muscle, and microbiological compartments.

Activation of the EGFR drives proliferation of normal human urothelial cells and occurs in the absence of exogenous growth factors, implying that urothelial cells themselves produce EGFR ligands. To identify pathways leading to urothelial cell differentiation, the autocrine EGFR loop was blocked and activation of the nuclear hormone receptor peroxisome proliferator-activated receptor-gamma (PPARγ) was shown to activate expression of uroplakin and claudin genes associated with urothelial differentiation. EGFR activation leads to phosphorylation and inactivation of PPARγ. Within 4 hours of adding an EGFR inhibitor to the culture, PPARγ is de-phosphorylated and can then bind its ligand and interact with its heterodimerization partner, retinoid X receptor-α to act as a transcription factor by binding to peroxisome proliferator-responsive elements (PPREs). Contrary to expectations, PPREs were not found in the promoters of uroplakin genes, and, given the relatively long time course for activation of these genes, intermediate transcription factors activated by PPARγ activation may be responsible for uroplakin gene transactivation.

Mechanical and chemical sensing in the urothelium may occur through channels such as TRP channels or through urothelial cell release of neurotransmitters that in turn activate receptors on the urothelium. TRPV1 is expressed (mRNA and protein) by urothelial cells and has been implicated in normal micturition and in IC and overactive bladder (OAB) syndromes. Visualization of the capsaicin response of TRPV1 shows that the response is heterogeneous. Cells of the urothelium also respond strongly to purinergic signaling through purino-receptors.

Understanding the cross-talk between systems assists in understanding both normal physiology and pathological processes. A leaky urothelium may be due to a failure to differentiate and/or inappropriate tight junction structure or function. This could be caused by development of an inappropriate cytokine milieu arising from an aberrant immune response (e.g. chronic inflammation caused by the persistence of a pathogen or a failure to down-regulate the immune response). Inappropriate stimulation or secretion of neurotransmitters also could have a role in development of a leaky urothelium. Thus, it is not known if the etiology of the urothelium reflects a primary failure to differentiate and develop a functional barrier, leading to urine leakage and chronic inflammation, or if the damage to the urothelium is secondary to the *in vivo* environment. When urothelial cells from IC patients were placed in an *in vitro* environment to assess their differentiation capacity, approximately 50 percent of cases failed to differentiate properly; suggesting a subset of IC cases may be caused by aberrant differentiation potential.

Urothelial Deficiency in PBS/IC

Susan Keay, M.D., Ph.D., Department of Veterans Affairs Maryland Health Care System and the University of Maryland School of Medicine, Baltimore, MD

Historically, there is both microscopic and functional evidence that abnormalities exist in the urothelium of IC patients. Cells from IC patients grown *in vitro* have different responses than cells from normal controls. There is evidence of increased leakiness in IC urothelium, as well as

altered gene expression and cellular phenotype. Epithelial cells from IC urothelium have altered expression of cell matrix proteins and glycoproteins, including uroplakin, chondroitin sulfate, and E-cadherin.

Cells were cultured from the urothelium of IC patients to look for evidence of stable, heritable changes in epithelial cell gene expression as compared to cells from matched normal controls. Microarray studies found altered expression of genes encoding proteins involved in cellular differentiation or in formation of tight junctions, such as ZO-1, occludin, and claudins 1, 4, and 8. These cells also produce anti-proliferative factor (APF) and have a decreased rate of proliferation as well as decreased production of HB-EGF-like growth factors, but have increased production of other growth factors. The structure of APF was determined in collaboration with Dr. Christopher Michejda's laboratory at the NCI in Frederick, Maryland. APF is a small glycopeptide composed of nine amino acids and three sugar residues; the peptide backbone is homologous to a portion of the six transmembrane region of the protein, Frizzled 8. A synthetic APF that has the properties of native APF has been produced.

The role of APF in inducing changes in epithelial cells in IC patients was explored. APF was used to induce the IC phenotype in normal bladder cells. Normal cells that were treated with APF downregulated ZO-1, occludin proteins, and tight junction formation. Levels of E-cadherin, which are two-fold higher in IC cells compared to normal cells, also increased after treatment with APF. Similar changes occurred in the occludin protein, which also is important for tight junction formation. Normal cells treated with APF for 48 hours also developed increased paracellular permeability, similar to cells from patients with IC.

Other investigators have also been studying additional effects of APF on bladder epithelial cells that mimic changes seen in IC cells. Dr. Toby Chai and his group at the University of Maryland have found stable heritable changes in cells concerning neurotransmitters, including stretch-activated ATP release, ATP-stimulated ATP release, and stretch-activated P2X3 receptor, all of which are increased in cells from IC patients; these same characteristics can be induced by APF treatment of normal bladder cells. Dr. Ray Rackley and his group at the Cleveland Clinic also showed that APF treatment of normal bladder cells causes changes in the NFkappaB response to TNF similar to the response seen in IC cells.

A high affinity receptor for APF, CKAP4/p63, has recently been identified in collaboration with Dr. Tom Conrads and other investigators at the NCI campus in Frederick, Maryland. Antibody interference and siRNA experiments showed that this receptor mediates the activity of APF. Visualization of APF and CKAP4/p63 showed that CKAP4/p63 binds at the cell membrane and on the rough endoplasmic reticulum, and colocalizes with APF at both these sites. Expression of the APF receptor is similar in normal and IC patients.

Bladder epithelial cells from IC patients thus appear to produce an abnormal secreted Frizzled-related protein, APF, which alters bladder epithelial cell gene expression and results in aberrant expression of proteins involved in tight junction formation, resulting in a leaky urothelium. APF also promotes abnormal expression of other cell proteins and neurotransmitters, contributing to the abnormal IC cellular phenotype.

Detrusor Muscle and IC

Kirsten Bouchelouche, M.D., Smooth Muscle Research Center, Koege and Herlev Hospitals University of Copenhagen, Denmark

Many patients with IC have increased number of mast cells in close contact with muscle cells in the detrusor muscle. Up to seventy percent of the mast cells are activated and release mediators, including histamines and leukotrienes, which permit interaction between the mast cells and muscle cells. The cysteinyl leukotriene D4 (LTD4) induces edema and inflammatory cell migration in the lung and may be of particular interest in IC. To examine the effects of LTD4 on the human bladder detrusor muscle, cultures of human smooth muscle cells were exposed to LTD4. This resulted in an increase in cytosolic free calcium. The LTD4 antagonist Montelukast inhibits this calcium response to LTD4. Force measurements showed that LTD4 also induces constriction of the detrusor muscle. IC patients with high numbers of mast cells in the detrusor muscle have increased urinary excretion of LTD4. In a pilot study, 10 patients with IC and high mast cell counts were treated with an LTD4 antagonist (Montelukast). The patients reported decreases in the number of times they voided and a decrease in nocturia and pain. No further changes were observed after 6 and 12 months of followup.

LTD4 may also mediate histamine hyper-responsiveness; activated mast cells release histamines, and an increased cellular response to histamines often is observed in inflammatory disorders. Pretreatment of cultured human detrusor muscle cells with LTD4 in low concentration result in an augmented calcium response to histamine when measured using the calcium sensitive fluorescent probe fura-2. Increased isometric force measurements and increased frequency of oscillation of detrusor muscle biopsies also were observed after pretreatment with LTD4 followed by histamine treatment. This is the first study to show that LTD4 induces up-regulation of the histamine response in human detrusor smooth muscle and suggests that a combination of LTD4- and histamine H1-receptor antagonists may be an effective treatment for IC.

Because mast cells release leukotrienes, histamine and other inflammatory mediators, understanding the factors responsible for the maturation and/or migration of mast cells in IC is important. Detrusor smooth muscle cells were found to produce MCP-1, IL6, and SCF, which may mediate recruitment and accumulation of mast cells in response to proinflammatory mediators such as TNF-α and IL-1β, in areas of inflammation in the bladder; thus, during inflammation, human detrusor smooth muscle cells adopt a secretory phenotype. Identifying the sources of and mediators involved in bladder inflammation may provide targets for new therapeutic agents for the treatment of IC and other inflammatory bladder disorders.

Macrophage Migration Inhibitory Factor in Pelvic Viscera Inflammation

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Macrophage migration inhibitory factor (MIF) stimulates production of proinflammatory cytokines such as TNFα, IL1β and IFNγ and also counteracts glucocorticoids, thus controlling the magnitude of the immune response. MIF is constitutively expressed in the urogenital tract epithelium, and MIF expression is upregulated in bladder and prostate epithelium by inflammatory stimuli; MIF release into the bladder lumen also is induced by inflammation.

Increased levels of MIF are found in some inflammatory and autoimmune diseases, such as ulcerative colitis, rheumatoid arthritis, and type 2 diabetes.

MIF released into the bladder lumen is complexed to other proteins, although the role of these complexes currently is unknown. In rats, MIF is complexed with the proteinase inhibitor α-1-inhibitor-III (α1-I3). Substance P (SP) induces α1-I3 in the apical cells of the rat urothelium and induces MIF/α1-I3 complexes to colocalize to umbrella cells. In humans, MIF has been found to form complexes with α2-macroglobulin, ceruloplasmin, and uromodulin. Urinary MIF/ceruloplasmin levels are increased in the urine of patients with urinary tract infections (UTIs), and modest increases in the levels of this complex also have been observed in urine from IC patients. Release of MIF complexes into the bladder may involve both α-adrenergic and muscarinic receptors; release can be prevented by lidocaine, hexamethonium, and atropine. MIF exerts its effects through formation of the MIF-CD74 receptor complex, which binds to and activates the CD44 cell surface receptor, resulting in increased ERK phosphorylation. SP increases cell surface CD74 and MIF in the urothelium and also increases levels of ERK1/2.

Future research concerning MIF and its possible role in IC includes determining whether muscarinic and/or α-adrenergic receptors, expressed in urothelium or in nerve fibers in the bladder, can modulate MIF release; blockade of CD44/CD74 MIF signaling to determine the effects of this signaling pathway on inflammation; and elucidation of the function of MIF/protein complexes by identifying biologically active complexes and binding domains that may modulate MIF activity.

Questions and Discussion

A participant asked Dr. Apodaca whether activated HB-EGF in his model system is tethered or released in a soluble form. If it is released into urine, interaction with EGFR would be a random event. Dr. Apodaca answered that HB-EGF and EGF levels in urine may be very high, allowing cleavage and activation to occur in close proximity to receptors. At the apical surface, the vast majority of the surface is composed of plaques, resulting in receptors and ligands existing in close proximity. There is evidence of glycosaminoglycans associated with the apical surface that may assist interaction of HB-EGF with receptors. The participant added that mucous on the surface of the cells also would help trap growth factors close to cell-surface receptors.
Dr. Karen Berkley asked how the vasculature could contribute to the changes observed in the urothelium of IC patients. Dr. Apodaca answered that the capillary bed is intimately associated with the urothelium, thus chemokines traveling through the vasculature could easily interact with the urothelium; similarly, changes occurring in the urothelium could in turn interact with the capillary bed. In response to further questions from Dr. Berkley, the panelists added that they had not yet looked for possible structural changes in the vasculature mainly because of limitations imposed by cell culture models. Dr. Chai commented that differences in vascular endothelial growth factor (VEGF) have been observed in glomerulations.

A participant asked whether expression and localization of the APF receptor differs in IC patients compared to normal controls. Dr. Keay replied that this work had not yet been done. A participant asked whether APF-enhanced release of ATP was an acute effect. Dr. Chai answered that this effect occurred after pretreatment with APF for 24 hours. A participant commented that

many cells in culture do not express uroplakin, so these cells probably are not covered by an uroplakin membrane. He asked whether this resulted in exaggerated release of ATP and other substances from cultured urothelium, causing ATP to be released from the entire surface of the cell. Dr. Apodaca commented that ATP release appears to be regulated similarly *in vitro* as in tissue, but could be quantitatively different.

A participant commented that he had seen heterogeneity in the calcium response to carbacol and asked Dr. Southgate whether she had observed any differences in the capsaicin response between IC cultured cells and normal cells cultured in calcium. Dr. Southgate answered that this had not yet been explored, particularly in a differentiated system as opposed to proliferating cells.

A participant asked whether nerve stimulation decreased levels of APF and speculated on whether neural influence might have a role in maintaining APF levels. Dr. Keay answered that currently it was not known whether neural stimulation affected APF levels. Frizzled proteins are important for embryonic development of epithelial and neuronal structures. It might be useful to determine whether there are differences in Frizzled-related signaling in epithelial and neuronal cells of IC patients. APF does not appear to have a function in normal adult human cells; APF could have a normal function during development and perhaps is activated aberrantly in adults with IC. The APF receptor CKAP4 is expressed in vascular smooth muscle cells and type 2 pneumocytes and probably in many other tissues, suggesting that it may have other ligands.

SESSION 2: EPIDEMIOLOGY

Epidemiology in Context

Philip Hanno M.D., M.P.H., University of Pennsylvania, Philadelphia, PA

A significant issue facing epidemiologic studies of painful bladder syndrome (PBS)/IC is defining the problem—clearly delineating how IC should be defined and diagnosed. Over the years, a number of different definitions have been proposed for IC. Hunner's definition of IC in 1917 described a form of ulceration viewable by endoscopy that was resistant to ordinary treatments and found in patients with frequency and bladder symptoms. Messing and Stamey's seminal paper published in 1978 described symptoms (around-the-clock frequency/urgency and bladder pain somewhat relieved by voiding) associated with glomerulations apparent with bladder distension under anesthesia.

To help resolve this issue, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) develolped a list of criteria to define IC. These include pain associated with the bladder or urinary urgency and glomerulations or Hunner's ulcer on cystoscopy under anesthesia; exclusion of other disorders that might cause these symptoms; duration of symptom(s) for at least 9 months; eight voids per day and nocturia; and less than 350 cc bladder capacity when awake. Analysis of patients in the NIDDK IC database found that patients meeting the NIDDK criteria were considered by the vast majority of experts to have IC. However, sixty percent of patients diagnosed with IC by these experts did not meet the criteria; thus, the criteria must be broadened for clinical use.

Difficulties in defining IC contribute to difficulties in determining IC prevalence. A number of surveys using different methodologies have found IC incidences ranging from 1.6 per 100,000 women to 158 per 100,000 women. Self report as part of the National Household Interview Survey found a rate of 450 per 100,000; three studies that used O'Leary-Sant scores found prevalences of approximately 300 per 100,000. These wide ranges of prevalence estimates can be attributed to problems faced by IC epidemiologists, including lack of a uniform definition of PBS/IC, lack of readily available diagnostic marker(s), unknown etiology, uncertain pathophysiology, lack of standardized methodology, differences in the populations studied, and overlapping conditions and definitions. In particular, OAB (overactive bladder), which can be defined as urgency with or without urge incontinence, usually with frequency and nocturia, is often confused with PBS (pain related to bladder filling and often accompanied by similar symptoms), leading to confusion between these two conditions. PBS also is consistent with a number of overlapping conditions, including chronic fatigue, fibromyalgia, irritable bowel syndrome, and depression.

To improve IC epidemiology, tools including validated diagnostic markers; evidence-based, symptom-specific definitions of IC; studies on true incidence, prevalence, natural history, and risk factors; and the ability to differentiate PBS/IC from other causes of voiding dysfunction and bladder pain are needed. Population studies will help determine incidence, prevalence, and risk factors; cohorts of incidence cases will help to understand the etiology and natural history of PBS. Population studies provide the most accurate data, but they can be expensive. Case-control studies provide a cost-effective way to identify risk factors, demographic features, familial aggregation, and associated syndromes.

Events Preceding Interstitial Cystitis

Jack W. Warren, M.D., University of Maryland School of Medicine, Baltimore, MD

Events Preceding Interstitial Cystitis (EPIC) is a case-control study involving only women, which is designed to identify risk factors for IC/PBS. At present, the study is in the recruitment phase and has screened 1,022 women. Of these, 270 cases with recent onset IC/PBS have been enrolled and data from the first 222 are presented here. Questions about pain characteristics and pain affectors (pain that worsens with bladder filling, and/or improves with voiding, and/or worsens during voiding, and/or worsens with diet) could be used to identify 98 percent of EPIC patients—as well as 95% of patients from the Interstitial Cystitis Data Base who "definitely" had IC.

EPIC's proposed case definition includes 3 months or more of pelvic pain, pressure, or discomfort that: 1) increases with bladder fill, 2) increases with food or drink, 3) increases with void, and/or 4) decreases with void, and is accompanied by one or more of concurrent 1) urgency, 2) frequency (≥11 per 24 hours), and 3) nocturia (≥ 2 per night).

Epidemiologic Studies of IC
J. Quentin Clemens, M.D., M.S.C.I., Northwestern University Feinberg School of Medicine, Chicago, IL

Prevalence estimates for IC have been calculated based on patient self-report, physician diagnosis, or IC/PBS symptoms. As part of the National Health and Nutrition Examination Survey, patients answering "yes" to two questions regarding symptoms and previous diagnosis of IC or PBS were defined as having IC. This led to an overall prevalence estimate of 470 cases per 100,000 (60 per 100,000 men and 850 per 100,000 women). These figures are likely to be overestimates and reflect recall bias. Using data from the Kaiser Permanente Northwest HMO, physician-diagnosed cases of IC determined frequencies ranging from approximately 200 per 100,000 to 45 per 100,000 women. Using IC/PBS symptoms defined as pelvic pain for at least 3 months, either urgency or frequency for at least 3 months, and pain increasing as the bladder fills or pain relieved by urination to diagnose IC resulted in an IC diagnosis in 6.2 percent of women and 2.3 percent of men.

Analysis of the costs of IC using the Kaiser Permanente database found that women diagnosed with IC had a 2.4-fold increase in mean medical costs compared to controls; most of the cost increase was related to prescription and outpatient costs. Analysis of patient characteristics found that IC patients were no more likely to be obese or have conditions such as high blood pressure or type 2 diabetes than were controls. IC patients were found to have greater risks for some conditions, including endometriosis (odds ratio [OR]=10.4 for patients versus controls), late effect child abuse (OR=9.3), other intestinal disorder (OR=8.2), and stomach function disorders (OR=4.6).

Epidemiology of PBS/IC (prevalence, correlates, and quality of life): Results from Boston Area Community Health Study
John B. McKinlay, Ph.D., F.A.C.E., New England Research Institute, Watertown, MA

The aims of the Boston Area Community Health (BACH) study are to determine the prevalence of PBS (by age/gender, race or ethnicity, and socioeconomic status); estimate the magnitude of overlap of PBS symptoms with those suggestive of other urologic conditions; analyze the relationship of PBS with psychosocial factors, such as sexual abuse or depression; determine the relative effects of PBS on quality of life; and estimate the probable future magnitude of PBS. The BACH population includes 5,506 patients (2,200 men and 3,200 women) ages 30 to 70 years, and includes African Americans, Hispanics, and Whites. Using the operation definition of PBS as pain increasing when the bladder fills and/or pain relieved by urination, with a duration of at least 3 months, PBS was more common in women than in men in this sample and peaks at approximately 4 percent of the sample (prevalence peaks in women between the ages of 40 and 59 years and in men between the ages of 50 and 79 years). PBS symptoms are more prevalent in Hispanics than in African Americans or Whites and also are more prevalent in both men and women with low socioeconomic status.

Examining the overlap of PBS symptoms with other symptoms found that women often have PBS symptoms in conjunction with symptoms suggestive of other condition, such as UTI. There also appears to be a strong relationship between depression and PBS symptoms, although at

present, it is unknown whether depression causes PBS or PBS causes depression. Sexual abuse and symptoms of PBS also appear to be related, because patients with PBS report sexual abuse at twice the rate of those without PBS; similar results are found for emotional and physical abuse suffered as a child or adult.

PBS exerts a stronger negative effect on quality of life than a number of major chronic conditions, including high blood pressure, diabetes, and heart disease. This is probably because PBS represents a burden that significantly affects everyday life. PBS is likely to increase in the next 25 years as the population of the United States ages; urologic symptoms may become epidemic by 2025.

IC in the Swedish Twin Registry
Magnus Fall, M.D., Ph.D., Sahlgrens University Hospital, Göteborg University, Göteborg, Sweden

Probands for this registry were defined as those reporting bladder pain that improves with urination and/or worsens as the next urination approaches, frequency of urination (at least 11 times in 24 hours), and nocturia at least once a night. A Web-based questionnaire was used to select twins born between January 1959 and May 1985. Currently, only baseline data have been collected. Data on 23,058 responders to the questionnaire also are being analyzed; the total response rate currently is 61 percent.

Overview of the RAND Interstitial Cystitis Epidemiology Study
Sandra Berry, M.A., RAND Corporation, Santa Monica, CA

The goals of the RAND Interstitial Cystitis Epidemiology (RICE) study are to: (1) develop a case definition for IC in women for patient screening and epidemiological studies; (2) develop and validate a symptom questionnaire to identify female IC patients through self-report; (3) develop IC specific self-report measures of functional status and disease burden; (4) conduct first and second stage screening for IC; and (5) describe the impact of IC on quality of life compared to other disease.

A case definition for IC will be developed by adapting the RAND/University of California, Los Angeles Appropriateness Method. This will involve a panel consisting of nine experts with experience in PBS/IC and related diseases, literature review of case definitions of PBS/IC, initial ratings of symptoms as indicators of PBS/IC diagnosis, and discussion and a second set of ratings to establish criteria for diagnosis through patient reports. Symptom questionnaire development, based on the results of the case definition exercise, and validation currently is underway to identify populations of women with symptoms of IC who do or do not meet NIDDK criteria, which will help determine the specificity and sensitivity of the case definition for use in population screening.

Questions and Discussion

Ms. Jane Meijlink asked whether urgency should be divided into urgency because of fear of pain and urgency because of fear of leakage. Dr. Hanno answered that patients should understand

that urgency is defined as a sudden, compelling urge to void, implying fear of incontinence and not fear of pain. Ms. Meijlink suggested that no changes in the definition of IC/PBS be made until more studies on the nature of urgency, such as mechanism and location of the sensation of urgency in IC patients, have been performed. Most patients consider pain and urgency to be two different sensations. Dr. Hanno added that for PBS, pain must be included in the definition as well as urgency and frequency. "Urgency" may be an imprecise term because most patients define urgency in different ways. Dr. Abrams countered that urgency as defined by ICS 2002 (sudden, compelling urge to void, etc.) should not appear in the PBS definition. Ms. Meijlink said that in her surveys, patients stated they felt pain over the entire bladder and pelvic floor, but urgency was felt at the base of the bladder or the top of the urethra, and did not necessarily feel like pain.

Dr. Berkley asked whether data concerning the timing of symptoms, for example, with respect to the menstrual cycle or day of the week, had been collected. A panelist answered that in one survey, 75 percent of women claimed that pain worsened premenstrually and lessened afterwards.

Dr. Stanley Antolac asked panelists to consider the existence of cardinal symptoms. He referred to an article describing 13 men with prostatitis-like pain, in which 3 of the 4 sexually active men had painful ejaculations—a cardinal symptom of prostatitis; however, none of the 13 men have prostate glands. In addition, women who had pelvic exenteration for IC also had persistent chronic pain. In both cases, patients have cardinal symptoms rather than organ disease.

Dr. William de Groat asked whether there was evidence that certain symptoms occur earlier than others in women with multiple symptoms, such as urgency and pain. A panelist answered that in his survey, at the onset of symptoms, 58 percent of women reported 3 symptoms (pain, urgency, and frequency) and 82 percent reported 2 of these 3 symptoms. Dr. de Groat commented that this appeared indicative of a dysfunction in the sensory path that may drive the urgency sensation.

Dr. Nordling commented on the effects of urinary diversion. Of 11 patients, 10 became pain free after surgery. He added that perhaps diversion should not be considered a last resort, but rather should be considered earlier in treatment, because waiting could result in development of centralized pain that is more difficult to treat.

SESSION 3: DIFFERENT PERSPECTIVES ON PBS/IC

IC: The Autonomic Neurologist's Perspective

Thomas Chelimsky, M.D., University Hospitals of Cleveland, Case Western Reserve University, Cleveland, OH

Autonomic function abnormalities include disorders such as irritable bowel syndrome (IBS), fibromyalgia, and complex regional pain syndrome, some of which overlap with IC; IC thus may be an autonomic nervous system (ANS) disorder. Autonomic functions such as cardiac parasympathetic function, sympathetic cardiovascular function, and axon reflex response can be clinically tested. Autonomic testing can be used to localize lesions in the neuraxis (central

nervous system [CNS]—brain, spinal cord, or root; or peripheral nervous system [PNS]—ganglion or peripheral nerve), identify which branches are affected, suggest differential diagnosis and work-up, and direct management of syncope and orthostasis.

IC has in common with other autonomic disorders a predisposition to aberrant autonomic and sensory processing and a complex pathophysiology that involves interactions between the nervous system and end organ that are not yet understood. This aberrant processing may be maintained at either the end organ or nervous system level. Pathophysiologic research on other autonomic disorders may provide useful information concerning the diagnosis, etiology, and treatment of IC.

A Pharmacologist's View of PBS/IC

Karl-Erik Andersson, M.D., Ph.D., Wake Forest Institute for Regenerative Medicine, Wake Forest University School of Medicine, Winston Salem, NC

IC/PBS is a multifactorial disease and thus presents a challenge for pharmacologists attempting to define targets and develop effective drugs for treatment. The etiology of IC suggests numerous defects ranging from urothelial dysfunction to mast cells, autoimmune disease, and occult infection. IC also could be considered a bladder disorder with systemic problems or a systemic disorder with bladder symptoms, or both, further complicating the definition of targets. The bladder urothelium has both barrier and signaling functions, and both could be involved in IC. The glycosaminoglycan layer of the urothelium may be disrupted or thinned in IC, increasing bladder permeability; direct exposure of the urothelium will affect signaling processes.

The TRPV1 receptor may be a potential target for therapy, if it can be selectively blocked. The mean relative area of TRPV1 fibers, TRPV1 urothelial immunoreactivity, neurofilaments, and TRPV1 fiber-neurofilament ratio all are increased in patients with PBS. High levels of NO also are observed in IC; thus, NO and NO-related enzymes such as NO synthase, may be therapeutic targets. APF also may be a target, because IC may be caused by an inhibition of normal bladder epithelial cell proliferation, resulting in barrier dysfunction and exposure of sensory nerve cells in the bladder wall to urine. Bladder mast cells can be activated by smooth muscle cells in the bladder; aberrant activation of these cells may contribute to IC, so preventing their activation is another therapeutic goal. The pain of PBS/IC may involve nociceptive, visceral, and neuropathic components, and all must be considered in therapeutic approaches.

PBS/IC probably will be a multifactorial disease, with both major and minor players and innocent bystanders; the identity and roles of these players may be different in different patients. Therapeutic strategies should consider combinations of drugs to target different contributors to PBS/IC. Goals of these strategies should include treating pain, influencing pathological mechanisms, and stopping the progress of the disease.

Sexual Dysfunction Functioning in IC/PBS
J. Curtis Nickel, M.D., Queen's University, Kingston, Canada

Problems with sexual functioning often are ignored by IC researchers. Sex and sexual function are important to relationships and quality of life and should be addressed when treating IC. Prevalence of sexual dysfunction can reach as high as 40 percent in women who have undergone surgery for gynecologic malignancies; similar levels are reported in breast cancer survivors and women who have had hysterectomies for benign disease. In contrast, prevalence of sexual dysfunction in women with IC is unknown.

One study that examined sexual function in women with moderate to severe IC/PBS found that sexual function was significantly impaired in these women and predicted both mental and physical quality of life. Using the MOS Sexual Functioning Scale, which addresses interest, enjoyment, arousal, and orgasm related to sexual functioning, only 10 out of 163 women reported no dysfunction; greater than 50 percent reported moderate to severe sexual dysfunction, and more than 90 percent reported some form of sexual dysfunction. Another study of IC patients found that these patients reported levels of sexual dysfunction more severe than that reported by patients who seek help at sex clinics.

Analysis of patients treated with pentosanpolysulfate found that patients who experienced at least a 30 percent reduction in their symptom score had improved sexual functioning; reduction in sexual dysfunction was correlated with symptom reduction. Other suggestions for improving sexual dysfunction in patients with IC include physical therapy, massage and trigger point therapy, pelvic floor exercises, biofeedback, and vaginal dilation therapy. Patients also should be encouraged to increase noncoital behaviors, such as massage and oral and noncoital stimulation. Dyspareunia can be minimized by using different positions, lubricants, or precoital medications. Cognitive-behavioral therapy also should be considered.

Questions and Discussion

Dr. Iqbal Hussain asked whether the study of women and sexual functions included sexual histories. He asked if urgency in these women was accompanied by incontinence and whether sphincter electromyography (EMG) analysis had been performed. Dr. Nickel answered that most of the women had small bladders and an urge to void early. Urinary sphincter EMG analysis had not been performed, and details of the sexual dysfunction were lacking.

Dr. de Groat commented on the challenges of identifying major and minor players. Patients with IC/PBS have sensory symptoms, which implies abnormalities in the nervous system, either abnormal input or abnormal processing of normal input; understanding neurological aspects of this condition should be a priority. Dr. Andersson answered that from a therapeutic point of view, patients with pain should have the pain treated, regardless of whether the etiology is known. A participant commented that the primary afferent pathway would be a good target for therapy.

A participant commented that during bladder constriction, vesicovascular reflex is enhanced in people with spinal cord injury and bladder irritation. He asked whether there were any studies of

ANS problems that examined bladder filling and pressure in IC patients; for example, does blood pressure rise as the bladder fills? A panelist answered that in spinal cord injury cases, blood pressure is controlled autonomously and will rise as the bladder fills, but it is unknown whether this is the case in IC patients.

A participant commented that endometriosis or severe dysmenorrhea are major risk factors for IC. One symptom of endometriosis is subfertility, which could be related to sexual function. She asked whether these two conditions had been included in the sexual function survey. Dr. Nickel answered that endometriosis and IC often are diagnosed concurrently. Diagnosis of endometriosis, however, often is not substantiated by endoscopic study; in these cases, patients are referred for treatment for IC. Conversely, endometriosis, which may not cause pain, ofetne is found during endoscopy. Dr. Chelimsky added that steroids may help treatment of any pain because of their broad effects.

SESSION 4: EUROPEAN OPINION ON PBS/IC CHARACTERIZATIONS

Diagnosis and Standard Investigations for PBS/IC

Arndt van Ophoven, M.D., Ph.D., University of Munster, Denmark

Standardized patient evaluation is necessary to develop a specific definition and characterization of IC. In May 2003, several European physicians formed the European Society for the Study of IC/Bladder Pain Syndrome (BPS) (ESSIC) to develop a consensus on how to evaluate patients with suspected IC. Evaluation includes a thorough general medical history focused on previous bladder-related conditions and surgeries, the location and characteristics of pain, a physical examination focused on a vaginal examination in women (to exclude vulvitis, endometriosis, and cervical pathologies) and a digital rectal examination in men (to exclude prostatitis and malignancies) to map and localize pain, and laboratory tests to rule out any infections that could contribute to pain.

Symptom evaluation should include having patients keep a voiding diary (volume intake and output for 3 days, then the number of voidings during day and night), O'Leary-Sant Symptom score supplemented with the Quality of Life Score from the International Prostate Symptoms score, and a Visual Analogue Scale to evaluate pain. Further evaluation should include urodynamic analysis to determine the presence of overactive bladder or bladder outlet obstruction in males. Flowmetry, post-void residual urine volume, and a pressure-flow study are optional in women; flowmetry should be done in all men, and pressure-flow study and measure of residual urine volume should be performed in men if the maximum flow rate is less than 20 ml/sec. Potassium sensitivity testing is recommended, because it has shown prognostic value in bladder irrigation studies, but this testing is considered optional.

Cystoscopic and Morphological Findings in PBS/BPS/IC

Magnus Fall, M.D., Ph.D., Göteborg University

Cystoscopy is not useful in the diagnosis of PBS/IC but is needed to exclude other conditions. PBS/IC is a heterogenous disease with pain that can be felt in the urethra, vagina, groin and/or the lower back; a significant characteristic of PBS/IC is pain that increases during urination.

PBS/IC can be either the classic subtype, characterized by the presence of Hunner lesions, or patients may have similar symptoms but no typical signs of inflammation. The classic subtype of PBS/IC is characterized by symptom onset at an older age, slightly lower functional capacity, and lower capacity under general anesthesia than the non-ulcer subtype of PBS/IC.

Cystoscopy with bladder distension can be used to examine the interior of the bladder for inflammation or lesions characteristic of PBS/IC. This also may reveal small cracks in the mucosa that appear upon distension but quickly subside, which often is observed in normal bladders as well. Distension also may reveal edema around a lesion caused by mast cell degranulation. A dedicated endoscopist is required to effectively use cystoscopy as a diagnostic tool. Biopsies of the bladder must include detrusor muscle. Histopathological features to look for with endoscopy include the state of the urothelium, presence of inflammatory cells, fibrosis, and detrusor myopathy. Focal inflammation that may contribute to PBS/IC is characterized by aggregates of lymphocytes, plasma cells, and mast cells. Mast cells and lymphocytes also can be observed in urine. Naphtholesterase and toluene blue can be used to visualize mast cells; mast cells penetrating the mucosa, stroma, and the detrusor muscle are characteristic of the classic subtype of PBS/IC. Detrusor smooth muscle cells also may be abnormal and intrafascicular fibrosis may be present in PBS/IC.

A biopsy classification system based on morphological subgroups that correlate with severity of symptoms has been proposed. Clustering will be based on baseline frequency, urgency, and pain, and compared to inflammatory features, urothelial denudation, and edema. Development of biomarkers for PBS/IC also will help distinguish classic from nonulcer PBS/IC. Promising markers include APF, HB-EGF, and EGF. Additionally, intralumenal urinary bladder NO content may be increased in patients with classic Hunner PBS/IC.

Mast Cells in PBS/IC

Kirsten Bouchelouche, M.D., Smooth Muscle Research Center, Koege and Herlev Hospitals University of Copenhagen, Denmark

An increased number of activated mast cells often are seen in the urothelium, lamina propria and in the detrusor of PBS/IC patients leading to the theory that mast cells may play a pathogenic role in some cases of PBS/IC. Mast cells often are increased in classic ulcerative IC (6- to 10-fold) and approximately 2-fold in non-ulcer IC compared to controls. Mast cells are triggered by numerous stimuli, including infections agents, cytokines, certain drugs, hormones, or growth factors; when stimulated, they release mediators of inflammation that may contribute to the pathology of PBS/IC. All human mast cells contain the proteinase tryptase $MC_{(T)}$; another population also contains the proteinase chymase $MC_{(TC)}$. The $MC_{(TC)}$ may be the type of mast cells dominantly present in the bladder of IC patients. A study showed that high mast cell count, fibrosis, and severe inflammation were associated with poor outcome.

Biopsies to assess mast cells, fibrosis, and inflammation in the bladder must be performed in standardized way. After distension to full capacity during cystoscopy, bladder biopsies should be taken at roughly half-full bladder capacity. At least three biopsies should be taken from two lateral walls, and the bladder dome and biopsies of lesions also should be performed; detrusor muscle should be present in the biopsies. ESSIC has developed recommended procedures for

fixing, handling, and staining biopsies, and for counting mast cells. The epithelium and propria should be examined for ulceration, inflammation, granulations, and fibrosis, as well as nonspecific inflammation, hyperemia, and hemorrhage. Detrusor muscle abnormalities, the presence of intrafascicular fibrosis, and mast cell count also should be reported. Detrusor muscle myopathy is observed in other bladder diseases but appears to be associated with more severe PBS/IC. Intrafascicular fibrosis in IC is reproducible and may be correlated with clinical outcome and stage.

ESSIC has developed a number of recommendations concerning how to perform biopsies and evaluate the morphologic findings of the biopsies. These recommendations have been published in *European Urology* (2004).

ESSIC Approach to the Design of Diagnostic Criteria in Confusable Diseases
Joop P. van de Merwe, M.D., Ph.D., Erasmus MC Rotterdam, The Netherlands

Classification criteria are needed to distinguish patients with IC from patients with other confusable diseases. Diagnosis of PBS/IC will be based on eliminating confusable diseases and confirming the presence of PBS/IC. Elimination of confusable diseases is necessary because such diseases often are more common than PBS/IC, and many can be treated. Diseases that can be confused with PBS/IC include a number of urologic or gynecologic malignancies; infections caused by bacteria, viruses, or yeast; bladder stones; pelvic floor-related muscle pain; prostatitis; and endometriosis. Confusable diseases can be excluded by performing a thorough medical history and physical exam, urinalysis, serum prostate-specific antigen in males, flowmetry and postvoid residual urine volume measurement, and cystoscopy with biopsy if necessary. Each of these procedures can eliminate a number of distinct confusable diseases; if all have been eliminated, confirmation of PBS/IC is the next step in diagnosis.

PBS/IC is difficult to confirm because there are no features that are unique to this disease. In contrast to common belief, symptoms and signs for use in diagnostic criteria do not need to be specific for the target disease. On the contrary, if a specific symptom or sign existed for the target disease, a diagnosis would only require the presence of the specific feature and diagnostic criteria are not necessary. As is the case when individual people or music compositions are recognized, diseases can be recognized by their specific combination of features.

Similarly, it may be possible to recognize a combination of symptoms and signs for the diagnosis of PBS/IC. ESSIC obtained consensus that the following findings confirm the diagnosis of PBS/IC in patients with typical symptoms in whom confusable diseases were excluded: glomerulations and/or Hunner lesions observed upon cystoscopy with hydrodistension; and/or the presence of inflammatory cells, detrusor mastocytosis, granulation, and intrafascicular fibrosis.

The proposed actions for the diagnosis of PBS/IC can be summarized as follows:

1. **Selection of patients** who need further evaluation for the presence of PBS/IC on the basis of the symptom of (chronic) pain related to the urinary bladder accompanied by at least one other urinary symptom

2. **Exclusion of confusable diseases** as the main cause of urinary symptoms on the basis of:
    a. medical history and physical examination
    b. dipstick urinalysis, various urine cultures and serum PSA in males over 40 years
    c. flowmetry and post-void residual urine volume by ultrasound scanning
    d. cystoscopy and, if indicated*, biopsy

3. **Confirmation of PBS/IC** by hydrodistension at cystoscopy and, if indicated**, biopsy

** if needed to make a diagnosis*
*** if needed to make a diagnosis or to document the type of PBS/IC*

Consensus was obtained to distinguish types of PBS/IC on the basis of whether cystoscopy with hydrodistension is performed and/or biopsies are taken, and if so, the findings. Consensus was also obtained to no longer use the name interstitial cystitis but instead to use bladder pain syndrome (BPS) in order to comply with the current nomenclature of other pain syndromes.

ESSIC Classification of PBS/BPS
Jørgen Nordling, M.D., University of Copenhagen, Denmark

The original NIDDK guidelines for diagnosing IC failed to include a number of patients believed by experts to have IC. To include these patients, the term "Painful Bladder Syndrome" was developed and defined as "suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and nighttime frequency in the absence of infection or other pathology." IC was defined as having the symptoms of PBS in addition to "typical cystoscopic and histological features." In 2006, the ESSIC group concluded that the diagnosis of PBS/IC would be made on the basis of "the symptom of pain related to the urinary bladder, accompanied by at least one other urinary symptom such as daytime and nighttime frequency, exclusion of confusable diseases as the cause of the symptoms and cystoscopy with hydrodistension and biopsy if indicated." Findings such as glomerulations and Hunner lesion during cystoscopy with hydrodistension and inflammatory or other changes at morphological investigation of bladder biopsies would be used to classify types of PBS/IC.

Because PBS did not fit into the taxonomy of other pelvic pain syndromes such as urethral or vulvar pain syndromes, and because IC is open to different interpretations, ESSIC decided to rename PBS to BPS, followed by a type indication. BPS type is indicated by two symbols, the first of which corresponds to cystoscopy with hydrodistension (1, 2, or 3 indicating increasing grade of severity) and biopsy (A, B, and C indicating increasing grade of severity of biopsy findings).

PBS/IC (BPS) in Context of Pain Syndromes
Andrew P. Baranowski, M.D., University College London Hospitals, The National Hospital for Neurology and Neurosurgery, United Kingdom

BPS is defined as pain with a collection of symptoms, the most important of which is pain perceived to be in the bladder. Pain is a perception, similar to hearing, and is composed of

activation of nociceptors by stimuli; it is associated with an unpleasant sensory and emotional experience and with actual or potential tissue damage, or described in terms of such damage. Magnetic resonance imaging can show activation of pain centers in the brain but does not indicate the source of the pain. When examining patients showing signs of BPS, very few of these patients actually have the abnormalities associated with IC. IC should be distinguished as end organ, visceral-neural pain syndrome, while BPS can be considered a pain syndrome that involves the end organ (bladder) and neuro-visceral (myopathic) mechanisms. In IC, end-organ pathology will be found; end organ treatment should be the first line of treatment, and symptomatic and pain treatments should be secondary. In contrast, no end organ primary pathology usually is found in cases of BPS and thus pain treatments should be primary and symptomatic treatments secondary.

Pain involves changes at multiple levels, including the CNS and may involve psychological changes that may make it difficult for people to cope with pain. Chronic pain syndromes, such as rheumatoid arthritis often need to be addressed at many levels; treatment can involve anti-inflammatory agents, disease-modifying drugs, analgesics, and physical and occupational therapy. BPS and IC similarly may need to be treated as chronic pain conditions.

A symptom-based classification of BPS will help exclude confusable conditions and will account for pain and depression suffered by patients with BPS. BPS must be treated and managed from many angles, both physical and psychological. In the absence of specific treatment, it is important to manage the whole patient, which will require management of chronic pain mechanisms and symptoms.

Questions and Discussion

Ms. Meijlink suggested that the name of IC/PBS should be changed only if there is a compelling reason to do so, because such a change will have a significant impact on medical systems, insurance systems, patient records, and the patients themselves. There currently is no compelling reason to change the name; instead, a name change impact study to examine the impact on patients caused by problems with computer systems, hospital and insurance systems, and payers such as Medicare, should be performed. Dr. Baranowski countered that, although discussions concerning any changes should be held, it is important to change the name because "IC" suggests a pathology that does not exist in most patients who nonetheless have symptoms. ESSIC supports the change, because it is appropriate to patient treatment and management. Dr. Peters added that currently too many patients are diagnosed as having IC, but the true problem may not be in the bladder; clinicians need to learn how to separate out confusable conditions.

A participant recommended developing a central registry to validate biopsy results and provide second opinions and analysis of interobserver reliability. A panel member agreed and added that such a registry exists for fibrosis biopsies. He added that first a description of standardized biopsy techniques and a classification system should be agreed upon before establishing a central registry.

A participant commented that a 2003 literature review showed that no test had an evidence base for diagnosis of IC; in 2006, this evidence base still does not exist. A database should be

developed to determine if the tests have prognostic or therapeutic value, because these tests tend to be expensive and invasive and should be validated before their routine use is recommended. A panel member agreed that these tests are not currently recommended for routine use. At present, elimination of confusable diseases is recommended. A set of recommendations does exist concerning how the tests should be performed, if the clinician decides to perform these tests.

A participant asked whether mast cell metabolites present in urine during distension versus during urination could be possible diagnostic markers. Dr. Bouchelouche answered that current studies on mast cell metabolites vary, and the studies cannot be compared because distension was not always performed in the same manner.

Dr. de Groat commented that it is premature to exclude end organ defect because no pathology is observed; a molecular defect may be causing the symptoms associated with IC. Dr. Baranowski agreed that molecular changes should be researched, but researchers should not assume that the change is in the bladder. Dr. de Groat asked whether PBS/IC was similar to complex regional pain syndrome (CRPS) because pain in PBS/IC is driven by bladder filling and can be abrogated by local anesthesia to the bladder. Dr. Baranowski answered that pain from CRPS can be stopped with a nerve block.

Dr. Edward Stanford stated that the term "syndrome" and the proposed name change could cause confusion among clinicians; instead, he recommended a focus on overlapping diseases and concomitant disorders. Dr. Baranowski agreed that most patients had multiple problems and that was why a descriptive diagnosis was needed. A participant suggested that focus should be kept on pain, urgency, and frequency, and where these symptoms originate. This will help determine where therapy should be directed. Dr. Hussain added that the name should best serve the patients. Taxonomy and classification may be essential as academic exercises, but fundamentally, clinicians and drug developers want to know how biopsy and cystoscopy reflect patient symptoms. Dr. Paul Abrams reminded participants that a similar evolution in name occurred as prostatitis became distinct from benign prostatic hyperplasia. Clarification of these two conditions has led to better, more targeted treatments for both. Dr. Hanno recommended that a similar transition take place for PBS/IC.

FRIDAY, OCTOBER 27, 2006

SESSION 5: ADVANCES IN RESEARCH ON SENSORY PROCESSING

Inflammation and Visceral Afferent Activity

Chet de Groat, Ph.D., University of Pittsburgh Medical School, Pittsburgh, PA

For patients to experience bladder pain, sensory information from the bladder or urinary tract must reach the CNS. The bladder is innervated by myelinated (Aδ) and unmyelinated (C-fiber) afferent nerves. Aδ dorsal root ganglion (DRG) cells respond to bladder distension, evoking a feeling of fullness, but not pain or urgency. C-fiber DRG cells are silent during distension. Noxious stimuli, however, activate C-fiber DRG cells, triggering urgency, pain, and/or incontinence and are an important target for therapies designed to reduce symptoms. Recordings

from neurons in rats show that C-fiber afferent neurons comprise 70 percent of the total population of afferent nerves in the bladder, and that they respond to capsaicin by generating an inward current. The threshold for C-fiber activation is very high, compared to the threshold for Aδ activation; Aδ DRG cells also are unresponsive to capsaicin. Prolonged depolarizing current pulses trigger multiple action potentials in Aδ DRG cells (tonic activity) but only single action potentials (phasic activity) in C-fiber DRG cells**.**

The differences in action potential generation and pattern of activity between Aδ and C-fiber neurons are related to the different types of ion channels expressed in these neurons. C-fiber neurons have an unusual combination of ion channels that contributes to their reduced electrical excitability. These neurons have tetrodotoxin-resistant sodium channels that have a high activation threshold, and therefore must be excessively depolarized to induce firing. C-fiber neurons also have potassium channels, which are activated by depolarization at a lower threshold than the sodium channels and depress the generation of the action potential. Activation of potassium channels prevents the C-fibers from firing, which could explain why C-fibers do not respond to bladder distension and normally are silent. On the other hand, bladder distension activates Aδ afferents. Increased firing of these afferents triggers the sense that the bladder is filling.

Aberrant activity of the C-fiber afferents may be an issue in PBS/IC. Urothelial cells can release chemicals that affect excitability of these afferents and also may cause release of inflammatory mediators, which may alter afferent excitability. Afferents themselves can release chemicals (such as SP) that can act back on afferent receptors to regulate excitability. In addition, autonomic efferent nerves (sympathetic and parasympathetic) can release chemicals that affect afferent activity.

Chronic inflammation of the bladder can change the properties of the C-fiber afferent nerves. After chronic cystitis is induced, the C-fiber action potential threshold is lower and phasic firing is converted to tonic firing. Thus the C-fibers appear to develop the properties of Aδ afferents. The C-fibers may now respond to mechanical distension, which could account for the allodynia observed in PBS/IC. Similar changes have been observed in other visceral afferent pathways (i.e., colon and stomach).

Thus, a molecular defect that cannot be observed by microscopic analysis of bladder tissue may have a role in ion channel dysfunction in sensory pathways. Under conditions of inflammation, the sodium channel current can activate before the potassium channel current, resulting in generation of action potentials and induction of painful sensations. This mechanism has been observed in cats with IC and also may occur in humans. SP can acutely inhibit potassium channel activity and sensitize C-fiber afferent neurons; whereas nerve growth factor (NGF) can induce both a rapid and delayed increase in excitability of the C-fiber afferent system. Intravesical administration of NGF is known to acutely induce bladder hyperactivity and sensitize C-fiber bladder afferent nerves. Prolonged administration of NGF also may produce changes in K^+ channel expression in afferent nerves, suggesting a molecular mechanism by which a neurotrophic factor can modulate bladder sensory mechanisms. Suppression of potassium channels, which induces tonic firing in C-fiber afferent neurons, could be a marker for

sensitized afferent neurons in various pathological conditions, although it is not yet known if this change occurs in human sensory neurons.

Thus, potassium channels are a major focus of attention for the development of new treatments for urinary bladder disorders. If blocking potassium currents sensitizes C-fibers, then potassium channel openers may be able to reduce sensitization. The potassium channel opener, KW-7158, which reduces C-fiber afferent excitability and hyperactivity in chemically irritated bladders in rats, is being tested clinically to determine if it reduces voiding dysfunction in patients with neurogenic bladder disorders. Since balancing sodium and potassium channel activity is necessary for proper function, afferent hyperexcitability also can be regulated by suppressing the sodium channels. Down-regulation of the tetrodotoxin-resistant sodium channels by intrathecal injection of an antisense oligonucleotide suppresses detrusor overactivity induced by bladder irritation. In addition, the sodium channel blocker NW1029, which reduces detrusor hyperactivity in a chemically-induced model of IC, produces a frequency-dependent suppression of sodium currents in capsaicin-sensitive sensory neurons, increases the threshold for action potential generation in these neurons, and suppresses tonic firing induced by SP.

In summary, inflammation can trigger the release of various chemicals that can impinge on the afferent nerves and change their excitability and induce firing. Certain intracellular signaling pathways activated by inflammatory mediators can down-regulate potassium channel activity or enhance sodium, capsaicin, and calcium channel activity to cause abnormal afferent nerve function and contribute to the generation of bladder pain in pathological conditions. Thus ion channels in afferent neurons are targets for new drugs to treat chronic pelvic pain and bladder overactivity.

Early-In-Life Bladder Inflammation and IC
Alan Randich, Ph.D., University of Alabama, Birmingham, AL

Along with urothelial and immunological abnormalities, IC also may have a developmental etiology; it is possible that an early-in-life bladder event, such as inflammation during the neonatal period, contributes to the development of IC. Between 10 and 28 percent of adults with IC report urinary bladder symptoms as children, and animal data have shown that exposing a neonatal rat to painful and/or inflammatory stimuli results in augmented response to those stimuli in adulthood. This early-in-life "priming" could result in generation of overly sensitized afferents or in greater spinal distribution of afferents and central sensitization of dorsal horn neurons. Priming also could result in less inhibition of second order spinal dorsal horn neurons.

Induction of acute bladder inflammation in rats results in bladder hyperalgesia, as determined by increased EMG response, upon distension and an inflammatory response that increased systematically over time. To determine how early-in-life events affect adult EMG responses, neonatal rats (14-16 days old) were given intravesical zymosan, saline, or anesthesia alone. A group of "adolescent" rats (between 28 and 30 days of age) were treated similarly. As adults, the rats were re-exposed to zymosan and tested 24 hours after treatment. Rats treated with zymosan as neonates showed significantly increased EMG response compared to control groups, and there was marked enhancement of inflammation; this was not seen in rats treated with zymosan as adolescents. Neonatal zymosan treatment also increased frequency of micturition and seemed to

increase urgency. Thus, early-in-life experience with bladder inflammation could contribute to the pain, frequency, and urgency experienced by PBS/IC patients.

Inflammation-induced bladder hyperalgesia is suppressed concomitantly by endogenous spinal opioids; administration of systemic or intrathecal naloxone at the time of bladder distension significantly increased the magnitudes of the EMG response. Opioid inhibition was triggered by the bladder inflammation itself. Rats treated with zymosan as neonates also showed evidence of reduced effectiveness of naloxone during adult testing, which suggests that neonatal bladder inflammation impairs function of the endogenous opioid inhibitory system. In addition, neonatal bladder inflammation altered the response properties of type I spinal dorsal horn neurons; responses of type I neurons to bladder distension were enhanced in animals with neonatal bladder inflammation compared to controls.

Brief inflammation of the bladder during the neonatal period can result in chronic susceptibility to bladder hypersensitivity, including both pain and frequency of micturition. Bladder pain likely represents the net nociceptive effect or function of two opposing factors: enhanced nociceptive input from the bladder (perhaps reflecting sensitization of dorsal horn neurons) and suppression by an opioid pain inhibitory system. The relative balance between these two factors will determine whether bladder pain will or will not occur following bladder inflammation. This may be affected developmentally, based on when exposure to bladder inflammation occurs. Thus, some types of adult urinary bladder pain experienced by patients with PBS/IC may be a consequence of bladder inflammation during the neonatal period that may impair the function of the developing opioid pain inhibitory system.

Neurophysiology of Bladder Pain Sensation

Jyoti Sengupta, Ph.D., Medical College of Wisconsin, Milwaukee, WI

The sense of fullness, urge of micturition, discomfort, and pain are the main sensations arising from the urinary bladder. These sensations are conveyed to the CNS primarily by the hypogastric (thoracolumbar outflow) and pelvic (lumbosacral outflow) nerve afferent fibers. The integrated functions of these nerves regulate bladder functions. The pelvic nerve is the major pathway involved in consciously perceived sensation, particularly discomfort and pain. However, patients with bilateral sacral rhizotomy could still perceive pain during over-distension of the bladder, implicating the involvement of the hypogastric pathway in conscious sensation. In rats, the hypogastric nerve projects mainly to the T13 and L1 segments of the spinal cord, whereas the pelvic nerve projects to the L6 and S1 segments. These afferent fibers are mainly pseudounipolar cells with their cell bodies located in the dorsal root ganglia (DRG). In this study we have characterized mechano- and chemo-transduction properties of pelvic nerve afferent fibers innervating the urinary bladder. Recordings were made from the sacral S1 dorsal root and the pelvic nerve afferent fibers were detected by electrical stimulation of the pelvic nerve near the major pelvic ganglion (MPG). Subsequently, the innervation of the bladder was detected by distending the urinary bladder. A total of 184 fibers were identified by electrical stimulation of the pelvic nerve and the majority of these fibers were unmyelinated C-fibers (conduction velocity < 2.5m/s). Of these 184 afferent fibers, 68 (37%) responded to urinary bladder distension, 60 fibers (33%) were unresponsive to urinary bladder or colon distention, 27 fibers (14%) responded to colon distension, but not urinary bladder distension.

To determine whether these fibers respond reproducibly to urinary bladder distension, 10 fibers were repeatedly distended to a noxious intensity (60mmHg) of distension. Upon repeated distension the fibers exhibited a reproducible response. During slow filling of the bladder, fibers showed linear increasing response when a certain pressure was reached. Similarly, upon phasic distension (5 mm to 80 mmHg) there is a linearly increasing response of the fiber to the increasing distension. Analysis of the threshold for response to mechanical distension showed that a large population (80%) of the fibers had a low threshold for response (less than 5 mmHg) and a small population (20%) of the fibers had a high threshold (greater than 30mmHg) for response. The high-threshold fibers do not respond to bladder contraction and intravesicular pressure changes and are possibly involved when pressure reaches a painful intensity.

When the bladder was irritated with protamine sulfate, the pelvic nerve afferent fibers exhibited significantly higher spontaneous firing as well as a significant increase in response to mechanical distension indicating the ability to sensitize to change in the chemical environment of the bladder. Protamine sulfate treatment also resulted in an augmented response of the C-fibers to capsaicin, which can be blocked by selective TRPV1 channel blockers (JYL1421). TRPV1 contributes to pain perception and also to inflammation. This channel is quite promiscuous and multimodal, responding to different kinds of endogenous ligands (i.e., endovanilloids) including H^+, anandamide, LTB4, and HEPTEs, that are release during neurogenic and myogenic inflammation. It is known that activation of TRPV1 channel in the mucosal epithelium results in release of platelet-activating factor, which can produce inflammation. Our recent study has shown that blocking the TRPV1 channel preemptively can block colonic inflammation as well as visceral hyperalgesia. A similar phenomenon may occur in the urinary bladder because TRPV1 channels are present in the urothelium.

In summary, mechanosensitive afferent fibers in the pelvic nerve exhibit a linearly increasing response to increased intravesical pressure. Nearly 80% of these fibers have a low threshold for response to mechanical distension and respond to bladder contraction. A small population of fibers, however, has a high threshold for response and does not respond to bladder contraction. Induction of bladder irritation enhances the responses of these fibers to mechanical distension and capsaicin. Since these fibers undergo sensitization of response following bladder irritation, they may be involved in hypersensitivity occurring in pathological conditions.

Questions and Discussion

Dr. Karen Berkley asked about other possible mechanisms involved in the altered response after neonatal inflammation. Dr. Randich answered that neonatal treatment could prevent development of a descending inhibitory system. Alternatively, the number of afferents may be increased to a level that makes it impossible for the developing inhibitory system to functionally compensate. Another possibility is that neonatal inflammation could cause a decrease in expression of endogenous enkephalins and endorphins.

Dr. Vera asked whether changes in micturition thresholds were observed in the neonatally treated animals. Dr. Randich answered that there is a small, yet significant decrease in threshold compared to control animals. Dr. Vera asked whether the neonatally treated rats were tested for

reactivity to other pelvic viscera inflammation or distension. Dr. Randich answered that in his study, they only tested somatic sensitivity of the hindpaw to thermal and mechanical stimuli in addition to bladder sensitivity. If the mechanism involving aberrant development of a descending inhibitory system creates the effects discussed, there also will be central sensitization and perhaps peripheral sensitization and greater segmental distribution of afferents, which could allow system crosstalk that did not previously exist. Dr. Sengupta added that his group has pretreated neonates with cycolophosphamide and tested their response to colonic distension; these animals show significant hyperalgesia to colonic distension. Recordings from dorsal horn cells show hyperexcitability and a low threshold for response, indicating central sensitization.

A participant asked whether problems with the descending inhibitory pathway or accentuation of the ascending pathways were more likely to be a mechanism. Dr. Randich answered that currently, his data do not allow him to definitively answer this question. The participant asked whether Dr. Randich had checked for an increase in nerve fibers in chronically inflamed bladders. Dr. Randich indicated that he had not yet examined this.

In response to a participant, Dr. Randich explained that in normal adult rats, hyperalgesia from bladder inflammation is suppressed by opioid inhibition; in the neonatally treated rats, this inhibition is lost, leading to the exaggerated response. This effect appears to occur only if the rats are treated as neonates.

Dr. Abrams asked the speakers to consider the implications of this research for humans with IC, and to explain how urgency and pain are analyzed in rats. It also was noted to Dr. Sengupta that the distending pressure that was applied in his experiments was supraphysiological, and he was asked how that relates to normal bladder function. Dr. Sengupta admitted that the pressure ranges applied in the experiments do exceed the physiological range in humans, but the intent was to show the response characteristic of these spinal neurons to a wide range of distension pressure and whether these neurons can linearly encode the increasing intensity. He pointed out that the response characteristics of spinal neurons differ from those of vagal afferent fibers. Vagal afferent fibers innervating the GI tract at a similar pressure range exhibit saturation of firing frequency when intraluminal pressure exceeds 30mmHg. This difference in encoding pattern suggests that vagal afferent fibers are not capable of transmitting noxious stimuli to the CNS.

SESSION 6: CNS INVOLVEMENT IN PBS/IC

Central Changes in IC and Related Disorders

Emeran A. Mayer, M.D., David Geffen School of Medicine, University of California, Los Angeles, CA

There exists a close connection between micturition and emotion. Evolutionarily, micturition has had roles in behaviors such as territorial demarcation and sexual attraction implying a close neuroanatomical relationship between the limbic and cortical systems in humans. Imaging technologies allow noninvasive analysis of brain areas to examine this relationship.

Bladder afferents in the CNS enter the lateral dorsal horn; many continue to the periaqueductal gray area, an integrated brain area that receives both afferents from the periphery and also signals from the limbic system and the corticolimbic circuits. Pathways from the periaqueductal gray area descend to the micturition center, which then triggers reflexes back to the bladder. The close proximity of the pontine micturition center with the pontine locus coeruleus is likely to play a role in generating arousal in association with bladder filling. Even though this basic loop regulates the reflex action of urinary bladder filling and emptying, there are inputs from the limbic and cortical regions into this loop, mediating the effects of cognition and emotions. Like other afferent information from the viscera, the perception of bladder sensations is processed in the anterior insula, while the affective and motivational component is processed in the dorsal anterior cingulate cortex (dACC).

Imaging studies have been performed to examine the brain/bladder axis. Partial bladder filling provoked activation of the pontine micturition center and the periaqueductal gray area. Intermittent slow infusions into the bladder showed activation of regions in the brain known as the homeostatic afferent processing matrix, including the anterior insula and the dACC. Studies of brain activity associated with certain emotional stimuli can activate similar regions of the brain.

Analysis of the effects on brain activity of small volume bladder filling in patients with poor bladder control is similar to that of controls, but in response to high-volume filling, there is exaggerated activation; this could include an emotional response activated during filling. One region in which healthy people showed greater activation at high-volume bladder filling was in the orbital frontal or prefrontal cortex. In people with normal bladder control, activation of the orbital frontal cortex, in particular in the right hemisphere, has an inhibitory influence on limbic regions and indirect inhibitory influences on the micturition center. Thus, an ineffective corticolimbic response to a visceral stimulus, which in turn results in an abnormal modulatory influence on pontine regions either for pain inhibition or for bladder control, could be involved in mediating symptoms in PBS/IC.

Patients with IC rarely have bladder symptoms alone. Visceral disorders and other idiopathic pain syndromes may be linked by shared changes in the CNS in addition to peripheral changes. One hypothesis is that input from various somatic and visceral sites that is processed within the homeostatic afferent processing network (composed of insular cortex, dACC, and thalamus), undergoes modulation by corticolimbic networks related to cognition, belief systems, and emotional factors. This altered corticolimbic modulation of afferent processing could be an important mechanism underlying central pain amplification implicated in several idiopathic pain syndromes which frequently co-occur with PBS/IC.

Symptom-related anxiety and visceral hypersensitivity may be related in patients with IBS. One experiment found that fear and anxiety potentiated greater startle responses in IBS patients. The startle response is a simple brain stem reflex which can be modulated by outputs from the amygdala complex. This observation suggests that IBS patients anticipating an abdominal pain stimulus generate greater amygdala complex outputs; this effect was seen for an abdominal stimulus, but also in response to the threat of a somatic stimulus. To demonstrate the relationship between pain-related fears and pain perception, a study was performed using rectal

balloon distension, with each stimulus being stronger than the preceding one, and in which subjects are warned beforehand to expect increasing discomfort with each subsequent stimulus. The amplitude of the threat-potentiated startle response increased with decreasing pain threshold; e.g. the greater their arousal/fear response, the more sensitive the patients were to the visceral stimulus. Thus, consistent with preclinical evidence, there appears to be a direct relation between the emotional response to an expected aversive stimulus and the perception of pain.

Regardless of additional processes in the bladder and periphery, it is hypothesized that IC patients share with many other functional pain syndromes a tendency for central amplification of signals coming from the periphery. Failure to downregulate sensory and limbic areas by engaging cortical mechanisms, as well as other central pain amplification mechanisms may result in the enhanced response of central arousal circuits during expected discomfort.

Pain Produced by Autonomic-Sensory Couples: A Neural and Endocrine Affair
Jon Levine, M.D., Ph.D., University of California-San Francisco, San Francisco, CA

Pain can be nociceptive, inflammatory, neuropathic, generalized, or of mixed etiologies. Generalized Pain Syndromes (GPS) involve multiple organ systems. Sensitization of primary afferent nociceptors by inflammatory mediators or cytokines lowers the activation potential of the afferents and results in pain. Receptors for mediators released by the neuroendocrine stress axis are found on primary afferents. Coupling between the neural and endocrine systems represents a novel sensory-sympathetic coupling in which the neuroendocrine system-generated mediators act on sensory systems and may have a role in GPS. A number of GPS exist, among them fibromyalgia (FMS) and IBS. Major symptoms of GPS include systemic symptoms as well as specific pain, and a higher rate of diagnosis in women; IC shares similar characteristics.

Major features of FMS include pain, tender points, and fatigue, but normal routine laboratory tests. Analysis of tender points in FMS patients and normal women found that both groups had similar tender points, but FMS patients had lower thresholds for pressure pain. A model integrating visceral and somatic pain involves the subdiaphragmatic vagus nerve, which impacts the adrenal medulla. A decrease in subdiaphragmatic vagus nerve stimulation leads to an increase in the release of catecholamines, which in turn act on the vagus nerve to sensitize it. In rats, severing the subdiaphragmatic vagus nerve decreases the nociceptive threshold. Denervation of the adrenal gland reverses this effect. This work also showed that cytokines enhance the nociceptive response, and that this effect also can be reversed by denervation or removal of the adrenal medulla. This effect is mediated through β2-adrenergic receptors and can be reversed by receptor antagonists.

Inputs from the viscera must impact the subdiaphragmatic circuit to evoke this pain response. Experiments performed in female rats found that starvation enhanced the pain response to formalin; this effect was not reversed by the addition of glucose, but was reversed by distension of the proximal gastrointestinal tract. The sensitization effect of fasting in female rats involves the vagus nerve and adrenal medulla and also gonadal hormones, which may explain the higher rate of GPS in females. Androgen and estrogen receptors are expressed in dorsal root ganglia and in ascending and descending pain circuitry. Gonadectomy of female rats caused β2-adrenergic receptor effects to be transmitted through protein kinase A and protein kinase Cε,

rather than MEKK and caused the pain to be experienced as chronic rather than acute; treatment with estrogen reverses the effect.

Neuromodulation for IC/PBS
Kenneth M. Peters, M.D., William Beaumont Hospital, Royal Oak, MI

Sacral nerve stimulation has been approved by the Food and Drug Administration (FDA) for urinary urgency, frequency, urge incontinence, and nonobstructive urinary retention. It also may be useful for treatment of fecal incontinence, chronic constipation, IBS, sexual dysfunction, and IC/pelvic pain. Advances in neuromodulation technology have made this a minimally invasive procedure; in the past, surgery on the spine itself was required, meaning this procedure was used only for the very worst cases. Neuromodulation involves placement of a sacral implant with the wire leads initially located outside of the skin to contact the external stimulator. If neuromodulation is successful in alleviating symptoms, the wires can be placed subcutaneously. Several studies have shown that a majority of patients receiving the implants have decreases in symptoms, including pain and frequency of daytime and nighttime voids; 96 percent of patients say they would undergo implant again and would recommend the therapy to a friend.

Work is in progress to determine if neuromodulation using the permanently implanted InterStim® device can be used to decrease pain in general. Long-term morphine dose equivalents (MDE) in patients with refractory IC were assessed before and after implantation with the InterStim® device. Baseline narcotic use was compared to narcotic consumption after long-term use of the InterStim® implant. In this analysis, 20 of 21 women reported moderate or marked improvement in pain on the seven-point scale after receiving the devise. MDEs decreased from 81.6 mg/day to 53.0 mg/day, and 5 of 18 patients stopped use of all narcotics.

Stimulation of the third sacral nerve has been shown to be effective in treating voiding dysfunction. The pudendal nerve is a distal branch of S2, S3, and S4; pudendal nerve stimulation may offer the benefit of increased afferent stimulation through the sacral nerve roots. Sacral nerve stimulation was compared to pudendal nerve stimulation for the treatment of IC/PBS. Patients receiving sacral nerve stimulation reported a 44 percent overall improvement in symptoms; patients receiving pudendal nerve stimulation reported a 59 percent improvement. Pudendal stimulation was superior to sacral for urgency and frequency. Both implants reduced the number of voids per day and increased void volume. These benefits were retained for at least 6 months, and no significant adverse events were reported.

A new implantable device, the bion® device, is being tested for pudendal nerve stimulation. One patient enrolled in the bion® trial reported less frequency, pain, and urgency; decreased reliance on pain medications; and regaining the ability to work full-time after receiving the device. A second patient reported reduced reliance on pain medications, improvements in urge and frequency, and improvement in sexual function after receiving the device.

Questions and Discussion

Dr. Antolak asked whether patients with multiple peripheral compression neuropathies along with pudendal neuropathies could have congenital issues. He also asked whether patients with

symptoms such as pain in the legs and feet; restless leg syndrome; aggravation of pelvic pain during sensual ideation; pelvic pain with gastroparesis and weight loss; taste abnormalities; and colitis-like symptoms and/or obstructed defecation could have spinal cord wind-up. Many of these patients respond to therapies such as avoiding activities that place pressure on the perineum. Peripheral nerve blocks to innervation cure many of these patients permanently. A panelist (Mayer not sure he answered) answered that when pain rapidly disappears after nerve block, spinal wind-up is unlikely to be the mechanistic cause of the pain. In other syndromes in which nerve injury has been implicated, the therapeutic response can last beyond the clear affect of blocking nerve activity, which is strong evidence for involvement of a central component.

Dr. Chelimsky commented that he has found that tapering off opiate use in one group of patients resulted in a significant decrease in pain levels. He asked Dr. Levine to speculate on events that occur when the vagus nerve is cut to enhance pain. Other investigators have reported that spinal cord transection results in severe gastroparesis, which is reversed when the vagus nerve is cut. Atropine, however, does not reverse gastroparesis probably because it involves an afferent mechanism. The vagus is a very heterogeneous nerve carrying many different functions; future research will determine which branches and stimuli are important.

TOP 4 POSTERS—PRESENTATIONS

Identification of Autoantibodies As Biomarkers of IC Using the "Reverse Capture" Autoantibody Microarray.

Robert J. Caiazzo Jr., B.A., Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Microarray technology was used to identify autoantibodies to serve as potential biomarkers of IC. Development of IC biomarkers will allow better diagnosis, identification of subsets of patients, prediction of therapeutic response, and personalized treatment. A reverse capture autoantibody array was used to capture autoantibodies present in patient urine samples. Captured autoantibodies from urine of patients with IC were compared to those from normal controls. Twenty-five autoantibodies significant for IC were identified; three of these bound antigens for IL-6, the chemokine CXC motif ligand 7, and the transcription factor E2F2.

Uroplakin III-delta4 messenger RNA as a Promising Marker to Identify Nonulcerative IC

Yu Zeng, M.D., Ph.D., Kagawa University, Kagawa, Japan

Uroplakins (UPs) are expressed by urothelial cells and have a role in the barrier function of the urothelium. Immunohistochemical staining and RT-PCR were used to analyze the expression of UP Ia, Ib, II, III, and III-delta4 in bladder biopsies from IC patients and normal controls. No changes were observed in UP Ia, Ib, II, and III, but expression of III-delta4 was increased in IC patients. UP Ia, Ib, and II were decreased in patients with ulcerative tissue compared to those without ulcers. UP III and III-delta4 were upregulated in patients without ulcerative tissue compared to patients with normal tissue. UP III protein expression was increased in nonulcerative IC. Because UP III-delta4, an alternative splicing variant of UP III, was highly upregulated in IC patients without ulcerative changes, UP III-delta4 mRNA is a promising marker for identifying nonulcerative IC.

P53 as a Downstream Mediator of Signaling by APF
Jayoung Kim, Ph.D., Harvard Medical School, Boston, MA

APF is a glycoprotein involved in growth inhibition and cell cycle arrest at G_2/M phase in bladder urothelial cells. Intracellular levels of p53 are increased after treatment with APF; knockdown of p53 using siRNA partially reversed the growth-suppressive effect of APF. Ectopic expression of p53 inhibits cellular proliferation in mock APF-treated cells, implying that p53 and APF share the same signaling pathway.

Future work will explore whether the p53 target protein, p21Cip1/WAF1, is important during bladder urothelial cell growth suppression in the presence of APF and whether APF exposure affects p53 protein level by suppressing proteasome-mediated protein degradation to cause cell growth inhibition.

Toxicokinetic Study of Recombinant HB-EGF in Female Sprague Dawley Rats
Susan Keay, M.D., Ph.D., University of Maryland, Baltimore, MD

HB-EGF can abrogate the effects of APF on cell proliferation,and permeability *in vitro* and may be useful as an IC treatment. A preliminary toxicokinetic study of ^{125}I-labeled HB-EGF was performed to evaluate dose and delivery route (intravenous and intravesical). Intravescial administration of HB-EGF resulted in absorption saturated at 10 mg/kg, but intravenous administration resulted in linear absorption. For both delivery routes, the highest concentrations of HB-EGF were found in bladder tissue. No adverse effects, including behavioral, blood chemical, or histologic evidence for toxicity related to HB-EGF, were found after daily injections for 28 days.

SESSION 7: PAIN AND PBS/IC

Genetic Contributions to Individual Differences in Pain and Analgesia
Roger B. Fillingim, Ph.D., University of Florida and North Florida/South Georgia Veterans Health System, Gainesville, FL

Individual differences in pain perception and tolerance have long been recognized, and are relevant for predicting those at risk for pain and for identifying treatment options. Sources of individual variability include genetic and environmental factors and genetic and environment interactions. The biopsychosocial model of pain contends that the experience of pain is affected by complex interactions between biological, sociocultural, and psychological factors.

Previous work has shown that genetics may impact IC pain. Challenges to the study of pain genetics include how to phenotype pain (pain is subjective), multiple pain subtypes, and the need to distinguish between genes involved in the disease process and those involved in pain. Pain mechanisms also are complex, involving both the PNS and CNS, as well as psychological and sociocultural contributions. The genetics of pain also may vary across pain measures, with certain genes being more strongly associated with certain types of pain. Rodent data have shown that heritability for pain and analgesic response is between 20 and 50 percent. A number of chronic pain conditions, including migraine, low back pain, and pelvic pain, also have moderate

heritability estimates. Women show higher heritability than men, and heritability decreases with age.

Candidate pain genes should encode a molecule involved in pain processing, should have specific variants, and there should be evidence that single nucleotide polymorphisms affect function. Two candidate genes of interest are catechol-O-methyltransferase (COMT) and the mu-opioid receptor (OPRM1). COMT metabolizes catecholamines, and variants of COMT have been associated with higher or lower activity. Variants of OPRM1 have been associated with higher or lower pain-related mu-opioid receptor binding and certain OPRM1 alleles also have been associated with higher pressure pain thresholds. OPRM1 allele frequencies vary across ethnic types, with Whites more likely than African Americans to have a rare allele that confers lowered sensitivity to some types of pain. Interestingly, preliminary data suggest that this same allele confers heightened sensitivity among Hispanics. OPRM1 alleles also are differentially associated with morphine requirements after surgery. A quantitative trait loci associated with kappa-opioid analgesia in female, but not male mice, was located in the region of chromosome 8 where the melanocortin-1-receptor gene (MC1R) is located. Differences in the MC1R gene also have been associated with pentazocine analgesia; women who are "genetic redheads" appear to have a more significant response to this class of analgesics. No association between red hair and analgesia was observed in men.

(Afferent) Hypersensitivity in IC Patients
Timothy J. Ness M.D., Ph.D., University of Alabama, Birmingham, AL

A hypersensitive bladder is a hallmark feature of IC, but IC patients may also be hypersensitive in other body sites, similar to disorders such as fibromyalgia and IBS. Investigation of the psychophysics of sensation in IC patients has shown that they differ from the healthy population. Psychophysical studies of bladder distension in women showed that in healthy women, repeated distension increased the physiological response and pain rating, and also increased the size of the area of referred pain.

The effects of repeated bladder distension in IC patients also were tested, along with temperature measurements taken on the arm, analysis of pressure points, ischemic forearm tasks, and distress. A symptom measurement showed that IC patients had more symptoms and problems, and perceived themselves as having "poor health." IC patients also appear to be hypervigilant and highly sensitive to environmental and body cues. On tests of pain coping measures, IC patients resembled chronic pain patients, especially concerning an increased tendency to catastrophize. IC patients also were found to have hypersensitive bladders and find bladder distension to be more unpleasant than intense. IC patients were more sensitive to intravesical pressure, with lower volumes prompting the need to void; healthy subjects were more likely to report "discomfort" rather than pain when compared to IC patients. IC patients also were hypersensitive to deep tissue stimulation. As a group, IC patients showed normal sensitivity to thermal sensation, but within this group, there was significantly greater variability in sensitivity.

Multisite, multimodal hypersensitivity has been attributed to various causes, including inflammation, psychological factors such as anxiety (stress), previous injury (neuropathic-developmental), or failure of an endogenous control system. Failure of endogenous inhibitory

systems could cause similar effects as hypersensitivity. Pain induced at one site often can inhibit sensations of pain in other parts of the body; IC patients often lack this analgesic response and also have a decrease in pain tolerance. Female IC patients also report variation in pain during their menstrual cycles (usually pain and number of voids increase during the perimenstrual period, then decrease after menstruation), which could indicate hormonal involvement in pain perception in these women. The IC population also is heterogeneous, with one group reporting increased total body sensitivity and the other bladder-selective sensitivity; the latter group reported early-in-life UTIs.

Treatment of Non-Malignant Pain

Ursula Wesselmann, M.D., Ph.D., Johns Hopkins University School of Medicine, Baltimore, MD

Patients with chronic pain often have more than one chronic pain syndrome, indicating involvement of multiple systems. The recognition of chronic urological and gynecological pain as a "chronic pain syndrome" is fairly new in the fields of urology, gynecology, and gastroenterology. Pain should be treated, because acute pain is essentially an "early warning sign" that alerts a person to potentially damaging stimuli. Pain is initiated by specialized sensory nociceptors and has a behavioral impact—in response to pain, reflexes to withdraw from the pain are activated. Chronic pain states are characterized by pain that appears to arise spontaneously, pain produced by stimuli that normally do not produce pain, and noxious stimuli evoking a greater and more prolonged pain response.

Pain mechanisms can be characterized by three phases. During Phase I, transient activation of the nociceptive system occurs in response to appropriate stimuli, and the response is processed by the CNS. Acute plasticity is invoked during Phase II; at this point, these processes are reversible. Phase III is characterized by chronic abnormal pain sensations because of modification of the nociceptive system. Chronic pain could be considered a disease in that the pain persists after its usefulness as an alarm signal has passed, often after any tissue damage has healed, and therefore chronic pain is not directly related to the initial injury, but rather to secondary changes. Chronic pain has immune-suppressive effects and negatively impacts quality of life.

Few, if any, analgesics have been evaluated specifically for chronic pelvic pain, and there are no FDA-approved analgesics specifically indicated for IC. The goal of pain treatment is to find a medication that provides significant pain relief, with minimal side effects. Potential medications for treatment of chronic pain include antidepressants, anticonvulsants/antiarrhythmics, and opioids. None of these medications have been approved for IC treatment, but many are used in clinical practice. The ability to effectively treat IC pain with medication is hampered by a lack of clinical trials. Additionally, many different underlying causes of chronic pelvic pain might exist; these different causes may require different pain treatment strategies, and the coexistence of multiple pathogenic pain mechanisms in the same patient could require simultaneous use of several different pain treatment strategies.

Cross-System Viscero-Visceral Interactions: What is the Source of PBS/IC/BPS Symptoms?

Karen J. Berkley, Ph.D., Florida State University, Tallahassee, FL

A large table of potential therapies for pain can be generated that includes lists of drugs, somatic treatments, and situational adjustments. Despite this optimistic table, many women continue to suffer from pain associated with PBS/IC. A change in our conceptualization of pain mechanisms from the traditional "pain pathway" or "pain matrix" to another view could alter the way we currently use this table in a manner that improves pain relief.

Studies that support conceptual change have shown that neurons in CNS regions that are currently considered components of the "pain" or "touch" pathways/matrixes respond, sometimes surprisingly, to stimulation of the skin, bladder, cervix, uterus, colon, and vagina in a complex way, involving inhibition as well as excitation. In addition, the response properties of the neurons vary dramatically, either cyclically across the ovarian cycle, or over the lifespan as a function of past history such as injury (i.e., the neurons "learn"). Such a situation suggests that all of these components can be considered interactive elements of dynamic distributed systems that process information from the different parts of body. The CNS thereby provides a framework by which pathophysiology in one organ can influence the healthy functioning or response to pathology of other organs. Furthermore, the experience of pain becomes a "call to action" that emerges from this CNS processing in a dynamic manner unique to each individual.

Two studies were described as examples of such cross-organ effects. The first study showed that inflammation of the colon or uterus produced signs of inflammation in the untreated bladder. These effects were observed during proestrus but not metestrus, and were eliminated by hypogastric neurectomy. Several mechanisms could have produced the cross-organ effects, including branching sensory afferents, the dorsal root reflex, or multisynaptic processes within the CNS involving both afferents and efferents. The most likely mechanism, especially considering the ovarian cyclic effects, however, was the third (CNS).

The second study relates to clinical observations that endometriosis and PBS/IC often coexist. This study was carried out in an anesthetized rat model and showed that surgically-induced abdominal endometriosis produced bladder inflammation and reduced bladder capacity. Furthermore, although a sham surgery had little effect on the healthy bladder, it prevented inflammation from reducing bladder capacity (i.e., it produced a "silent" bladder inflammation). In the awake rat, endometriosis induced signs of an overactive bladder and the sham surgery induced mild signs of urinary retention. Innervation of the ectopic growths seen in the endometriosis but not the sham surgical condition probably underlies these effects.

These observations raise the question of the "source" of PBS/IC symptoms. Obviously the bladder is involved, but the source of the bladder dysfunction in these examples could, via interactive CNS processing, be the colon, the uterus, or the abdominal endometrial growths.

Considering the table of therapies discussed above, the findings presented here strongly support the logic that using simultaneous combinations of therapies uniquely suited to each individual

could be a more effective strategy for alleviating pain and other symptoms in patients with PBS/IC than using sequential, one-at-a-time trials of different therapies.

Questions and Discussion

A participant commented that unpublished data have indicated that 75 to 80 percent of IC patients report that cystometry replicates the pain of IC. He asked whether Drs. Ness and Berkley had asked their patients if cystometry replicated their pain and if this would help identify the source of the pain. Dr. Ness answered that his patients rated their pain and compared it to cystometry. Most patients described their pain as similar to that of a UTI. Additionally, IC patients always reported cystometry to cause pain, but the normal population did not always report that bladder distension was painful. Concerning identifying the source of the pain, Dr. Berkley explained that although bladder inflammation contributes to the pain, pain as a perception has its source in the CNS. Dr. Ness added that identifying the source of the pain is not the same as defining the disease.

Ms. Meijlink commented that treating pain in IC patients is difficult because many are intolerant of, or have strong responses to, the medications; she asked how side effects could be overcome. Dr. Wesselmann agreed that this was a common clinical observation that necessitates titrating medications at regular intervals, starting with low doses. Regarding use of antidepressants in a number of pain conditions, side effects are observed at significantly lower doses in IC patients than in patients who are depressed but have no pain syndromes. This could be because of the disease itself or because of genetic influences and should be examined in epidemiological studies. Dr. Ness added that such side effects are why his group tests patients for hypervigilance, which is a common problem in chronic pain populations—these patients are immensely aware of every internal and external cue, and are often intolerant of side effects. Drs. Ness and Berkley agreed that this underscores the need for combinatorial therapy to treat PBS/IC.

Dr. Maurice Chung asked whether Dr. Berkley had removed the endometriosis implants from the rats to see if the rats' conditions returned to normal or if, once the bladder is involved, the problems persist. Dr. Berkley answered that this experiment was in progress, but that Maria Adele Giamberardino's group in Italy has reported that in treatment of patients with co-occurring conditions, treating one condition often improved the other. This implies that treatment should start with the least invasive form of therapy available, because this will help treat any co-occurring conditions as well.

SESSION 8: NEW CONSIDERATIONS IN PBS/IC TREATMENTS

Identification and Treatment of Pelvic Floor Dysfunction in PBS/IC

Mary P. FitzGerald, M.D., Loyola University Medical Center, Maywood, IL

Somatic changes including tenderness of skin, subcutaneous tissues, or muscle, and shortened resting position and decreased contraction strength of the pelvic floor are usually found in patients with PBS/IC. Abnormal tissues found outside the pelvic floor also can be involved, including areas of abdominal muscle. Pain also can be generated by connective tissue that, along with muscle, comprises the pelvic floor.

Referred muscle pain and hyperalgesia from viscera is found in conditions such as renal colic, cholecystitis, and dysmenorrhea. Muscles that refer pain to the pelvic floor include the adductor magnus, abdominal wall muscles, and the ilopsoas. In women with IC, connective tissue restrictions and trigger points are found in the buttocks, back muscles, along the sides of the thighs, around the umbilicus, and around the vaginal and anal sphincters. A survey of 49 women with symptoms of PBS/IC found that 40 reported subcutaneous connective tissue restrictions of the abdomen, 45 reported levator ani trigger points, and 32 reported suprapubic trigger points.

Pelvic floor abnormalities also are observed in PBS/IC. These include a short, contracted pelvic floor, a short distance between urethra and perineal body, with little movement in the area during contraction, and little or no ability to contract or relax the pelvic floor. Many trigger points are found around the vagina and anus. These trigger points are associated with pain upon bladder filling because of the role of the pelvic floor and abdominal muscles in holding the bladder as it fills; pain is temporarily reduced as the bladder empties. Because of the association of muscular abnormalities with PBS/IC pain, a thorough musculoskeletal screen should be performed during diagnostic exams.

Treating these disorders should involve treatment of somatic abnormalities and any ongoing visceral problem (UTI, Crohn's disease) and modulation of the central response to visceral pain. Therapies include neuromuscular re-education, biofeedback, manual physical therapy (focused on abolishing active trigger points), trigger point injections, and possibly botulinum toxin. Of these treatments, manual physical therapy appears most promising for treating pelvic floor dysfunction. This form of treatment involves external and internal manipulations of the trigger point areas to find and release tissue restrictions. Three case series show benefits from manual therapy; a majority of patients with IC or urgency/frequency who received manual therapy had moderate to marked improvement over baseline. NIDDK is sponsoring a randomized trial of physical therapy for PBS/IC, beginning in December 2006.

Current Status of Intravesical Treatments for PBS/IC

Jurjen Bade, M.D., Ph.D., Department of Urology Curacao, Maatschap Urologie, St. Elisabeth Hospital, Willemstad, The Netherlands

The etiology of PBS/IC likely involves the bladder; intravesical treatments that can directly affect the urothelium represent a logical form of therapy for this condition. Medications administered into the bladder may also be preferred because many PBS patients do not respond to oral medications or are allergic to many types of oral medications, and intravesical treatments represent a step between oral and surgical treatment. Successful intravesical treatment will require identification of appropriate medications and determination of their efficacy.

Meta-analyses of placebo-controlled trials of intravesical treatments have shown that there is a significant placebo effect on incontinence and prostate symptom scores. At our IC clinic we performed a double-blind study of intravesical Cystistat® which resulted in three patients receiving placebo reporting improvements, compared to two patients receiving Cystistat®; further analysis showed that there was no difference in improvement between patients receiving placebo and those receiving Cystistat®. In recent literature, a double-blind study of RTX

resulted in patients reporting side effects (primarily pain) and a nonstatistically significant trend toward decreased symptom scores. A double-blind randomized cross-over study to evaluate the effect of changes in urinary pH on PBS/IC symptoms found no significant difference in either subjective pain score or "treatment-order" effects.

In conclusion, there are no new intravesical treatments with a high efficacy. From long-term empathic and scientific evidence, intravesical treatment options under consideration include dimethyl sulfoxide; pentosan, heparin, or hyaluronic acid for pain; oxybutynin for frequency; a cocktail of pentosan, lidocaine, and bicarbonate; or RTX as a single instillation in case of exacerbation.

Gene Therapies for PBS/IC

Naoki Yoshimura, M.D., Ph.D., University of Pittsburgh School of Medicine, Pittsburgh, PA

One approach to gene therapy for PBS/IC involves targeting delivery of genes encoding precursors of endogenous opioids to the bladder wall and/or bladder afferent pathways. A non-replicating herpes simplex virus (HSV) vector containing the preproenkephalin gene (PPE) under control of a cytomegalovirus promoter was created and injected directly into the bladder wall of rats using a Hamilton syringe. A metabolic cage study was performed to determine the frequency of voiding 2-4 weeks after injection of the PPE vector. Rats were challenged with cyclophosphamide (CYP) to induce bladder irritation. Animals who received the PPE vector had no increase in frequency of urination after CYP challenge. The PPE vector also suppressed the reduction in bladder volume that occurs after CYP treatment.

A second study used cystometry to measure the bladder pressure in rats receiving the PPE vector after challenge with capsaicin, naloxene methiodide (opioid receptor blocking agent), and naloxene hydrochloride, which passes through the blood-brain barrier. Capsaicin did not induce an increased frequency in voiding in animals receiving the PPE vector. The effects of the vector were blocked by naloxone hydrochloride but not by naloxone methiodide. Using licking behavior as a test of pain, capsaicin induced licking behavior, but this behavior was decreased in animals receiving the PPE vector. PCR analysis showed that PPE mRNA was expressed in the bladder wall and in the L6 and S1 dorsal root ganglia.

Use of the GeneGun was explored as a way to deliver PPE or pro-opiomelanocortin (POMC), an endorphin precursor, to the bladder wall without using an HSV vector. Genes encoding PPE or POMC were attached to gold particles and "shot" directly into the bladder wall. POMC prevented bladder overactivity induced by acetic acid; this effect was blocked by naloxone hydrochloride. PPE suppressed capsaicin-induced overactivity and increases in voiding frequency; these actions were antagonized by naloxone hydrochloride. Increased endorphin and enkephalin immunoreactivity was observed in bladder treated with POMC and PPE, respectively. This work demonstrated that POMC or PPE gene therapy can suppress bladder pain responses induced by bladder irritation.

Update on IPD-1151T (Suplatast Tosilate) Clinical Trials
Tomohiro Ueda, M.D., Ph.D., Kyoto City Hospital, Kyoto, Japan

IPD-1151T is a Th2 cytokine inhibitor that has been used in the treatment of bronchial asthma, atopic dermatatis, and allergic rhinitis. The drug inhibits production of IL4 and IL5, which is involved in allergic inflammation. IPD-1151T is thought to work by suppressing the inflammatory response.

A Phase II open-label study is underway in Japan to investigate the effects of IPD-1151T on PBS/IC. The trial involves 30 cases, the majority of whom are women. The primary endpoint is changes in IC symptom score, and the secondary endpoint is voided volume per micturition. IPD-1151T was found to reduce IC symptom scores in a dose-dependent manner, and also increased voided volume. A Phase III, randomized, double-blind, placebo-controlled study also has been conducted, involving 100 cases the majority of which were female. The primary efficacy endpoint was improvement in IC symptom scores. No significant differences were found regarding IC symptom scores between patients receiving placebo and patients receiving IPD-1151T. Mild adverse drug reactions were observed in both groups. Hydrodistention had a relevant impact on improvement of symptoms and may be a confounding factor for the assessment of the effects of IPD-1151T.

Two studies—one in Japan and the other in the European Union/United States—are planned for investigation of IPD-1151T's efficacy for treatment of PBS/IC and effects on urine markers, such as histamine, APF, IL4, IL5, IL6, IL10, and INFγ. Goals for the clinical study of IPD-1151T include enrolling patients with bladder pathology, understanding the effects of hydrodistension, and clarifying the mechanism of IPD-1151T regarding treatment of IC.

Novel Therapies for PBS/IC
Michael Chancellor, M.D., McGowan Institute for Regenerative Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA

Three new ideas for PBS/IC therapies include treatment with cannabinoids, botulinum toxin (Botox), or coating of the bladder with liposomes. Ajulemic acid is a potent synthetic analog of tetrahydrocannabinol (THC) and is effective for pain relief, but does not cross blood-brain barrier. Oral administration of ajulemic acid has been effective for treatment of patients with chronic neuropathic pain. Cannabinoid receptors are found in the urothelium, and ajulemic acid was found to have an effect on contractions without changing detrusor function. THC analogs may suppress bladder pain by suppression of cannabinoid receptor-mediated bladder sensing activity and thus may be effective for treatment of bladder pain and frequency symptoms.

Botox blocks neurotransmitter release and there is some evidence that injection of botox into the sphincter, bladder, or prostate may improve voiding dysfunctions. Intravesical administration of botox to rats had an inhibitory effect on bladder overactivity induced by acetic acid. Botox also blunts the irritating effects of CYP on the bladder and inhibited c-fos induction by CYP in L6 spinal cord. A study of 13 women receiving intravesical administration of botox resulted in a majority of the women reporting some improvement in pain and daytime frequency.

The symptoms of IC may be caused in part by defective bladder coating. Liposomes, which are stable fat bubbles filled with water that adhere to a surface, may serve as a "lotion" for bladder irritation. In rats, naked liposomes worked as well as those carrying capsaicin to decrease bladder contraction frequency. Intravesical administration of liposomes also appears to reduce inflammation observed in IC bladders. Coating the bladder with liposomes may protect against challenges that induce inflammation. This treatment also is stable, with a single dose remaining effective for weeks or months.

PANEL DISCUSSION SESSION
Moderator: Dr. Chancellor

Dr. Chancellor asked whether pelvic floor biofeedback treatment was the same for men and women. Dr. FitzGerald answered that the treatment was the same, but surface electrodes are used in men and vaginal electrodes are used in women. She cautioned that she has not found biofeedback to be helpful in treating painful disorders.

Dr. Iqbal asked the panel to discuss their experience with endocannabinoids. A participant commented on the endogenous cannabinoid receptor agonist anandamide, which has affinity to cannabinoid receptors. Specific cannabinoid receptor agonists might be effective against IC pain. Dr. Bade commented that in the Netherlands, cannabinoids often are used successfully for severe refractory pain. Cannabinoids can be prescribed in tea or capsule form, but smoking is more effective. Dr. Chancellor noted that an oral THC spray appears to be more effective than oral doses, because oral absorption of THC is poor and inconsistent.

Ms. Jill Osborne asked whether Dr. Peters considered Interstim to be a first-line therapy for IC, because her group has observed a trend for doctors to use Interstim on newly diagnosed patients. Dr. Peters answered that Interstim should not be considered first-line therapy for IC or overactive bladder. Doctors treating patients with pelvic pain should first rule out confusable conditions, particularly pelvic floor dysfunction. Bladder filling can reproduce the pain felt by these patients, but in many cases, palpating a trigger point in the levator muscle provokes the same pain sensation. Ms. Osborne asked Dr. Peters to comment on complications and a fatality associated with use of Interstim. Dr. Peters asked whether the fatality was associated with surgery or Interstim itself, because it is clinically unlikely that Interstim could cause a fatality.

Dr. Fall commented that patients with classic IC responded better to transcutaneous electrical nerve stimulators therapy than non-ulcer IC types. Unexpectedly, after long-term treatment (more than 1 year), lesions disappeared in a small subgroup of patients. He asked Dr. Peters if this has been observed with Interstim treatment. Dr. Peters answered that they observe changes in cystoscopy, such as increased bladder capacity, after use of Interstim, but that ulcers appear to come back in these patients.

Dr. de Groat asked Dr. Peters whether he uses the same frequency and parameters of stimulation for sacral neuromodulation or pudendal nerve stimulation for treatment of overactive bladder, urgency, incontinence, IC, and pain. Dr. Peters answered that they currently are analyzing data collected from patients receiving sacral neuromodulation for pain. These patients require a much higher frequency (Hz) of stimulation than patients with urgency or urge incontinence. Patients

receiving pudendal nerve stimulation require lower frequency (5-6 Hz versus 14-16 Hz) than sacral neuromodulation patients, and require fewer reprogramming events. Dr. de Groat described studies using spinal cord injured cats in which the optimal frequency for pudendal nerve stimulation to promote bladder storage and suppress detrusor hyperreflexia is approximately 5-7 Hz. The response also appears to be bimodal; stimulation at low frequency inhibits the bladder while stimulation at 20-40 Hz excites the bladder. Stimulation of the pudendal nerve suppresses bladder activity in part through activation of sympathetic efferent pathways. In cats, the sympathetic efferents strongly inhibit bladder activity through β-receptors, and the bladder neck is contracted through alpha receptors. Dr. de Groat asked whether Dr. Peters had any evidence that sympathetic reflexes driven by pudendal afferents may have a role in humans. Dr. Peters described one case in which pudendal stimulation led to new onset stress incontinence; this resolved by reprogramming the Interstim device from continuous to cycling stimulation.
Dr. Deborah Erickson asked Dr. Chelimsky whether there were any autonomic modifying drugs that might be useful therapies for PBS/IC. Dr. Chelimsky answered that treatment of one patient with a β-blocker was successful; he does not, however, treat many IC patients. Other autonomic disorders, such as fainting and IBS, respond well to β-blockers. This treatment presumably blocks the sympatho-sensory connection. In the venous system, β-blockers prevent the effects of epinephrine on the veins, resulting in a narrower vein and better return of the blood to the heart. The urethra has some similarity to veins because it dilates; a major side effect of drugs used to maintain pressure, such as α-agonists, is urinary retention. A phenylephrine cream has been used over the anal sphincter to improve sphincteric retention, but it is unknown whether this would have an effect on pain.

Dr. Abrams commented that the disappointing effects of many PBS/IC trials could be because of inappropriate inclusion criteria. There may be a variety of diseases involved in PBS. There is, for example, an assumption that glomerulations are diagnostic of pathology, but there is little information to support this. Trials have shown that approximately 40 percent of people who have prolonged bladder distension, but no symptoms develop glomerulations. Better information is needed, such as biopsy evidence of inflammation, if therapies are to target inflammation. He added that the O'Leary Sant-Symptom score can rarely discriminate between patients with overactive bladder and patients with PBS, and therefore is a poor entry criteria. Dr. Ueda commented that this is why simple markers for IC are needed. He added that glomerulation is a common phenomenon observed after over-distension of the bladder and also can be observed after prostate resection.

Dr. Hussain asked Dr. de Groat about the paradox that Interstim works for IC, overactive bladder, and PBS, but also works for women who have retention. Dr. de Groat answered that stimulation helps some people void, but helps others not to void. Pudendal nerve stimulation has both excitatory and inhibitory effects on the bladder. In humans and animals, stimulation of the skin in the perineal region evokes a voiding reflex. He speculated that in patients with failure to void, there may be a problem in the central pathways within the spinal cord or brain, which has prevented development of the normal mature voiding reflex. He added that the emergence of the pudendal excitatory reflex of the bladder is probably occurring in women with retention. This neonatal reflex also reappears after spinal cord injury and could explain why pudendal nerve

stimulation works for some people. Dr. Peters added that pudendal stimulation has helped treat two women with retention.

A participant asked whether the RTX trial failed because of a failure to stage the patients in the trial. He speculated that if IC originates in the periphery and moves into the CNS, RTX should be started at an early stage, before central sensitization. Pain should be the first indication for treatment.

Dr. Fall asked about trying to identify relevant subgroups within the IC spectrums and whether glomerulations are primary symptoms or develop when the bladder does not expand properly because of pain. Dr. Peters answered that in all IC studies, there are subsets of patients who respond well to treatment, in part because this population is highly heterogeneous; some may have confusable conditions rather than IC/PBS. Dr. Erickson asked Dr. Fall whether the ulcerative form of IC is a late form of the non-ulcer disease, or if these are two different diseases. Dr. Fall answered that he has never seen progression from non-ulcer to ulcerative form; thus, these are two different diseases that are different in many aspects although they share the same symptoms. He added that IC originally was called Hunner disease. Dr. Abrams commented that Hunner disease might be a less confusing name than IC. Dr. Hanno recommended use of the typing system within the BPA system to confirm that ulceration existed or there was, at least, a search for it.

Dr. Hussain commented that the word "confusable" has a negative connotation, and that some of the conditions considered to be "confusable" within the realm of PBS/IC may not, in fact, be confusing to many clinicians. He added that the challenge is to exclude any other pathology that might explain the symptoms.

A participant commented that in 1987, at the first PBS/IC meeting, pictures of Hunner ulcers were shown to urologists, who could not agree on what constitutes a Hunner ulcer. She speculated that this still was not clear to physicians and added that it also still takes 5 to 7 years to diagnose PBS/IC. Dr. Bade noted that the first time he saw a Hunner ulcer, he recognized it immediately—Hunner ulcers are easy to diagnose. Dr. Fall speculated that perhaps nomenclature is the problem. Hunner ulcer is a lesion, not necessarily an ulcer; it is a weak spot that ruptures when the bladder is distended. Sometimes it is obvious, but at times these ulcers will be more difficult to see. Dr. Peters disagreed and said that in most ulcer patients, the ulcers can be easily seen, even without hydrodistension. Dr. Baranowski stated that naming this syndrome may always be problematic; clinicians and researchers must clearly describe their observations. A symptom-based classification for this condition also would be useful.

Dr. de Groat commented on Dr. FitzGerald's presentation and noted that multiple problems likely affect IC. Bladder distension could activate pathways to the striated muscles, perhaps causing a contraction of muscle, exacerbating any pain occurring from the trigger point. In addition, a person might have an inappropriate bladder to spinal cord to brain pain response. Because there is probably more than one component to IC, more than one treatment probably is needed, e.g., one treatment to treat bladder afferent pathways and the visceral pain response and another to treat the somatic component of the pain response. He asked whether anyone had tried skeletal muscle relaxants in addition to manipulations to turn off the spasm of the trigger point,

and then combine this with pudendal nerve stimulation or sacral neuromodulation. Dr. Peters answered that he commonly uses valium, Atavan, Xanax, and muscle relaxants to treat IC pain, but the most common treatment for PBS patients is physical therapy and muscle relaxants; urgency/frequency is treated with standard overactive bladder medications or bladder-directed therapy. He commented that a combination of physical therapy and neuromodulation is very effective; he described a report showing that 82 percent of IC patients have pelvic floor dysfunction, and most get better with pelvic floor dysfunction therapy. Dr. de Groat asked whether trigger points in the patients were consistent from week to week and whether the sensitivity of the trigger points could be altered by stimulation. Dr. Peters answered that the trigger points are not consistent, but he speculated that neuromodulation does have a direct effect on the pelvic floor because it can allow relaxation of the pelvic floor.

PRESENTATIONS FROM CO-SPONSORS

Meeting co-sponsors included the American Urogynecologic Society, Associatiazione Italiana Cisite Interstiziale (Italy), the Comfortable Urology Network (Japan), International Painful Bladder Foundation, Interstitial Cystitis Association of America, Interstitial Cystitis Association Deutschland (Germany), Interstitial Cystitis Association Österreich (Austria).

Interstitial Cystitis Association of America

The Interstitial Cystitis Association of America (ICAA) has worked with the NIDDK for 20 years to ensure that a community of IC researchers would be created and sustained. This year provided further evidence that this community is as robust as ever. Participants agreed that it is exciting to see new research and to see new investigators join the field. Because of the NIDDK's investment in IC-specific research, much progress has been made since 1987. Generally, clinicians realize that IC is not simply a bladder disease, but also involves the CNS and other organs. This meeting has demonstrated that the commitment to understanding IC across the globe has tremendous momentum.

There are serious concerns in the worldwide patient community about the process by which ESSIC developed its definition of IC and established the nomenclature, without input from other researchers, including those in the United States. The Association hopes the U.S. researchers will engage with ESSIC, hopefully with the leadership of the NIDDK, and refine the definition to everyone's agreement.

The patient community realizes that progress seems slow, but that this community benefits from the hope generated by this research. ICAA will meet this weekend and discuss the progress described at this meeting. ICAA expresses its thanks to the many clinicians, researchers, physical therapists, and others for their dedication to treating this difficult disease.

Associatiazione Italiana Cisite Interstiziale (Italy)

The Associatiazione Italiana Cisite Interstiziale (Italy) (AICI) expresses thanks to the researchers and medical specialists involved in this area for their long-term dedication to this destructive and neglected disease. AICI was formed in 1995, and today is the only reference point in Italy for people with IC or those in search of a diagnosis. Currently, legislation has been passed in Italy that facilitates access to free medicine, social assistance, and health care in all regions, specifically for IC. In the past year, AICI has achieved the first successful recognition of invalidity of up to 76 percent for IC patients, which serves as recognition that IC is a debilitating, although not visible, disorder. Another important success has been obtaining a decree from the Italian minister of health concerning the use of cannabis-based analgesics, which will be discussed by the Italian parliament next month.

AICI thanks the colleagues with whom they have built important solidarity, particularly the NIDDK for their persistence and stimulation of research. The patients in AICI are concerned about changing the name of IC. Changing the name does not take into consideration the important legal and social aspects regarding IC, such as obtaining recognition of IC as a condition and receiving health and social assistance for the disease. Changing the name may mean IC patients face a renewed battle for recognition of IC as a serious disease and must be discussed further with the entire IC community.

International Painful Bladder Foundation

The International Painful Bladder Foundation (IPBF) would like to thank the NIDDK for organizing this symposium. This meeting has provided participants with the opportunity to update their knowledge about the latest research, insights, and treatment, and to spend time networking. IPBF also would like to thank the NIDDK for permitting patient representatives to attend the meeting, so updated information can be passed on to other patient organizations and patients who were unable to attend.

International cooperation is vital. Members of the IC community are from different countries, cultures, backgrounds, disciplines, and education levels. Nonetheless, multiparty cooperation and consultation must occur, even if this sometimes means compromise. Researchers, doctors, and patient representatives all are working to achieve the same objective, which should bind participants together internationally, because the ultimate objective is to improve the situation for IC patients in all countries around the world.