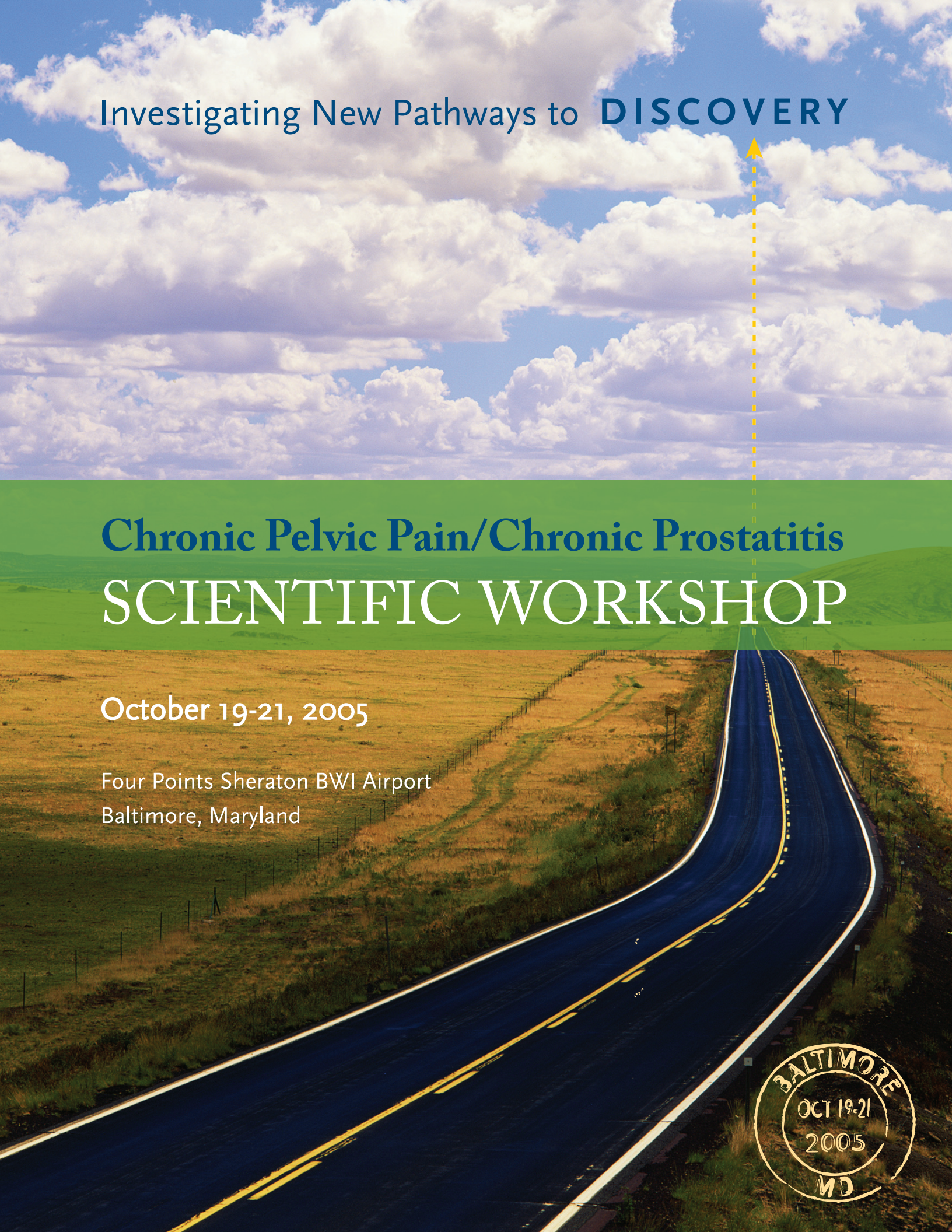
Investigating New Pathways to DISCOVERY
Chronic Pelvic Pain/Chronic Prostatitis
SCIENTIFIC WORKSHOP
October 19-21, 2005
Four Points Sheraton BWI Airport
Baltimore, Maryland
BALTIMORE
OCT 19-21
2005
MD

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Produced and designed by **the Hill Group**

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ADJOURN

SPEAKER ABSTRACTS

The History of Prostatitis: What We Know, What We Thought We Knew, What We Used to Think

J. Curtis Nickel, Queen's University, Kingston, Canada

Throughout history, answers to life's most difficult and profound questions have been found, lost and found again. The history of the world and the history of medicine and perhaps, the history of prostatitis research have illustrated this point so well.

There has been more progress, landmark papers and understanding of the disease we refer to as prostatitis in the last decade as there has been for the last century. Or are we deluding ourselves that we are discovering new directions in the prostatitis research field? Have we missed the scientific directions indicated by our predecessors, only to rediscover what was known before?

It is an interesting experience to discover that many of our important, 'groundbreaking" studies have already been conceived many years before, forgotten in the fog of pre-electronic literature searches. This discovery should humble the bright, intelligent, well-funded and equipped contemporary researchers, but also be used to guide our path in the difficult field of prostatitis research.

A researcher in prostatitis must have at least an understanding of the studies carried out decades ago to truly understand the significance of our recent findings. It is true that unless we study the history of prostatitis research, we will continue to follow blind alleys and rediscover old truths that were known even before we began our experiment or study.

What Have We Learned?

Anthony J. Schaeffer, Northwestern University Feinberg School of Medicine, Chicago, IL

Since September 1997, the Chronic Prostatitis Clinical Research Network (CPCRN), initially comprised of six clinical centers and one data coordinating center, has expanded to ten clinical centers* and one data coordinating center**. Major achievements of the CPCRN include:

1. Development and validation of the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) to quantify pain, urinary symptoms, and quality of life impact of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). The Index is responsive and has been translated into Spanish.
2. A cohort study that enrolled 488 men and determined that CP/CPPS had a significant negative impact on both mental and physical domains of quality of life. Although anti-inflammatory and antimicrobial therapy was routinely administered, leukocyte and bacterial counts did not correlate with severity of symptoms.
3. A case-controlled study which demonstrated that men with CP/CPPS were more likely to have a history of significant co-morbidities than asymptomatic controls. Men with CP/CPPS have higher leukocyte counts in segmented urine samples compared to asymptomatic controls but the clinical significance requires further investigation because of the high prevalences among the controls. There was no difference in the rate of localization of cultures.
4. Measures indicating that the economic impact of CP/CPPS is substantial, approaching $5,000 per person annually.
5. A randomized clinical trial with 2+2 factorial study design. 184 men received placebo, ciprofloxacin, tamsulosin, or a combination. There was no significant change in the CPSI score from baseline at six weeks. These agents might be more effective in men who received less pre-treatment.
6. Basic research studies have demonstrated a correlation between elevated levels of some cytokines in the expressed prostatic secretions of men with both inflammatory and non-inflammatory CPPS as compared to controls.
7. Clinical studies have shown an association of CPPS with increased oxidative stress, a potential benefit for antioxidant therapy, and the possibility in an uncontrolled pilot project that bladder training and biofeedback might provide benefits.

In conclusion, the CPCRN has achieved remarkable success during the past eight years and provided a strong foundation for further basic science, translational and clinical research studies.

*Cleveland Clinic, Cleveland, OH; Harvard Medical School, Boston, MA; Northwestern University, Chicago, IL; Queen's University, Kingston, Ontario, Canada; Stanford University, Stanford, CA; Temple University, Philadelphia, PA; UCLA, Los Angeles, CA; University of Maryland, Baltimore, MD; University of Mississippi, Jackson, MS; University of Washington, Seattle, WA;

**University of Pennsylvania Data Coordinating Center, Philadelphia, PA

The Evolution of Pain Management

John D. Loeser, University of Washington, Seattle, WA

The history of pain management from its conception in the 1950's through its gestation in the 1960's, its infancy in the 1970's, its childhood in the 1980's, its maturity in the 1990's and its threatened premature demise in the first decade of the twenty-first century will be discussed. The roles of key individuals and social, political and economic factors will be presented. An attempt to predict what is going to happen in the new millennium will be made, looking at both the basic and clinical sciences. The dichotomy between those who envision the complaint of pain as a broken part to be fixed and those who see pain as a human symptom requiring multidisciplinary management will be explored. This issue is likely to loom large in the immediate future. The loose linkages between injury, pain, suffering, impairment and disability will also be discussed. There is reason to be concerned that medical efforts to abolish pain by the application of procedures aimed at fixing a broken part may lead not to the abolition of pain but instead to the perpetuation of chronic pain patients and the disappearance of pain management specialists.

There are identifiable goals for those of us who are working in the present environment in respect to patient and health care provider education. Improved technology and better understanding of how the human nervous system functions will offer the opportunity to improve what we can do for our patients. We need to carefully define the mission of pain management and the boundaries of our activities. Better methods of classifying pain syndromes and establishing diagnoses are needed. We must be able to demonstrate that what we do as pain management specialists has better outcomes than what other types of health providers can offer. We need to figure out how to be reimbursed for our activities. Finally, we must generate useful outcomes data if we are to be part of the health care delivery system of this new century. At the present, outcomes data can be found for multidisciplinary pain management, but not for any of the modalities utilized by a myriad of specialists. These will be interesting times to look back on, although they might not be too pleasant for health care providers and pain specialists who are working through them.

Comparisons of Acute and Chronic Pain

Ursula Wesselmann, Johns Hopkins University School of Medicine, Baltimore, MD

Chronic visceral pain from pelvic viscera and urogenital pain syndromes are prominent medical problems, however, diagnosis and management are often problematic due to lack of complete knowledge about their pathophysiological mechanisms. Several properties of visceral pain distinguish it from other pain entities, i.e., the low number of afferents, referred pain, accompanying autonomic reflexes and pain stimuli not necessarily associated with tissue damage. In recent years, increasing attention has been focused on the presence of viscero-visceral and viscero-somatic interactions/reflexes and on the concept of visceral hypersensitivity. While studies in animal models and psychophysical studies in patients with pelvic and urogenital pain have focused on some of these visceral and neuropathic pain mechanisms, the clinical importance of these findings remains not fully elucidated.

Chronic visceral pain of the pelvis or urogenital floor often begins with an inflammatory event (vulvodynia – recurrent vaginal yeast infections, interstitial cystitis – recurrent urinary tract infections, chronic prostatitis – recurrent infections of the prostate), which results in acute visceral pain. However, despite the fact that the infection is successfully treated the initial noxious event leaves in its wake a persistent pain that lasts for months or year. Thus the pain becomes independent of the initiating event, a chronic pain syndrome develops. It has been proposed that modifications of the nociceptive system are responsible for this chronic clinical pain hypersensitivity (modifications of primary sensory neurons and pain transmission neurons) mediated by induced expression of gene products, loss of inhibitory interneurons, and establishment of aberrant excitatory synaptic connections).

Crucial clinical questions are:

1. Is there a possibility to prevent these modifications of the nociceptive system and thus the progression from an acute nocicepetive event to a chronic pain syndrome?
2. Are there means to predict, which patients are at risk to develop a chronic pain syndrome after an acute noxious event?

Supported by NIH grants DK066641 (NIDDK), HD39699 (NICHD) and the Office of Research for Women's Health.

Mediators of CNS Neural Plasticity

Margaret A. Vizzard, University of Vermont College of Medicine, Burlington, VT

Interstitial cystitis (IC) is a chronic inflammatory bladder disease syndrome characterized by urinary frequency, urgency, suprapubic and pelvic pain. We hypothesize that pain associated with IC involves an alteration of visceral sensation/bladder sensory physiology. Altered visceral sensations from the urinary bladder that accompany IC may be mediated by numerous factors. The central hypothesis of our recent work is that the vasoactive intestinal polypeptide (VIP)/ pituitary adenylate cyclase activating polypeptide (PACAP) system is a prominent modulator of bladder sensation and function and that inflammation-induced changes in neurotrophic factors and/or neural activity arising in the bladder alter PACAP/ PACAP receptor expression in the lower urinary tract (LUT) to mediate altered micturition function in IC.

1. We have examined changes (neurochemical, organizational) in micturition reflexes using cyclophosphamide (CYP)-induced cystitis. We have demonstrated increases in the expression of substance P, calcitonin gene-related peptide and PACAP in bladder afferent cells in the lumbosacral dorsal root ganglia and spinal cord. We have identified PAC1 receptor isoforms in LUT tissues and have demonstrated that intrathecal or intravesical administration of PACAP antagonist (10 or 50μg) reverses bladder overactivity induced by cystitis. VIP and PACAP have well-established direct contractile effects on a variety of smooth muscles in a species- and tissue-specific manner. Our recent studies on isolated bladder strips demonstrate that 50-100 nM PACAP elicits a transient contraction and a sustained increase in the amplitude of spontaneous phasic contractions and also increases the amplitude of nerve-mediated contractions. Incubation of bladder strips in 1 μM tetrodotoxin prior to PACAP application did not alter observed increases in spontaneous phasic contractions, indicating that PACAP does not mediate its effects by facilitating presynaptic neurotransmitter release but elicits a direct contractile response from bladder smooth muscle.
2. Possible mechanisms underlying the neural plasticity after CYP-induced cystitis may involve alterations in neurotrophic factors and/or the production of pro-inflammatory cytokines in the urinary bladder. Recent studies from this laboratory have demonstrated changes in the mRNA/protein expression of a number of neurotrophic factors in the urinary bladder and pelvic ganglia. We determined NGF dependence of CYP-induced changes in bladder function by using a recombinant NGF sequestering protein (REN1820). Rats examined four hours or 48 hours after CYP treatment + REN1820 exhibited significantly ($p \leq 0.01$) fewer non-voiding contractions (NVCs) with smaller amplitude. Rats examined 48 hours after CYP

treatment + REN1820 exhibited decreased ($p \leq 0.01$) voiding frequency. No changes in filling, threshold or micturition pressures were observed with REN1820 treatment. Rats treated with CYP + REN1820 exhibited greater mobility and normal resting postures compared to rats treated with CYP + vehicle.

These studies suggest that dramatic alterations in micturition reflex organization and function occur after cystitis and may be mediated, in part, by production of neuropeptides and neurotrophic factors in the urinary bladder.

Supported by: DK60481, DK051369-06, DK065989, NS40796

Pudendal Neuropathy

John S. McDonald, UCLA and Harbor UCLA Medical Center, Torrance, CA

Pudendal neuropathy was really not even referred to just twenty years ago. Mostly patients with pain secondary to this entity were warehoused in the general category of "pelvic pain" told they had undiagnosed pain, sent on their way, or were simply dismissed as having a "psychological" problem.

So many physicians face this enigmatic and poorly understood entity without preparation or understanding; and, because of their experience just did not understand the clinical picture and did not have sufficient background and understanding to be able to be helpful in either diagnosis or treatment.

The incidence and impact of pudendal neuropathy is difficult to come by. It is not available in data bank studies, it cannot be calculated from medical outpatient review data, and it cannot be retrospectively estimated from analysis of various patient's chief complaints on initial office workups. The reason for this is it can be manifest clinically and primarily involved in several rather "camouflaged" medical complaints. Examples of such include but are not limited to endometriosis, dysmenorrhea, dyspareunia, sitting pain, urinary pain, defecation pain, vulvo-vestibulitis and vulvadynia pain in the female and prostatitis, proctalgia, prostadynia in the male.

One survey, performed by Dr. Barbara Reed from the University of Michigan, revealed that a survey of some 3,000 women, statistics revealed 50% had pain with intercourse, and 28% said they had pain in the introitus at some point in time. The summary of the final data from this study revealed that the frequency of vulvar pain was equivalent to 15 patients in every family physician's practice and double that, or 30 patients, in every gynecologist's practice. These figures extrapolated out to more than 2.4 million women in the overall general population. This study also illustrates the frustration among so many patients in regard to work up and diagnosis. For example, the statistics on number of physicians visited by patients with pudendal neuropathy reveal 50% of patients had seen more than two physicians and 25% had seen four doctors. Finally, the average time to diagnosis was also alarming; because, many patients averaged over 5 years for diagnosis and the overall range was from less than one year to amazingly as long as 29 years. (Vulvodynia: Toward Understanding a Pain Syndrome Proceedings from the Workshop April 14-15,2003 NIH) Another study was an NIH funded vulvar dysesthesias problem inclusive of 7,000 women; a population-based questionnaire survey to identify prevalence's of vulvar pain. Sixteen percent of all women reported chronic burning pain on contact or pain of a knife-like and sharp sensation.

Forty percent of these women never sought medical therapy for their problem. For those who sought medical care, 30% saw five or more doctors and 40% were never diagnosed. (Vulvodynia: Toward Understanding a Pain Syndrome Proceedings from the Workshop April 14-15,2003 NIH and iterated by Dr. B. Harlow)

Additional contemporary studies included a UCSF study of 280 women with associated pain, a reduction in quality of life, and depression/ anxiety. The following statistics underscored the huge numbers of involved patients and the expenses; namely, that there were in excess of 600 million visits to alternative health practitioners and 35 billion dollars spent on alternative medications in the fiscal 1997 year. Finally, one dramatic statistic revealed that 96% of patients with vulvar pain treatment used at least one form of complementary medication.

A national based prospective questionnaire estimated 18% of women had some variety of pudendal neuropathy with pain and suffering due to lack of accurate diagnosis and lack of adequate treatment. This translated to some 18 million women who suffered from pudendal neuropathy. Male counterparts have symptoms of sitting pain, bladder and rectal pain is similar to that in females. The etiology is different in males for the most part, but, nevertheless, both males and females can suffer from pudendal neuropathy from excessive straining at the time of defecation.

Suffice it to say pudendal neuropathy is a massive problem overall nationally that has not precipitated national awareness due to its confusing nature, and a capacity to escape widespread detection and exposure in regard to its visibility. This presentation will outline diagnostic problems, underlying pathophysiology, and novel treatment regimens that are designed for non-invasive utilization in reduction of pain score levels and improvement in quality of life functionality.

The presentation will identify "pudendal neuralgia/neuropathy" as a clinical symptom complex that encompasses multiple other pain complaints. Symptomatology is broad and expansive and includes the organs of reproduction, the bladder, and bowel. One discussion will highlight "sitting pain" that is relieved upon standing. Relational aspects of physiology will be offered to help explain the symptomatology.

A second discussion will highlight "vulvar vestibulitis". In general gynecologic practice the prevalence of this condition may be as high as 15%. The characteristic pain of vulvar vestibulitis is generally long-standing, not subject to spontaneous remission and the signs and symptoms are typified by a) severe pain with normal pressure stimulus b) vestibular burning, stinging raw sensation c) vestibular redness d) urge to urinate frequently and e) inability to have intercourse due to pain. An exam most often reveals erythema and pain with even gentle touch in that region of the vulvar vestibule. Unfortunately medical based

therapy has resulted in treatments with poor to fair outcomes. These have included multiple analgesic medications, topical medications tricyclic antidepressants or anticonvulsants, physical therapy, biofeedback therapy, and injection therapy. As a last resort, surgical excision of the vulvar vestibule, with a success rate near 50% has also been tried. Such results and the suffering of patients stimulated our interest in trying to find some other type of treatment that may have better success. We developed a newly designed neural multi-level-treatment approach that was proposed to allow for elevation of the threshold for firing in the affected peripheral area or in other words a new approach that was based upon "down regulation of the nerves" supplying the vulvar area. The fond hope was that this approach that counter affects excessive nerve ending sensitivity is accomplished by interrupt of pain signals at three separate and distinct areas, locally, regionally, and centrally. The end result is an altering or down regulation of nerves locally in the affected tissues, by down regulation of the dorsal root ganglion signals regionally, and by down regulation of the pain signals located in the spinal cord by means of reduction of any facilitation centrally at the spinal cord level.

The third discussion will entail an entity the male counterpart suffers from, namely, prostate ailments. A group of male pelvic pain patients have been treated with a similar approach as outlined above with downgrading of the nociceptive signaling being the endpoint advantage. These also will be presented and compared to the above group of female patients with the vulvovestibulitis syndrome.

The Neurophysiological Relationship of Pain and Sex

Richard J. Bodnar, Queens College, City University of New York, Flushing, NY

Evidence in animal research has accumulated over the past twenty years demonstrating marked sex differences in the analgesic responses to systemic and central opioid agonists, stress responses and nonopioid compounds with male rats and mice typically displaying greater magnitudes of analgesia at lower doses than female rats. These sex differences appear to be more consistent for analgesic responses induced by mu opioid agonists relative to delta and kappa opioid agonists, and are more pronounced when more potent agonists are employed. In contrast, pharmacokinetic factors fail to explain the sex differences in mu agonist-induced analgesia. Whereas adult gonadectomy produces profound reductions in stress-induced analgesic responses in both sexes that suggest an activational role for gonadal hormones, adult gonadectomy produces more modest effects upon opioid agonist-induced analgesia.

In contrast, organizational roles of gonadal hormones play an important role because male rat pups castrated one day after birth display adult analgesic responses to morphine similar to that of intact adult females, and female rat pups androgenized with testosterone propionate one day after birth display adult analgesic responses to morphine similar to that of intact adult males. Marked sex differences have also been observed following direct administration of morphine and other opioid agonists into the rostral ventro-medial medulla as well as the ventro-lateral periaqueductal gray, a site of close interaction between pain-inhibitory systems and sexually-dimorphic hypothalamic nuclei.

Thus, the ventro-lateral periaqueductal gray is a site that displays sex differences in opioid analgesia that is more sensitive to organizational relative to activational effects of gonadal hormones, more sensitive to estrogen replacement in ovariectomized female rats, and is sensitive to the phase of the estrus cycle during which analgesic tests take place. These data are discussed in terms of larger sexually-dimorphic sexual and non-sexual motivational responses mediated by these sites as well as applying the sex difference findings in animals with those in humans.

Visceral Pain

Gerald F. Gebhart, The University of Iowa, Iowa City, IA

Pain arising from the internal organs can be compelling in its insistence and significance. It is often associated with a malignancy, but can also arise in the absence of any apparent pathology (e.g., functional visceral disorders – irritable bowel syndrome, interstitial cystitis), illustrating one way in which visceral pain differs from somatic pain. Visceral pain differs from somatic pain in several additional ways. It is:

- diffuse and poorly localized.
- referred and not felt at the source.
- produced by stimuli different than those adequate for somatic pain. Adequate stimuli that cause visceral pain include hollow organ distension, traction on the mesentery, ischemia and chemicals.
- associated with stronger emotional and autonomic responses.

Innervation of the viscera is unique among tissues in the body. All organs receive dual innervation from anatomically distinct nerves, either vagal or spinal nerves or pelvic and spinal nerves. It has long been held that visceral pain is conveyed to the central nervous system only by spinal ("sympathetic") and the pelvic nerves. The vagus nerve is considered to play no role in transmission of visceral nociceptive information. Contemporary evidence contradicts these assumed functions. For example, growing evidence suggests that vagal afferent input is important to chemonociception and contributes to the affective dimensions and unpleasantness associated with visceral pain.

Finally, like nerves that innervate somatic tissues, visceral nerves exhibit the property of sensitization, which is a change (increase) in how easily they can be excited. When visceral nerves are "sensitized," lower intensities of normal stimuli can lead to unwanted sensations such as pain. For example, normal, low volume filling of the urinary bladder can generate sensations of urgency, discomfort and/or pain when bladder nerves are sensitized. Individuals with functional disorders such as irritable bowel syndrome or interstitial cystitis, in which tissue pathology is absent, are believed to have a sensitized nervous system and are characterized as having a visceral hypersensitivity. In such individuals, normal events are misinterpreted by the sensitized nervous system and lead to altered sensations. Significantly, the quality of life can be seriously compromised in these patients.

Comparison of Epidemiological Factors, Medical History and Voiding Function in the ICDB vs CPCRN

Michael Pontari, Temple University School of Medicine, Philadelphia, PA

OBJECTIVE

The goal was to describe and compare lifestyle factors and medical history in subjects diagnosed with interstitial cystitis (IC) or chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).

SUBJECTS AND METHODS

Data at study entry were evaluated on 562 women and 56 men enrolled in the Interstitial Cystitis Data Base (ICDB) and 439 men enrolled in the Chronic Prostatitis Cohort (CPC). Factors examined included demographics, medical history and co-morbid conditions, and prior treatments for urological symptoms.

RESULTS

The average age at study entry for CPC men and ICDB women was 42 years; ICDB men were approximately 10 years older. Women with IC were more likely to report a history of sinusitis, fibromyalgia, , migraine headaches, Chronic fatigue syndrome, asthma and food allergies than men with either IC or CP/CPPS. Arthritis was more common in men and women with IC than the CP/CPPS patients. Men with CP/CPPS were more liekly to report a history of STD than the IC patients. Patients with IC were more likely to have been treated with anticholinergic medications and urinary tract analgesics than men with CP/CPPS.

CONCLUSION

Our results indicate that there are more differences between men and women diagnosed with pelvic pain than between the specific diagnoses of IC and CP/CPPS. Both IC and CP/CPPS also overlap other poorly explained functional somatic syndromes.

Antiproliferative Factor in Interstitial Cystitis (IC) and Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS)

Susan Keay, University of Maryland School of Medicine, Baltimore, MD

Chronic nonbacterial prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a recognized clinical disorder in men characterized by pain in the pelvic region for at least three months within the past six months in the absence of bacteriuria. Several similarities exist in the discomfort experienced by patients with CP/CPPS and that experienced by patients with interstitial cystitis (IC), a chronic painful bladder disorder for which the pathogenesis is unknown. IC is currently diagnosed by the presence of chronic increased urinary frequency along with pain and/or urgency in the absence of other identifiable causes. Essential criteria for the diagnosis of IC in research study participants have also included the presence of either Hunner's patches or glomerulations at cystoscopy.

We previously showed that bladder epithelial cells from IC patients produce an "antiproliferative factor" (APF) whose activity is found specifically in the urine of approximately 95% of IC patients. This APF profoundly inhibits bladder epithelial cell proliferation via regulation of gene expression and alterations in production of specific growth factors. Recent data indicate that APF also decreases tight junction formation of bladder epithelial cell monolayers *in vitro.* Treatment of normal bladder epithelial cells with purified APF causes the same changes in gene expression, tight junction formation, and proliferation seen in IC cells, suggesting that this factor may play a critical role in the pathogenesis of IC. APF is a small sialylated glycopeptide whose backbone peptide sequence bears 100% homology to the sixth transmembrane segment of frizzled 8. We hypothesize that APF may cause the bladder epithelial abnormalities associated with IC, and propose that it may be useful as a noninvasive diagnostic biomarker for this disorder.

Patients with IC also have significantly decreased urine levels of heparin-binding epidermal growth factor-like growth factor (HB-EGF) and significantly increased levels of epidermal growth factor (EGF) as compared to age-, race- and gender-matched controls. These findings appear to be linked to APF: HPLC-purified APF stimulates EGF production while profoundly inhibiting HB-EGF production by bladder epithelial cells *in vitro,* and recombinant human HB-EGF can inhibit APF's antiproliferative effects in cells from both IC patients and controls in a dose-dependent manner. In addition, APF and HB-EGF appear to be coordinately regulated following bladder hydrodistension or stimulation of the 3rd sacral nerve root as therapy in IC patients.

The sensitivity and specificity of urine APF activity and HB-EGF/EGF levels as IC biomarkers have been confirmed by studies on patients with a variety of urogenital disorders, including

CP/CPPS. However, the number of CP/CPPS patients was small in that study, as were the number of men with IC and the number of asymptomatic control men for comparison. Therefore, to determine more definitively whether these markers can differentiate between CP/CPPS and IC in men, we screened urine specimens from a larger number of CP/CPPS patients for APF activity, HB-EGF and EGF levels, and compared them to specimens from age-and gender-matched IC patients and asymptomatic controls. Clean catch urine specimens were collected from 41 symptomatic CP/CPPS patients, 36 asymptomatic control men without bladder disease, and 24 men with IC. APF activity was determined by ^{3}H-thymidine incorporation into primary normal adult human bladder epithelial cells. HB-EGF and EGF levels were determined by ELISA.

The men with CP/CPPS did not differ significantly from asymptomatic controls for any of the three markers tested ($p > 0.49$). In comparison, APF activity was present significantly more often and HB-EGF levels were significantly lower in urine specimens from men with IC than in urine specimens from controls or urine specimens from CP/CPPS patients ($p < 0.00001$ for all four comparisons). Although EGF levels also tended to be higher in IC urine than in urine from controls the difference did not reach significance ($p = 0.06$).

These findings indicate that at least two of the urine biomarkers previously identified in women with IC are also found in men with IC, but not in men with CP/CPPS. This finding suggests that IC and CP/CPPS are two different disorders with distinct pathophysiologies. They also confirm the utility of APF and HB-EGF as markers for IC in men, as well as women with this disorder.

REFERENCES

Keay S, Zhang C-O, Chai T, Warren J, Koch K, Grkovic D, Colville H, Alexander R. *Antiproliferative Factor, Heparin-Binding Epidermal Growth Factor-Like Growth Factor, and Epidermal Growth Factor in Men with Interstitial Cystitis vs. Chronic Pelvic Pain Syndrome*. Urology 2004; 63:22-6.

Chai TC, Zhang C-O, Warren JW, Keay S. *Percutaneous Sacral Third Nerve Root Neurostimulation Improves Symptoms and Normalizes Urinary HB-EGF Levels and Antiproliferative Activity in Patients with Interstitial Cystitis.* Urology 2000; 55: 643-46.

Keay S, Zhang C-O, Shoenfelt J, Erickson DR, Whitmore K, Warren JW, Marvel R, Chai T. *Sensitivity and Specificity of Antiproliferative Factor, Heparin-Binding Epidermal Growth Factor-Like Growth Factor, and Epidermal Growth Factor as Urine Markers for Interstitial Cystitis.* Urology 2001; 57 (6 Suppl 1): 9-14.

Keay S, Zhang C-O, Shoenfelt JL, Chai TC. *Decreased In Vitro Proliferation of Bladder Epithelial Cells from Patients with Interstitial Cystitis.* Urology 2003; 61: 1278-1284.

Keay S, Seillier-Moiseiwitsch F, Zhang C-O, Chai TC, Zhang J. *Changes in Human Bladder Cell Gene Expression Associated with Interstitial Cystitis or Antiproliferative Factor Treatment.* Physiological Genomics 2003; 14: 107-115.

Keay SK, Szekely Z, Conrads TP, Veenstra TD, Barchi JJ, Jr., Zhang C-O, Koch KR, Michejda CJ. *An Antiproliferative Factor from Interstitial Cystitis Patients is a Frizzled 8 Protein-Related Sialoglycopeptide.* Proc. Natl. Acad. Sci,, USA 2004; 101:11803-11808.

Zhang C, Wang J, Koch K, Keay S. *Regulation of Tight Junction Proteins and Bladder Epithelial Paracellular Permeability by an Antiproliferative Factor from Interstitial Cystitis Patients.* J. Urol. 2005 (on press).

Update on Mediators of Bladder Afferent Activity

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One of the bladder's functions is to store urine quiescently without disturbing its host with unwanted afferent activity. This unwanted activity is to be differentiated with normal sensory activity which the patient does not find to be inconvenient, annoying, uncomfortable, aggravating or unbearable. When the patient perceives a sensory abnormality beyond a certain degree, the patient reports this as symptoms to their health care provider. More times than not, the source of the sensory abnormality will never be discovered. This leaves the patient and his healthcare provider in a bind—what do you do?

The models used to study bladder afferent activity fall into several categories. Most of studies on bladder afferent activity involve animal models in which agents (e.g. cyclophosphamide or acetic acid) or situations (e.g. bladder outlet obstruction or spinal cord injury) that cause bladder irritation are introduced. The animals presumably have a painful bladder, or at least certainly a bladder that is overactive based on in vivo measurements of voiding frequency. This approach often results in many interesting mechanisms (primarily neural mechanisms) which in turn often generate new hypotheses. For example, the model of bladder outlet obstruction in rats lead to the observation of that nerve growth factor (NGF) mediated many of the afferent changes seen in obstruction. The NGF effect on afferent pathway has been delineated further in cyclophosphamide treated rat models. Another example is the discovery of c-fiber mediated afferent reflex in spinal cord injured rats. Further analysis of the afferent dorsal root ganglia neurons after spinalization revealed interesting changes in sodium channel conductance in these cells. Recently, the body of literature developed regarding bladder urothelium as a sensor-transducer (capable of sensing signals and capable of transmitting signals like neurons) has highlighted the role of the urothelium as an active participant in bladder afferent pathway.

Human studies on bladder afferent pathways are more difficult for the obvious reasons. The human model cannot be as controlled or as available compared to the animal model. The condition of "interstitial cystitis" or "painful bladder syndrome" (IC/PBS) provides an opportunity for investigators to study bladder afferent mechanisms presumably because these patients represent the extreme spectrum of patients with increased bladder afferent activity (with probably increased afferent activity from other pelvic visceral organs as well). While findings from IC/PBS will help highlight treatment for this particular condition, the findings may have impact across different disciplines including other visceral hypersensitivity syndromes such as chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). The central

role of the bladder urothelium in the pathogenesis of IC/PBS will be discussed. Also the findings of the sensory testing in IC/PBS subjects will be discussed.

The number of patients who seek physicians help with complaints of bladder hypersensitivity and other visceral organ hypersensitivity without an identified etiology is much higher than most suspect. Developing a better understanding of the visceral afferent pathways will be immeasurable helpful to developing effective treatments based on pathophysiology rather than empiricism.

Urinary Cytokines in CP/CPPS

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According to the NIH classification system, CP/CPPS is subdivided in an inflammatory form (category IIIa) and a noninflammatory form (category IIIb) which are based on the presence or absence of white blood cells (WBC) in the expressed prostatic secretions (EPS) or post-prostatic massage urine (VB3) or semen. However, there are increasing questions about the role and the importance of WBC in CPPS. A recent NIH CPCRN Study demonstrated that site specific WBC and bacterial counts did not correlate with symptom severity. The unresolved issue is why the minority of patients with inflammation in EPS, VB3 or semen have exactly the same symptoms as the larger group of patients with no objective findings.

Given the lack of correlation between WBC and symptoms, research focused on other markers and mediators of inflammation. The most important class of such mediators is cytokines. Produced not only from members of the WBC line but also from epithelial, endothelial, and several other cell types, they act locally over short cellular distances as initiators and modulators of inflammatory responses. Proinflammatory cytokines include tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and several interleukins (IL) such as IL-1β, IL-8, IL-12 and IL-18. These cytokines are involved in promoting the inflammatory response. Anti-inflammatory cytokines such as IL-4, IL-10 and IL-13 inhibit inflammation due to their ability to suppress the genetic expression of proinflammatory cytokines. Generally the balance between pro- and anti-inflammatory cytokines determines the outcome of the inflammatory process.

Several cytokines have been investigated in CP/CPPS and there is substantiating evidence to support their role in the pathogenesis of this disease. TNF-α and IL-1β were found in the seminal plasma as well as in the EPS of men with CPPS. These cytokines were usually detectable and appeared to be higher in men with CPPS IIIa than in those with CPPS IIIb and healthy controls, respectively. Increased levels of the primary inflammatory cytokine IL-8 and the chemotactic cytokine epithelial neutrophil activating peptide 78 (ENA-78) were found in situations related to the presence of an inflammatory reaction such as bacterial prostatitis, CPPS IIIa and asymptomatic inflammatory prostatitis. Since one of their key features is to aid in the recruitment of neutrophils and mononuclear cells into sites of inflammation, increased production and release of these cytokines is important for WBC to leave the circulation and infiltrate tissues.

Because EPS is often hard to obtain, cytokine profiles in the urine of men with CPPS were investigated. It was demonstrated that assessment of some proinflammatory cytokines,

e.g. IL-8, in urine is feasible and again the results seem to confirm it's role in the pathogenesis of CPPS. An interesting study on genetic polymorphisms that can alter cytokine gene expression showed that men with CPPS were more likely to express a genotype associated with low IL-10 production. Since IL-10 is known to be an anti-inflammtory cytokine, men with a low IL-10 expression may be more predisposed to inflammatory conditions such as CPPS.

Exciting data from other medical specialities indicate that several antibiotics such as qinolones, macrolides and tetracyclines not only exhibit antimicrobial but also antiinflammatory properties. It has been shown that antibiotics are able to inhibit proinflammatory cytokine expression in conditions such as pancreatitis, chronic obstructive pulmonary disease and sepsis. This could explain the fact that CPPS-patients treated with antimicrobials often report improvement of symptoms despite the lack of a demonstrable infection. Although this mechanism has not yet been demonstrated in CPPS it might lead to a different thinking and revival on the use of antimicrobials in this mysterious disease.

Macrophage Migration Inhibitory Factor (MIF) in Pelvic Viscera Inflammation

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Macrophage migration inhibitory factor (MIF) is a ubiquitously expressed 12 kDa cytokine that functions as a key regulator of inflammation and both specific and nonspecific immunity by counter-regulating the effects of glucocorticoids. As a proinflammatory cytokine, MIF, via ERK activation, stimulates the expression of other inflammatory mediators. MIF is expressed constitutively in luminal epithelial cells that are continually exposed to environmental insult. In the epithelial cell, intracellular MIF stores help maintain normal cell inflammatory response by acting in concert with glucocorticoids to control both the "set point" and the magnitude of the inflammatory response. While this action is important in the immune response, any shift toward MIF upregulation induces sustained responses that include increases in TNF-α, IL-1β, NGF, c-fos and cox-2. Thus, MIF assumes a pivotal role in the pathogenesis of inflammatory and immune disorders. Our laboratory is investigating MIF function in pelvic viscera inflammation by correlating data from animal models of cystitis and prostatitis to clinical conditions by determining MIF amounts in human samples. Our research has focused on the mechanisms of MIF-mediated inflammation in pelvic viscera by examining the interaction of MIF with cell-membrane receptors along with the ensuing activation of signal transduction pathways.

We have demonstrated constitutive MIF expression and release by lower genitourinary tract epithelial cells. Since MIF is also expressed by neurons in the peripheral and central nervous system structures that innervate the pelvic viscera (including bladder and prostate), MIF potentially regulates pelvic visceral inflammation by acting not only at the end organ, but also at the peripheral and central nervous system level. Inflammatory stimuli upregulate bladder and prostate MIF expression, as well as induce MIF release into the lumen. In addition, MIF is also upregulated in lumbosacral dorsal root ganglia and spinal cord. Increased luminal MIF release appears to be nerve mediated since it can be elicited by activation of C-fiber afferents in the bladder and prevented by intravesical lidocaine or section of the pelvic nerves. Our hypothesis is that increased luminal MIF maintains and/or increases pelvic visceral inflammation, since we have documented that MIF upregulation occurs prior to induction of other proinflammatory mediators. In support of this hypothesis, neutralization of luminal MIF with intravesical antibodies reversed or prevented MIF induced inflammatory changes in the bladder and prostate (including histological changes and induction of numerous inflammatory cytokines). Therefore, as an "upstream" inflammatory regulator, MIF mediates pelvic visceral inflammation.

MIF's mechanism of action is still poorly understood. Recently we determined that released MIF found in the lumen is associated with other proteins that may modulate MIF activity. Presently, we are studying urothelial cell-surface proteins that bind to MIF and/or MIF protein complexes and result signal transduction pathway activation. In particular, we have determined that CD74, the MIF receptor, is localized in the urothelium and is upregulated during inflammation and that MIF complexes bind to glucose-regulated protein 78, an endoplasmic reticulum stress response protein that is also upregulated in the bladder during inflammation.

Our findings demonstrate that MIF and the cell surface proteins that bind MIF and/or MIF complexes are upregulated during pelvic visceral inflammation. As an "upstream" inflammatory mediator, MIF regulates other inflammatory responses. Further understanding of MIF's effects and mechanisms of action will prove valuable in understanding pelvic visceral inflammation and offer new potential therapeutic targets.

Role of TNF in Bladder Inflammation

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Interstitial cystitis (IC) is a chronic inflammatory disease of the bladder that causes severe morbidity due to voiding dysfunction and pelvic pain. IC is often regarded as a neurogenic cystitis because of the involvement of pain, the voiding reflex, and the partial efficacy of neuromodulatory therapies. Urothelial lesions are also common in the IC bladder and are thought to contribute to symptoms because defects in the bladder permeability barrier may allow urinary substances to activate sensory nerves. The mast cell has long been postulated to play a central role in the pathogenesis of IC where mast cells transduce neural signals by liberating a complex mixture of inflammatory mediators that, in turn, elicit inflammatory responses in bladder tissues. To address the potential role of mast cells in inducing urothelial inflammatory responses, we previously incubated human urothelial cells with supernatants of cultured mast cells, and markers of urothelial inflammation were induced including NFκB, IL-8, and ICAM-1. Treatment of mast cell supernatants with blocking antibodies against tumor necrosis factor a (TNF) abrogated these responses, suggest that TNF mediates urothelial responses to mast cells.

To develop a genetic model of neurogenic cystitis, we adapted an existing rat model of neurogenic cystitis to the mouse by infecting mice with the Bartha's strain of pseudorabies virus (PRV), an attenuated a-herpesvirus that undergoes retrograde transport within the CNS but is incapable of anterograde transport. Although an acute model, PRV-induced neurogenic cystitis in the mouse results in several changes that mimic key findings in IC. PRV induced a 2.8-fold increase in non-PMN leukocytes in the bladder within 5 days ($P<0.001$). This leukocytic influx was also associated with increased vascular permeability, as determined by Evan's blue dye extravasation ($P<0.001$). The prevalence of $ICAM^+CD31^+$ blood vessels also increased from 18.1% on Day 0 to 50.2% on Day five ($P<0.001$), consistent with previous findings of $ICAM^+$ blood vessels in bladder biopsies of IC patients.

We next characterized the state of mast cells in this murine model of neurogenic cystitis. While inspection of bladder cross sections did not reveal an increase in total mast cell numbers, the localization of mast cells within the bladder changed during neurogenic cystitis. Mast cell counts from the lumen-proximal half of the detrusor (D1) were found to decrease by Day three of infection, and mast cells accumulated in the lamina propria (LP). As a result, the ratio of LP:D1 mast cells increased from 0.88 in sham-treated animals to 10.9 in PRV-treated animals ($P<0.001$), whereas the lumen-distal mast cell counts were unchanged. Since the increase in LP mast cells correlated with decreased D1 mast cells, these data are most consistent with trafficking of bladder mast cells from D1 to LP. Infection of

TNFR1/2-deficient mice did not result in a similar trafficking of mast cells from D1 to LP, suggesting that mast cell trafficking during neurogenic cystitis requires TNF signaling. These data are consistent with a model of differential TNF-induced trafficking of distinct mast cell pools during neurogenic cystitis. The trafficking of mast cells to the lamina propria may lead to elevated local concentrations of TNF sufficient to induce apoptosis of overlying urothelial cells, contributing to the formation of urothelial lesions. These findings demonstrate that PRV-induced murine neurogenic cystitis provides a suitable genetic model for dissecting events in IC. Furthermore, these data suggest a mechanism for the formation of urothelial lesions in the IC bladder and indicate anti-TNF therapy for the treatment and management of IC.

Meaning of Pain to the Pained

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There is good evidence, contemporary and historical, that pain is for many people pain experience pre-endowed with meaning (as in certain religious traditions) or in need of explanation. An explanation that focuses on lesions or on neurotransmission, while it would seem to erase or negate the quest for meaning, may compete or coexist with other meanings relevant to the person in pain, meanings held consciously or non-consciously. This talk explores the meanings of pain to "the pained"—that is, to persons-in-pain—from three directions.

First, a quick review of recent work in the area of pain beliefs leads to the question whether an understanding of pain beliefs should be extended beyond its current focus on causation, duration, and catastrophe.

Second, in an implicit critique of my earlier work on the meanings of pain, I ask if meaning has been construed too narrowly, with a focus that emphasizes cognitive (as distinct from emotional) experience. I argue for a concept of meaning—as applied to pain—in which emotion is intrinsic to cognition.

Third, with reference to the work of cognitive linguist George Lakoff, I focus on the concept of "framing" pain. Lakoff argues that humans set linguistic terms or concepts—such as *elephant* or *pain*—within a cognitive "frame." This frame, often invisible to or unrecognized by the framer, determines how a person understands specific terms or concepts. Pain patients surely understand and experience their pain within such "frames," and there is potential therapeutic value in exploring how patients "frame" their pain. The talk will conclude with examples illustrating both perils and benefits implicit in the cognitive-emotional frames that patients, as persons and as subjects within a culturally-specific system of medical care, apply to pain.

Influence of Cognition and Emotion in Pain Perception

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Clinical, experimental and anecdotal evidence shows that cognitive and emotional factors provide an important influence on pain perception. In psychophysical studies, we have shown that pain perception is altered by both attention and mood, but that the nature of the modulation differs (Villemure et al., 2003). When subjects are asked to rate both pain intensity and pain unpleasantness, attentional state alters primarily the perceived intensity of the pain, whereas mood alters primarily the unpleasantness associated with the pain. In recent years, brain imaging experiments have explored mechanisms underlying psychological modulation of pain.

Human studies examining the effects of attention and distraction show modulation of pain-evoked activity in thalamus and in several cortical regions, including somatosensory (S1), anterior cingulate (ACC) and insular (IC) cortices [see (Villemure and Bushnell, 2002) for review]. Other regions, including PAG, parts of ACC, and orbitofrontal cortex have been shown to be activated when subjects are distracted from pain, suggesting that these regions may be involved in the modulatory circuitry related to attention (Tracey et al., 2002;Valet et al., 2004). Less is known about the pathways involved in emotional modulation of pain. A recent study examined the effect of looking at fearful facial expressions on discomfort, anxiety and neural activation during non-painful esophageal stimulation in normal subjects (Phillips et al., 2003). The results show that negative emotional states enhance esophageal stimulation-evoked activity in limbic regions, such as ACC and IC.

In our lab, we used fMRI to directly compare the effects of attention and mood on pain processing in the cortex and found that, although both alter pain processing in multiple regions, mood changes alter most prominently activations in limbic regions such as ACC. Other of our studies, involving hypnotic suggestions that enhance the negative emotional component of pain, also show enhanced pain-evoked activity in limbic regions. In another study, we examined a patient with neuropathic pain who complained that certain odors evoked a lancinating pain in the affected hand and arm. In the laboratory, we found that a range of olfactory stimuli that evoke negative emotions enhanced the patient's ongoing pain in the patient. We also performed fMRI studies of the patient and control subjects, comparing activation after unpleasant odors that evoked pain in the patient and after pleasant odors that did not evoke pain. The imaging data revealed increased activation in thalamus and cortical pain-related areas, particularly insular cortex.

Together, these studies show that both emotional and attention state can alter pain perception, but that they do so differently. Changes in mood alter primarily the affective dimension of pain and correspondingly alter pain-evoked activity in limbic areas. Conversely, distraction from pain reduces the perception of pain intensity and correspondingly reduces pain-evoked activity in sensory processing areas of the cortex, including primary somatosensory cortex.

REFERENCES

1. Phillips ML, Gregory LJ, Cullen S, Cohen S, Ng V, Andrew C, Giampietro V, Bullmore E, Zelaya F, Amaro E, Thompson DG, Hobson AR, Williams SC, Brammer M, Aziz Q (2003) *The effect of negative emotional context on neural and behavioural responses to oesophageal stimulation.* Brain 126: 669-684.

2. Tracey I, Ploghaus A, Gati JS, Clare S, Smith S, Menon RS, Matthews PM (2002) *Imaging attentional modulation of pain in the periaqueductal gray in humans.* J Neurosci 22: 2748-2752.

3. Valet M, Sprenger T, Boecker H, Willoch F, Rummeny E, Conrad B, Erhard P, Tolle TR (2004) *Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain--an fMRI analysis.* Pain 109: 399-408.

4. Villemure C, Bushnell MC (2002) *Cognitive modulation of pain: how do attention and emotion influence pain processing?* Pain 95: 195-199.

5. Villemure C, Slotnick BM, Bushnell MC (2003) *Effects of odors on pain perception: deciphering the roles of emotion and attention.* Pain 106: 101-108.

Depression and Pain

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Many factors contribute to the emotional state of the individual experiencing pain, including individual factors such as genetic vulnerabilities, personality, and attitudes as well as the social/cultural context in which the individual lives. Coping strategies, perceptions of control, emotions, and behavioral disturbances, particularly sleep disruption, all interact with pain to determine adaptation to persistent pain. Depression often co-occurs with persistent pain and rates of depression in people with persistent pain, including chronic pelvic pain are higher than those seen in the general population. Prospective studies indicate that persistent pain increases risk for depression, and evidence also suggests that depression increases risk for persistent pain. Since individuals who are emotionally distressed are more likely to seek specialized treatment for persistent pain, caution is warranted in generalizing findings linking depression and pain outcomes observed in tertiary care samples to all individuals with persistent pain. Women with chronic pelvic pain report mild depressive symptoms that are comparable to those seen in low back pain, suggesting that the elevated rates of depression seen in chronic pelvic pain are related to the experience of pain, not the presence/absence of an organic cause. Depressive symptoms occur on a continuum of severity and even mild symptoms influence pain, pain-related coping, and pain-related disability. Health care providers need to be cognizant of depression as a psychiatric syndrome that includes severe symptoms and can include suicidal ideation, but clinicians should also be aware of the often subtle impact even mild symptoms of depression can have on the patient's pain, daily life, and outlook.

What factors link pain and depression? Both have common neurobiological substrates, including serotonin, norepinephrine, substance P, and corticotrophin-releasing factor. Much work in recent years has investigated the strategies that people use to cope with pain. One of these pain coping strategies—catastrophizing—has received a great deal of attention and is consistently associated with depression, as well as other important outcomes that promote depression including pain and disability. In addition to magnifying pain, catastrophizing appears to galvanize internal resources (e.g., attention, emotion, and behavior) and stimulates pain behavior to engage the social environment to provide support, comfort, or help in managing pain. While there is some evidence suggesting that catastrophizing can prospectively reduce depressive symptoms, more often social responses activated by catastrophizing consist of negative, punishing responses that enhance, rather than mitigate, pain and depression.

Recent clinical trials testing new psychological treatments indicate that early interventions reduce depressive symptoms in rheumatoid arthritis and protect individuals from increased disability with disease progression. Designing and testing similar self-management interventions for early and broad dissemination is an important direction for future research and may be quite effective in chronic pelvic pain/chronic prostatitis.

Pelvic Pain is Sexual Pain

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The more often discussed pelvic pain problems connected with sexual functioning have been in women, with vaginismus and dyspareunia being the primary conditions of interest. Recent work in these areas has called into question the diagnostic nomenclature, the classification of the pain as sexual, evidence that women with vulvar vestibulitis syndrome showed augmented genital sensory processing, hypervigilance for coital pain and a selective attentional bias towards pain stimuli (Binik, 2005; Pukhall et al 2005; Payne et al. 2005).

Chronic pelvic pain (CPP) conditions in men, particularly those diagnosed with idiopathic chronic prostititis (ICP), have received little attention with regards to sexual symptoms and impacts. This is somewhat surprising since sexual functioning has been shown to be quite important to men in general and ICP symptoms include pain symptoms in the perineum (Berghuis et al., 1996; Krieger & Egan, 1991; Litwin et al., 1999), as well as pain at ejaculation and urination (Berger et al 1990; Litwin et al, 1999; Turner et al, 2003). ICP has also been reported to have a seriously negative impact on the intimate relationship with spouses and threatened the survival of the couple relationship or prevented men with ICP from seeking new partners (Egan & Kreiger, 1994, Ambler et al., 2001; Berghuis et al, 1996; Egan & Kreiger, 1994; Maruta et al, 1981).

The majority of ICP men, when asked, have reported sexual problems of pain during or immediately after sexual intercourse, decreased frequency of sexual activities, partial or complete erectile dysfunction and decreased sexual desire. We have recent data from a sample of 78 ICP men and 98 controls who completed a variety of scales including one on sexual functioning and behavior. While the men with ICP had less frequent sexual activity in the past month and reported less desire, arousal, and orgasm, there were several findings that were not expected including only a trend ($p = .08$) for IPC men reporting less sexual pleasure and satisfaction and a higher than estimated percentage of ICP men (35.9%) who reported never feeling pain after intercourse (compared to 95.5% controls). While generalization from the small number of studies linking sexual functioning and chronic pelvic pain in men would be premature, they do suggest careful differentiation of pelvic pain samples, particularly in the degree to which sexual activity and symptoms are linked which is different from typical CPP women with sexual pain diagnoses.

Pelvic Pain – Special Problems in Methodology and Outcome Measures in Clinical Trials

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Pain is a perceptual experience and there are no objective methods to determine the extent of a person's pain. Rather, investigators and clinicians are dependent on what patients' report verbally, by observation of their behavior, or reports by surrogates. Pain effects multiple aspects of a person life—emotional, behavioral, social, as well as physical. Thus comprehensive assessment of the person who experiences pain should address emotional functioning, physical functioning, both positive and negative effects of treatments, and patients' overall appraisals of the benefits of any treatment initiated. Although there are a large number of measures used in clinical trials, many have been derived solely on the basis of what is believed to be important by a set of investigators or clinicians. Patient-reported outcomes need to be developed in conjunction with the groups for whom they are planned to be used. The target groups need to be involved in development of the content of any questionnaire. Although self-report of subjective states are important in pain clinical trials, behavioral observation by health care providers and surrogates also provide useful information and should be considered as additional important outcomes.

Traditional approaches to treatment outcome studies have focused on statistical significance; however, statistical outcomes do not indicate whether the effects are clinically relevant or meaningful. The issue of clinical significance incorporates concerns about the criteria that should be used to determine whether a treatment is clinically meaningful—30% reduction in pain?, 50% reduction?, return to usual (desired) activity?, ½ the standard error of measurement on a particular scale; and who should make the determination – patient, health care provider, third-party payer, governmental agency. For example, how much change would be required to establish that a treatment made an important difference to a patient in contrast to a health care provider? The criteria that a patient might use to determine that a treatment made a meaningful difference in his or her life would likely consist of a balance between the clinical effects weighed against the costs (e.g., adverse side-effects, inconvenience, financial requirements). An improvement of a small degree of pain following a specific treatment might be viewed as important to a patient if there were few negative side-effects, minimal cost, and little inconvenience. Conversely, a larger reduction in pain following a specific treatment might not be viewed as acceptable if it were very costly, inconvenient, and created a large number of distressing symptoms. A health care provider might weigh the benefits and cost differently.

Once there is some agreement as to the level of achievement that is clinically meaningful a "minimally important difference", it is useful to report responder analyses in which the

percentage of patients who achieve that level of improvement are reported. Curves can be provided indicating the percentage of patients in a clinical trial who achieve all levels of outcome (e.g., 10% to 100% improvement). In addition to considering the overall statistical significance of produced by a treatment, important parameters to consider include effect sizes and "numbers needed to treat/harm" should be included when reporting results of clinical trials. The availability of these parameters facilitates comparisons across studies and the performance of formal meta-analyses.

Designing clinical outcome studies in pelvic pain create some unique challenges, for example, pain may only be present when evoked by specific activities. Consequently, traditional pain diaries and retrospective reports may suggest low levels of pain however avoidance of pain-provoking activity will likely have an emotional impact. In this instance, reports of avoidance of activity and impairment of emotional functioning may be outcomes that are as important as reduction in pain intensity. Simulation of pain-prevoking activities may need to be added as important outcome measures.

In this lecture issues related to

1. clinical vs. statistical significance,
2. criteria for deciding what constitutes and important outcome,
3. who decides whether an outcome(s) is (are) important, and
4. relevant domains essential for evaluate efficacy of pelvic pain clinical trials will be discussed and suggestions will be offered for establishing the effectiveness of treatments in clinical trials.

Are All Diseases Infectious?

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A fundamental change is occurring in our understanding of the relationships between human beings and microorganisms. About twenty years ago we learned that most ulcers are due to infection with the bacterium, *Helicobacter*, and not due to excess acid, as had been taught for decades. We are now in the middle of a quiet revolution regarding disease pathogenesis as we learn that many diseases, including neurodegenerative illnesses, chronic inflammatory conditions and cancers, are, in fact, due to transmissible agents.

The new techniques of molecular biology have allowed the identification of links between infectious agents and disease even when the organisms can't be grown and Koch's postulates cannot be fulfilled. In some instances the presence of the organism is a *sine qua non* for the disease, in others it acts as a trigger, and, in still others, seems to be a risk factor.

Among the interesting and exciting developments are the association between *Campylobacter* and Guillain-Barre Syndrome, the most common cause of acute neuromuscular paralysis, and the possibility that heart attacks may be due to infection with *Chlamydia*. We need to keep our minds open to new possibilities, however unlikely they may seem on first look. Some of the postulated links between infection and chronic illness may quickly be proved wrong and rapidly fade from consideration, but others may reveal new worlds for disease treatment and prevention.

Unculturable Bacteria in Prostatitis

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BACKGROUND AND PURPOSE

Few men with symptoms of chronic prostatitis have bacterial pathogens identified by traditional microbiological approaches. Although most patients are treated with antibiotics careful localization studies identify pathogens in only a small. To evaluate their potential role, we used sensitive molecular methods to determine the presence and quantities of fastidious and unculturable microorganisms.

MATERIALS AND METHODS

We evaluated 135 men with CP/CPPS by standardized clinical evaluation, and by lower tract localization cultures and chamber counts of expressed prostatic secretions of leukocytes. We excluded from study patients with bacteriuria, bacterial prostatitis, urethritis or positive urethral cultures. Prostate biopsy was obtained using a double-needle technique to limit contamination. We chose molecular approaches because previous studies had used culture antigen detection in urine, urethral swabs and expressed prostatic secretions. However, interpretation of such studies is complicated because urogenital samples often acquire bacteria while passing through the urethra. We used specific and broad-spectrum polymerase chain reaction (PCR) assays.

RESULTS

Only 10 of the 135 (8%) subjects had positive specific PCR assays, including Mycoplasmia genitalium, Chlamydia trachomatis and Trichomonas vaginalis. Our findings suggested that C. trachomatis, T. vaginalis and M. genitalium may be identified in some patients with CP/CPPS, even among men with no evidence of urethritis and with negative urethral cultures and other assays. The broad-spectrum PCR assays provided the most provocative findings. DNA encoding tetracycline resistance was identified in 25% of subjects, and 77% of subjects had evidence of 16S rDNAs. The white blood cell concentration in the prostatic secretions correlated with identification of 16S rDNAs in prostate tissue ($p < 0.01$).

CONCLUSIONS

Delineating the precise role of these organisms in the etiology of CP/CPPS may help define better diagnostic and treatment algorithms.

Cellular Differentiation Modulates Urothelial-UPEC Interactions

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Urinary tract infections (UTIs) remain a significant social and economic burden, resulting in seven million clinic visits in the U.S. and costing over $1 billion annually. Uropathogenic E. *coli* (UPEC), a common cause of UTIs, invade uro-epithelial (urothelial) cells of the mouse bladder. Interestingly, UPEC pathogenesis varies depending on the differentiation state of the urothelial cell *in vivo.* Rapid intracellular proliferation occurs after invasion of terminally differentiated urothelial cells resulting in bacteria-loaded lesions on the bladder surface, while invasion of less differentiated urothelial cells does not lead to intracellular proliferation. Using an immortalized human urothelial cell line that can be induced to enter the urothelial differentiation program, we developed an *in vitro* model for studying UPEC invasion and intracellular proliferation that recapitulates the key findings of the murine model. We found that the invasion efficiency of the UPEC strain NU14 varied depending on the differentiation state of the urothelial cell. We also found that NU14 proliferated within urothelial cells and that the proliferation rate varied depending on the differentiation state of the cell. These data showing that NU14 responds differently to cells in various differentiation states suggests that urothelial physiology may modulate UPEC pathogenesis. While NU14 was capable of intracellular proliferation, the fecal isolate MG1655, though invasive, did not exhibit this proliferative capacity, indicating that UPEC may express virulence factors that facilitate intracellular proliferation. Thus, we developed a model for studying UPEC-host interaction that is amenable to biochemical and genetic analyses to investigate the roles of host cell physiology and UPEC virulence factors in invasion and intracellular proliferation.

Infectious/Immune Dysfunction

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This era may come to be remembered as one in which infectious diseases made a dramatic worldwide resurgence. The rise in antibiotic resistant pathogens, emergence of new diseases, and involvement of bacterial pathogens in diseases formerly thought to be due to non-infectious agents has rekindled the need to understand the "molecular logic" of virulent bacteria. My laboratory has diverse interests and has made a multitude of discoveries that have helped to establish unexpected paradigms in microbial pathogenesis. We have uncovered the fine details of a molecular machine, called the chaperone/usher pathway, used by diverse pathogenic bacteria to assemble adhesive fibers called pili on their surfaces. Pili initiate host-pathogen interactions critical in the pathogenic processes of a wide range of bacteria. We are using multidisciplinary approaches including functional genomics, molecular biology, genetics, immunology, cell biology, biochemistry, X-ray crystallography, and multiple imaging technologies in order to advance our understanding of human disease. Using uropathogenic *Escherichia coli* (UPEC) as a model system, we unveiled unanticipated mechanisms by which bacteria subvert innate host defenses. For decades UPEC was considered to be strictly an extracellular pathogen that colonized the bladder and urine. Our work revealed that bacterial entry into superficial umbrella cells lining the bladder lumen is a critical event in disease. Thus, we elucidated the structural basis of the host-pathogen interaction that triggers the invasion process. We found that bacterial entry into umbrella cells activates a complex genetic cascade leading to the formation of intracellular bacterial communities (IBCs) that undergo a defined maturation and differentiation program. Our understanding of the IBC program is changing the way urinary tract infections (UTIs) are evaluated and treated and is re-shaping models of bacterial infections in general. Our studies elucidating the host response to infection are teaching us fundamental aspects of bladder physiology that have implications for normal epithelial renewal and bladder cancer. Work in my laboratory is therefore spawning new insights into the most basic principles of molecular biology related to protein folding and macromolecular assembly and is providing a paradigm to understand infectious diseases, their relationship to cancer and better strategies for treatment and prevention.

Autoimmunity in Chronic Prostatitis

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Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common urologic problem that is poorly understood. The disease is defined only by clinical symptoms and the principal diagnostic criterion is pelvic pain in a man lasting more than 3 months. This pain is typically episodic and relapsing and is located most commonly in the perineum and genitalia. Voiding symptoms and effects on sexual function such as painful ejaculation are common. There are no objective tests of proven diagnostic, etiologic or prognostic significance and the disease is treated empirically. Antimicrobials, anti-inflammatory and alpha-adrenergic receptor blockers are the most common prescription agents used to treat the disease.

CP/CPPS has been postulated to have many causes. This includes conditions of the prostate as well as most of the other pelvic structures and organs because it is not clear that CP/CPPS is characterized by inflammation in the prostate or is even a disease of the prostate. Putative etiologies for men with CP/CPPS include infection, neuropathic pain, dysfunction of the pelvic floor, interstitial cystitis, voiding dysfunction and autoimmunity, among others.

It is increasingly clear that autoimmunity, the recognition of self by the immune system, contributes to the pathophysiology of many diseases such as rheumatoid arthritis, multiple sclerosis and insulin-dependent diabetes. Autoimmunity has been commonly postulated as an etiology for CP/CPPS because the disease is chronic, potentially characterized by inflammation in a normal organ, and presents with a pattern of episodic flare-ups and remissions, typical of the course of autoimmune diseases. Autoimmunity has also been postulated as a cause of asymptomatic inflammatory infiltrates (NIH category IV prostatitis) commonly observed in the prostate.

Does autoimmune prostatitis exist in any human condition? Data from our laboratory in support of this notion are summarized below as follows:

CD4 T cells from patients from the peripheral blood of some patients with CP/CPPS demonstrated a proliferative response to seminal plasma that was not observed in normal men[1]. The antigen in the seminal plasma appeared to derive from the prostate because the response was still observed when seminal plasma from men with seminal vesicle atresia was used in the experiments[1]. These experiments have been repeated by another group with similar findings[2]. These data support the notion that a secreted prostatic protein can be demonstrated to be a self-antigen in some men with CP/CPPS.

The secretions of the prostate contain three major proteins, prostate specific antigen (PSA), prostatic acid phosphatase (PAP) and β-microseminoprotein (β-MSP). When these three purified proteins were used with antigen presenting cells to stimulate CD4 T lymphocytes from men with CP/CPPS we observed a proliferation signal to PSA but not to PAP or β-MSP[3]. Hence we concentrated on PSA is subsequent experiments.

To directly characterize T cells recognizing PSA in men with CP/CPPPS we cultured T cells from men with CP/CPPS and identified antigen-specific, human leukocyte antigen (HLA)-restricted recognition of PSA in a patient who had chronic pelvic pain syndrome but also was found to have granulomatous prostatitis on prostate biopsy[4]. We identified HLA-DR15 as a restriction element for CD4 T cells in this patient. HLA-DR15 is of particular interest because this class II haplotype demonstrates the strongest linkage to the autoimmune disease multiple sclerosis.

Because of the linkage of HLA-DR15 to multiple sclerosis we wished to determine if granulomatous prostatitis might also be linked to this allele and found that, indeed, granulomatous prostatitis is linked to HLA-BRB1*1501 in white men with the disease[5]. Finally, we identified peptides from PSA that are naturally processed and presented from whole PSA by antigen-presenting cells[6].

These data comprise the strongest evidence to date that autoimmune recognition of the prostate is a reality and contributes to a naturally-occurring human condition. Whether a subset of men with CP/CPPS have an autoimmune component is under investigation.

REFERENCE LIST

1. Alexander, R. B., Brady, F., and Ponniah, S. *Autoimmune Prostatitis: Evidence of T Cell Reactivity with Normal Prostatic Proteins.* Urology, 50: 893-899, 1997.
2. Motrich, R. D., Maccioni, M., Molina, R., Tissera, A., Olmedo, J., Riera, C. M., and Rivero, V. E. *Presence of INFgamma-Secreting Lymphocytes Specific to Prostate Antigens in a Group of Chronic Prostatitis Patients.* Clin.Immunol., 116: 149-157, 2005.
3. Ponniah, S., Arah, I., and Alexander, R. B. *PSA is a Candidate Self-Antigen in Autoimmune Chronic Prostatitis/Chronic Pelvic Pain Syndrome.* Prostate, 44: 49-54, 2000.
4. Klyushnenkova, E. N., Ponniah, S., Rodriguez, A., Kodak, J., Mann, D. L., Langerman, A., Nishimura, M. I., and Alexander, R. B. *CD4 and CD8 T-Lymphocyte Recognition of Prostate Specific Antigen in Granulomatous Prostatitis.* J Immunother, 27: 136-146, 2004.
5. Alexander, R. B., Mann, D. L., Borkowski, A. A., Fernandez-Vina, M., Klyushnenkova, E. N., Kodak, J., Propert, K. J., and Kincaid, M. *Granulomatous Prostatitis Linked to HLA-DRB1*1501.* J.Urol., 171: 2326-2329, 2004.
6. Klyushnenkova, E. N., Link, J., Oberle, W. T., Kodak, J., Rich, C., Vandenbark, A. A., and Alexander, R. B. *Identification of HLA-DRB1*1501-restricted T-Cell Epitopes from Prostate-Specific Antigen.* Clin Cancer Res, 11: 2853-2861, 2005.

The Neurologic Evaluation of Pelvic Pain

Claire C. Yang, University of Washington, Seattle, WA

The study of CP/CPPS has recently begun to examine neurological aspects of pain. One aspect is the study of peripheral nerves, of which there are two general types: somatic and autonomic. The former are large diameter, myelinated nerves, which transmit neural impulses between the CNS and the endorgan (typically skin, muscles, and joints). The latter are small, poorly or unmyelinated fibers that do not transmit impulses as rapidly.

Examinations of the integrity of innervation can also be categorized as tests of somatic nerves and tests of autonomic nerves. Somatic nerve tests are well established and widely available, and include somatosensory evoked potentials (SEPs), evoked reflexes, nerve conduction velocity measurements, and electromyography (EMG). These tests examine myelinated nerves and nerve pathways, or the somatic/skeletal muscles they innervate. Tests of autonomic function are not as widely available and are not as standardized as their somatic nerve counterparts. These include quantitative sensory testing (QST) to determine thresholds to temperature and pain; sympathetic skin responses and skin conductance tests; and evoked cavernous activity.

The role of the nervous system has been examined in many pain syndromes, but with regard to pelvic pain, pain of gynecologic origin has had the most interest. In the context of CP/CPPS, only a few clinical studies have been performed using tests of somatic or autonomic nerves. This presentation will review the preliminary data pertaining to objective neurologic testing and possible roles for its expansion.

INTRODUCTION

- All pain is neurologic pain, that is mediated by nerves and the nervous system, but not all is neuropathic pain.
- A group of us thinks CPPS (in men and women) is neuropathic pain
- Definition of neuropathic pain

HISTORY

- May or may not be an identifiable inciting event
- Pain syndrome may already be present
- Visceral, somatic components
- Often, but not always, experience change in pelvic organ function (bladder, bowel, sexual)

PHYSICAL EXAMINATION

Both Males and Females:

- general appearance, carriage
- LE exam, including inner thighs (laterality): reflexes, strength, sensation (PP, LT, proprio, temp)
- GU exam (laterality)

Females

- external genitalia appearance: inflammation
- sensation to LT, PP, temperature: mapping
- reflexes: bulbocavernosus, anal wink
- deep palpation/bimanual: 4 walls of vagina: pelvic floor muscles, bladder/urethra, rectum, as well as deep structures: cervix, ovaries; palpate along bony structures
- motor strength/pelvic floor contraction strength, ability to sustain

Males

- external genitalia appearance
- sensation to PP, LT, temp: mapping
- reflexes: cremasteric, bulbocavernosus, anal wink
- palpation along urethra, testes, adnexae, bony structures
- digital rectal exam: anal sphincter tone and voluntary contraction strength

LABS

Complete urinalysis

IMAGING

- Pelvic CT/MRI: suspicion of non-neural structural problem
- MRI LS spine

FUNCTIONAL TESTING

- Urodynamics
- Rigiscan

Use of Antibiotics in CP/CPPS

Daniel Shoskes, Cleveland Clinic Foundation, Cleveland, OH

The most common therapy for all categories of chronic prostatitis by far is antibiotics. For categories I and II, an infectious agent by definition is the cause and therefore antibiotics are necessary and appropriate. Antibiotic selection is based upon culture results and the ability of the antibiotic to penetrate into the prostate. The most common antibiotic errors made in the treatment of category I and II are failure to treat long enough and failure to counsel the patients about side effects and complications of long term antibiotic use.

For category III prostatitis, every randomized placebo controlled study of antibiotics has failed to show a benefit. This result may be influenced by the inclusion of patients with relatively long histories in whom an initial infection may have resolved but symptoms persist due to inflammatory and neuromuscular processes. Furthermore, anecdotal symptomatic benefit with antibiotics may be related to their ability to block inflammatory cytokines such as IL-8 and TNF. Attempts at adjuvant therapy to improve the response to antibiotics include prostatic massage, alpha blockers, intraprostatic injection of steroids and calcium chelation. All experience with these adjuvant therapies is anecdotal so far.

There is currently no evidence to support the treatment of category IV prostatitis with antibiotics.

Non Antibiotic Treatment in CP/CPPS

J. Curtis Nickel, Queen's University, Kingston, Canada

Was it only five years ago that we had almost no clinical evidence to base our medical treatment decisions for chronic non-bacterial prostatititis and prostatadynia (which we now refer to as chronic prostatitis/chronic pelvic pain syndrome or CP/CPPS)? Antimicrobials were indicated for acute and chronic bacterial prostatitis and since there were no medications indicated for the 90% of patients with a non-bacterial etiology, antimicrobials were, of course, employed.

That situation is changing. The following advances in the field have brought about this rapid advancement in our understanding of medical therapy for CP/CPPS.

1. An accepted classification system for the prostatitis syndromes
2. An accepted definition of CP/CPPS
3. A validated symptom outcome tool (NIH – Chronic Prostatitis Symptom Index [CPSI])
4. Confirmation of the sensitivity of the NIH-CPSI in clinical trials
5. The funding, design, implementation, analyses and peer reviewed publication of randomized placebo-controlled trials (RCTs).

Traditional medical therapy includes the "Three A's" of prostatitis treatment; antimicrobials, anti-inflammatories and alpha blockers, as well as other medical therapies such as hormone therapy (5 alpha-reductase inhibitors), analgesics, anxiolytics, antidepressants and herbal therapies. There are now ten studies that meet the strict criteria for evidence based recommendations (well characterized population of patients, a randomized placebo-controlled design, a validated outcome analyses and peer review).

From these ten RCTs we can make the following recommendations

1. Antimicrobials are not recommended in CP/CPPS patients who have previously failed antimicrobial therapy and have had symptoms of long duration
    a. It is still rational to consider fluoroquinolone treatment of recent onset CP/CPPS in antimicrobial naïve patients.
2. Alpha-blockers are recommended as a primary therapy (either monotherapy or included in multimodal therapy) in alpha-blocker naïve patients with recent onset of symptoms. The therapy must be continued for longer than 8 weeks.

3. Anti-inflammatory therapy can only be considered adjuvant therapy
4. Hormone therapy cannot be recommended as primary therapy for CP/CPPS
    a. 5-alpha reductase therapy does not offer significant benefit as monotherapy
    b. 5-alpha reductase therapy may provide benefit in older men with benign prostatic hyperplasia and prostatitis
    c. Mepartricin should be further evaluated as a possible therapy in C/CPPS
5. Phytotherapies are intriguing and deserve more study
    a. Quercetin may be considered as a rational therapy with very few side effects

Based on our evolving understanding of the pathophysiology of CP/CPPS, the best future prospects for medical therapy of CP/CPPS appear to be neuromodulators and immune-modulators

Psychological Treatments for Chronic Pain Problems

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Clinical observations and empirical studies alike attest to the importance of psychosocial and environmental factors in chronic pain problems. There is substantial evidence that psychological and behavioral factors influence individuals' experiences of, and responses to, pain. Furthermore, psychotherapies that help patients to identify and change maladaptive cognitive and behavioral responses to pain, and that involve instruction and practice in adaptive cognitive and behavioral responses, are effective in reducing pain, suffering, and pain-related physical disability among patients with chronic pain problems. Randomized controlled trials (RCTs) have supported the efficacy of these so-called cognitive-behavioral therapies (CBT) for a variety of chronic pain problems, including low back pain and arthritis (Morley et al., 1999). The rationale behind such therapies is not that pain is caused by psychologic/psychiatric disturbance, but rather that patients with chronic pain often show maladaptive cognitive and behavioral responses and that when new responses are learned and practiced, pain, suffering, and disability improve.

Techniques often used in CBT include progressive relaxation training; thought diaries to identify excessively negative appraisals of pain, challenge these, and counter with alternate, more realistic appraisals; setting and working toward behavioral goals; and development of an individualized plan for maintaining gains and coping with pain flare-ups. Because many chronic pain problems are characterized by reduction of customary work, social, and recreational activities, CBT also often involves a program of gradual and systematic increases in such activities.

Little research has examined the effectiveness of CBT for chronic prostatitis/chronic pelvic pain (CP/CPPS). However, evidence is increasing that patients with CP/CPPS have important similarities to patients with other chronic pain problems, including unclear etiology of pain, tendency for pain to be persistent/recurrent (Nickel, 1998; Turner et al., 2004), psychosocial dysfunction (Berghuis et al., 1996), and significant worries about the pain (Turner et al., 2005). Furthermore, perceived psychosocial stress may play a role in CP/CPPS (Ullrich et al., 2005). These psychosocial characteristics are amenable to change with CBT.

Very recent RCTs provide support for the efficacy of brief psychological treatments that can be integrated into medical care. For example, a brief CBT and physical therapy intervention in a primary care setting was effective in reducing back pain and pain-related activity limitations (Von Korff et al., 2005). A brief CBT intervention in conjunction with dental

care in a specialty clinic for temporomandibular disorders (TMD) was more effective than an education/attention/dental care condition in reducing TMD pain and disability at a one-year follow-up (Turner et al., under review)

In sum, men with CP/CPPS have characteristics in common with patients who have other chronic pain conditions that have been demonstrated in RCTs to improve with CBT. CBT holds promise in reducing pain, activity limitations, and psychosocial dysfunction among men with CP/CPPS. However, research is needed to establish the efficacy of CBT for this patient population and to determine which patients are most likely to benefit from CBT.

REFERENCES

Berghuis JP, Heiman JR, Rothman I, Berger R. *Psychological and Physical Factors Involved in Chronic Idiopathic Prostatitis.* J Psychosom Res 1996; 41: 313-25.

Morley S, Eccleston C, Williams A. *Systematic Review and Meta-Analysis of Randomized Controlled Trials of Cognitive Behaviour Therapy and Behaviour Therapy for Chronic Pain in Adults, Excluding Headache.* Pain 1999; 80: 1-13.

Nickel JC. *Prostatitis: Myths and Realities.* Urology 1998; 51: 362-6.

Turner JA, Ciol MA, Von Korff M, Berger R. *Prognosis of Patients with New Prostatitis/Pelvic Pain Syndrome Episodes.* J Urology 2004; 172: 538-41.

Turner JA, Ciol MA, Von Korff M, Berger R. *Health Concerns of Patients with Nonbacterial Prostatitis/Pelvic Pain.* Arch Intern Med 2005; 165: 1054-9.

Turner JA, Mancl L, Aaron LA. *Short-and Long-Term Efficacy of Brief Cognitive-Behavioral Therapy for Patients with Chronic Temporomandibular Disorder Pain: A Randomized, Controlled Trial.* Under review.

Ullrich PM, Turner JA, Ciol M, Berger R. *Stress is Associated with Subsequent Pain and Disability among Men with Nonbacterial Prostatitis/Pelvic Pain.* Ann Behav Med 2005; 30: 112-8.

Von Korff M, Balderson BHK, Saunders K, Miglioretti DL, Lin EHB, Berry S, Moore JE, Turner JA. *A Trial of an Activating Intervention for Chronic Back Pain in Primary Care and Physical Therapy Settings.* Pain 2005; 113: 323-30.

The Stanford Protocol: Paradoxical Relaxation/Trigger Point Release for the Treatment of Prostatitis/CPPS

David Wise, Sebastopol, CA

The reason that prostatitis/chronic pelvic pain syndrome have eluded solution by the best medical minds for many decades is because investigators have proceeded from the paradigm that these conditions were essentially caused by inflammatory or infectious processes of the prostate. This paradigm has proven over the years to have little substance and the therapies that derive from it have failed to solve these conditions.

The Stanford Protocol presents a new paradigm for understanding the nature of prostatitis and chronic pelvic pain syndrome. The treatment that is informed by this new paradigm in my view is the most efficacious and safest treatment available. We agree with the increasing evidence that infection and inflammation play no primary or causative role in the presence and severity of symptoms in the overwhelming majority of patients. Neither do we see any convincing evidence naming autoimmune process or trapped pelvic nerves as the culprit for what is commonly called prostatitis nor do we see any real amelioration coming from therapies derived these from theories.

Our view is quite simple--that the vast majority of what is currently diagnosed as prostatitis/cpps is the result of a chronically contracted pelvic floor that has made an inhospitable environment for the nerves, muscles and organs in and around the pelvic basin creating a host of perplexing and distressing symptoms that are difficult to understand by someone whose pelvic floor has not been subject to chronic and intense hypertonicity.

It is the interaction of chronic pelvic floor tension, symptom-producing pelvis-related trigger points, and anxiety, all of which produce a self-feeding cycle. Even when the initiating events disappear, this self-feeding cycle of tension, anxiety, and pain appears to have a life of its own.

This new paradigm requires an different intervention than conventional medical treatment. We suggest that the key to the reduction and resolution of symptoms is as follows: training patients in Paradoxical Relaxation, a method developed to profoundly relax the pelvic floor and modify the tendency to tense the pelvis under stress, and the rehabilitation of the pelvic floor by deactivation of pelvic associated trigger points, using specific methods of trigger point identification and release and self-treatment strategies taught to patients for them to use regularly.

In an article in the July Journal of Urology, we reported an improvement rate of 72% using the Stanford Protocol with patients referred to us who were refractory to conventional treatment. These patients were the most difficult patients to treat as they usually were referred to Stanford because community urologists could not help them. While the data is not in, we expect better results than this of participants who comply closely with the 1+ hour's daily home treatment program. As this method is used and symptoms reduce, we expect an increase in reports of efficacy as participants become more skilled in the methodology. In other words, in selected patients that the Stanford Protocol initially helps, we expect increasingly better results the longer the Stanford Protocol is used.

Pain, Analgesics and Neuropharmacology

Alan Cowan, Temple University School of Medicine, Philadelphia, PA

A myriad of compounds, all possessing differing pharmacological actions, are claimed to be analgesic on the basis of testing in preclinical laboratories. Well established animal models of the various human pain states (e.g., acute, inflammatory, chronic, neuropathic, cancer) provide the chemical transmitters, receptors, channels, second-messenger molecules and physiological pathways that are necessary for assessing the potency, efficacy and overt behavioral effects of chemically novel analgesics. The pharmacological literature is replete with encouraging results from animal studies involving selective agonists or antagonists at, for example, neurokinin, cannabinoid, NMDA and TRPV1 receptors. Given such promising basic research, drug candidates should surely proliferate and advance to challenge the supremacy of historical opioids and NSAIDs in clinical medicine. This has not happened over the last decade although the commercial development of ziconotide (an antagonist at N-type voltage-sensitive calcium channels located on presynaptic terminals in the dorsal horn) and gabapentin, the anticonvulsant, helps to close the gap between bench research and the pain clinic. Recent advances have focused on opioid rotation and alternative routes of administration (e.g., transdermal, sublingual, intranasal) along with emerging drug delivery technologies involving improved formulations and sustained release systems. Drug combinations targeting multiple analgesic mechanisms (e.g., tramadol plus acetaminophen; opioid plus clonidine, the alpha-2 adrenoceptor agonist, both given epidurally) or unusual antinociceptive synergies (e.g., ibuprofen plus glucosamine) represent additional advances. Yet another ongoing approach has targeted the peripheral side effects of opioids (e.g., constipation) without compromising centrally mediated analgesia. This has been accomplished with peripherally restricted antagonists of mu opioid receptors (e.g., methylnaltrexone, alvimopan) that seem to penetrate the CNS only with difficulty.

The pelvic and suprapubic pain connected with interstitial cystitis has posed problems over the years and has been treated with a variety of oral medications including amitriptyline, antihistamines and calcium channel blockers. The associated irritable bowel syndrome (IBS; abdominal pain/discomfort) has been alleviated in other clinical contexts with tegaserod, an aminoguanidine indole derivative, which is a potent partial agonist at serotonin type-4 receptors in the gastrointestinal tract. Results will be reviewed from rodents and IBS-constipated individuals to demonstrate that tegaserod modulates the processing of sensory visceral information and thus the perception of pain.

Toward a Unified Diagnosis of Pelvic Pain

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There are two important components to consider when managing a disease process. Firstly, where possible, the aim should be to treat the underlying pathology. Secondly, and of equal importance, adverse symptoms should be reduced.

The current most widely adopted terms/taxonomy defining uro-genital pains often describe pathological process that are unsubstantiated by clinical and basic science research. The term prostatitis is such an example. Rarely is there evidence of prostate inflammation or infection. Treatment aimed at the proposed pathology of inflammation repeatedly do not work. The term prostatitis should thus be avoided as it may result in inappropriate treatment and false prognosis. Research is also jeopardised.

To move away from arbitrary terminology and diagnosis two approaches have been adapted in one form or another. The International Continence Society (ICS) (Abrams et al 2002) started to use the concept of a 'Syndrome' (a collection of symptoms and signs). This approach was similar to that used by the International Association for the Study of Pain's (IASP) Taxonomy for the new terminology for the condition they named Complex Regional Pain Syndrome (Merskey and Bogduk 2002). Essentially if the condition cannot be defined by pathology, define it by presenting symptoms and signs. The term 'Syndrome' also implies that multiple mechanisms and pathologies affecting several systems may be involved. Treatment may thus require several different approaches and may require a multidisciplinary team effort involving: specialists in end-organ pathology (for example, urologists and gynaecologists) and specialists in symptom control (for example, pain medicine consultants and psychologists).

The second approach adopted to define poorly understood pathologies is the 'axial approach' also utilised by the IASP. This was incorporated into the European Association of Urology (EAU) Guidelines along with the use of the term 'Syndrome'. The aim of the 'axial approach' is to try and indicate the primary focus for the pain (and not pathology) and hence the sites involved in producing the symptoms and signs. This approach utilises a stepwise progression of definition. By using an axial system of progressive terminology the clinician was allowed to be as vague or as specific as they felt it was appropriate. This is best understood by looking at an example. Pain perceived in the suprapubic area, deep within the pelvis could be referred to as Chronic Pelvic Pain a term which would cover all conditions within the pelvis capable of producing pain. However, if all well defined conditions have been excluded the clinician may prefer to use the term Pelvic Pain Syndrome. If the pain is associated primarily with bladder symptoms, the term Bladder Pain Syndrome could be utilised. For a fuller explanation please refer to the EAU document (*http://www.uroweb.org/files/uploaded_files/guidelines/chronicpelvicpain.pdf*)

There are criticisms of both of the above approaches. However, to a certain extent the tools are only as good as the people using them. The EAU system works quite well if you can see the weakness. The main concern is that the classification can result in the clinicians focussing on a single system where as usually more than one system is involved. In view of this weakness there are advocates for a new system that is purely symptom and sign based. It is suggested that were pathology is clear, that condition should be provided with a name that associates with the condition's pathology and that would result in appropriate management with the early introduction of the symptom management teams if appropriate. However, where the pathology is not well understood, a classification system based on symptoms and signs would lend itself to the early introduction of the best symptom control treatments and time would not be wasted on ineffective end-organ pathology type treatments. Within this classification the new pathology of 'Pain Mechanisms' needs to be recognised so that the most appropriate pain treatments are applied.

The ICS went some way to take onboard this approach to management when it produced its guidelines on Chronic Pelvic Pain (Abrams et al 2005). Unfortunately, gains made in the draft copy, where Pain Medicine assessment featured early on in the treatment algorithm, were lost from the final document where Pain Medicine was renegaded to the end!

For the future we need to ensure that the most appropriate classification system is adopted Worldwide by all professionals involved in the management of patients with uro-genital pain. We need a system that can evolve, but not require radical change, as time progresses and new mechanisms are understood. A system that encourages the most appropriate treatment whether that is end-organ or symptom based. We may need to consider a new radical system such as one relying upon symptoms and signs.

REFERENCES

Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck P, Victor A, Wein A. *The Standardisation of Terminology of Lower Urinary Tract Function: Report from the Standardisation Subcommittee of the International Continence Society.* Am J Obstet Gynecol 2002; 187:116-26.

Merskey H, Bogduk N. *Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms.* IASP Press 2002.

M. Fall (chair), A.P. Baranowski, C.J. Fowler, V. Lepinard, J.G.Malone-Lee, E.J. Messelink, F. Oberpenning, J.L. Osborne, S. Schumacher. *European Association of Urology Guidelines on Chronic Pelvic Pain.* Feb 2003. (*http://www.uroweb.org/files/uploaded_files/guidelines/chronicpelvicpain.pdf*)

Abrams P, Cardozo L, Khoury S, Wein A. *3rd International Consultation on Incontinance,* June 26-29, 2004. ISBN 0-9546956-2-3

Hanno P, Barabowski A, Fall M, Gajewski J, Nordling J, Nyberg L, Ratner V, Rosamilia A, Ueda T. *Chapter 23, Committee 21, Painful Bladder Syndrome (Including Interstitial Cystitis)*.

Summary Lecture/Overview

Mike Hennenfent, Prostatitis Foundation, Smithshire, IL

INTRODUCTION AND OBJECTIVES

We founded the Prostatitis Foundation in 1995 to promote research and public awareness about prostatitis. At that time, there was very little research or information available, and urologists were as frustrated as the patients were

Dr. Bradley Hennenfent established the Internet newsgroup, sci.med.prostate.prostatitis and the response was overwhelming. Patients were wondering why and how they had developed prostatitis. Even more urgent was their desire to find a cure or some relief.

During a visit to a major teaching hospital the problem was confirmed. Prospective organizers were told by one physician, "There will be no fame or wealth for those who discover the cause and cure for prostatitis."

On the assumption that there would be a lot of grateful patients plans were made to proceed. A delegation was sent to see Dr. Nyberg in at the NIH to ask for the needed research. Dr. Nyberg said that the NIH was very aware of the problem and would like to do the research if the funds were available. It was apparent that a foundation had to be formed to petition congress to allocate the needed funds for NIH research. Applications were prepared and the Prostatitis Foundation was chartered in October of 1995 to educate the general public about the prevalence of prostatitis and secure research funding. Dr. Richard Alexander spoke to the Congressional Appropriations Subcommittee of Labor, Health and Human Services, and Education in the spring of 1996. He was supported by an Internet survey about prostatitis he had completed in conjunction with Dave Trissel, a present board member of the Prostatitis Foundation. Report language was submitted and passed in the Appropriations bill of The Subcommittee of Labor, Health and Human Services, and Education directing the NIH to fund the needed research. Drs. Nyberg and Kusek began a five-year research study that was extended one year. Those trials were followed up with another series of clinical trials in progress now.

In the last ten years there have been many articles about prostatitis in most every medical journal and many magazines including: The Journal of The American Medical Society, Urology Times, The New England Journal of Medicine and Men's Health; also The Los Angeles Times, The Wall Street Journal, The South China Morning Post, The Toronto Sun, The Ottawa Citizen, The Saint Louis Post-Dispatch, Dallas Morning News, The Florida Sun-Central, and The Philadelphia Inquirer. The TV show Good Morning

America moderated by Charles Gibson interviewed medical correspondent Tim Johnson about prostatitis. .

The prostatitis website (www.Prostatitis.org), originally organized by Ken Smith, was cited by the London Times as an excellent site. In the past 12 months, the Prostatitis Foundation's website has had over 1,003,733 unique new visitors. The website has a feature called; *It Works for Me*, which collects testimonials by patients that receives a lot of attention. A Prostatitis Foundation director, Clark Hickman runs a telephone phone bank that supports patients and answers questions.

We know that many prominent people have suffered from prostatitis including President John Kennedy and the author Will Durant.

We do not yet have a magic bullet that applies to every ailment diagnosed as chronic prostatitis. There is still much to be done, and the Prostatitis Foundation, managed by unpaid volunteers, hopes to add more personnel to further the effort to conquer prostatitis.

POSTER ABSTRACTS

Treatment of Experimental Autoimmune Prostatitis by BXL-628, a Non-Hypercalcemic Vitamin D Receptor Agonist

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HYPOTHESIS/AIMS OF STUDY

Chronic non-bacterial prostatitis or chronic pelvic pain syndrome (CPPS, NIH category III) is a highly prevalent syndrome of suspected autoimmune origin, characterized by chronic pelvic pain with varying degrees of urogenital symptoms. Based on the marked inhibitory activity of the vitamin D receptor (VDR) agonist BXL-628 (1-α-fluoro-25-hydroxy-16, 23E-diene-26, 27-bishomo-20-epi-cholecalciferol) on basal and growth factor-induced proliferation of human prostate cells, and on its potent anti-inflammatory properties in different autoimmune disease models, we have tested its capacity to treat experimental autoimmune prostatitis (EAP).

STUDY DESIGN, MATERIALS AND METHODS

EAP was induced in non obese diabetic (NOD) mice, a strain genetically prone to develop different autoimmune diseases including prostatitis, by injection of mouse prostate homogenate in complete Freund's adjuvant (CFA). BXL-628 was administered orally 5 d/week at 100 μg/Kg from day 14 to 28 post immunization.

RESULTS

Administration of BXL-628, at non hypercalcemic doses, for two weeks in already established EAP is able to inhibit significantly the intra-prostatic cell infiltrate, leading to a profound reduction in the number of infiltrating leukocytes, in particular $CD4^+$ and $CD8^+$ T cells, B cells, macrophages and dendritic cells. Immunohistological analysis demonstrates decreased cell proliferation, assessed by reduced expression of the proliferation marker Ki 67, and increased apoptosis, shown by increased staining revealed by the TUNEL assay, in prostates from BXL-628-treated mice. In addition, decreased production of the pro-inflammatory cytokines IFN-γ and IL-17 is observed in T cells stimulated by TCR ligation of prostate-draining lymph nodes from BXL-628-treated NOD mice.

INTERPRETATION OF RESULTS

The results indicate that BXL-628, at non hypercalcemic doses, is able to interfere with key pathogenic events in already established experimental autoimmune prostatitis in the NOD mouse.

CONCLUDING MESSAGE

These data support the autoimmune pathogenesis of chronic non-bacterial prostatitis, and indicate that treatment with the VDR agonist BXL-628 may prove clinically beneficial in this syndrome. In addition, they extend the potential use of VDR agonists to a novel indication that represents an important unmet medical need.

Using the National Institutes of Health Chronic Prostatitis Symptom Index to Monitor Treatment of the Chronic Pelvic Pain Syndrome with Pudendal Nerve Perineural Injections.

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INTRODUCTION

The National Institutes of Health definition of the male chronic pain syndrome, "lower genitourinary symptoms, particularly pain in the perineum or genitalia, voiding symptoms, such as dysuria or frequency, and sexual dysfunction…" (Category III B) is similar to the symptom complex of pudendal neuralgia (PN). Robert called this pudendal nerve entrapment; perineal pain that is aggravated by sitting, reduced by standing and relieved sitting on a toilet seat. It is a 'tunnel syndrome'. Sufferers commonly have bladder, bowel, and sexual dysfunction. Several authors describe the use of pudendal nerve blocks as treatment for chronic pelvic pain due to PN.

METHODS

Men with pains in the territory of the pudendal nerve are considered to have PN when the pains are aggravated by sitting, relieved by standing or recumbence, and relieved sitting on a toilet seat. Examination includes evaluation of the skin at the coccyx for evidence of autonomic dysfunction, pinprick examination of 3 branches of the pudendal nerve bilaterally, and pressure on the nerve attempting to reproduce subjective pains (Valleix phenomenon). Expressed prostate secretions or VB3 urinalysis must be normal. Objective confirmation includes a Quantitative Sensory Test called a warm detection threshold (Physitemp NTE-2A) and the pudendal nerve terminal motor latency test (PNTMLT, Dantec Keypointe).

Three pudendal nerve perineural injections (PNPI) are performed at 4 week intervals using bupivacaine 0.25% 6 ml mixed with Kenalog 40 mg 1 ml, unilaterally or bilaterally as indicated. Two PNPI are given at the ischial spine and one into the Alcock Canal. Examination 2 hours after PNPI evaluates subjective pain and the degree of anesthesia. NIH-CPS, AUASI and IIEF-5 symptom scores are monitored.

RESULTS

Prolonged, durable, therapeutic response can be achieved using a series of 3 PNPI. Early, complete response is unusual. Occasionally a 4th PNPI is added to complete the pain relief. Response may be limited to a temporary, that is, diagnostic response. Preliminary data suggest that accuracy of needle placement near the pudendal nerve is a key factor in successful pain control. Therapeutic response also correlates with duration of CPPS symptoms, severity of NIH-CPSI score at time of diagnosis, and willingness of patients to restrict cycling, exercise, sitting, etc. (self-care). Repeat treatment series can accomplish long term relief of symptoms. Complications are minimal. Pending availability of complete 2004 data, cases are selected for demonstration.

Modification of the National Institutes of Health Chronic Prostatitis Symptom Index for Use in Females with Pudendal Neuralgia. A Preliminary Report

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INTRODUCTION

The National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) is a valuable tool in monitoring men with pudendal neuralgia (PN). Symptom indices for delineating and monitoring female pelvic pain are often unwieldy for frequent use or may focus on specific processes such as interstitial cystitis. We used a female modification (f-NIH-CPSI) in over 200 females with PN.

PN is perineal pain that is aggravated by sitting, reduced by standing or recumbency, and relieved when sitting on a toilet seat. Often pain is elsewhere in the territory of the pudendal nerve and is associated with variable sexual, bladder, and rectal dysfunction. PN in females meets the NIH definition of the chronic pelvic pain syndrome, namely, "lower genitourinary symptoms, particularly pain in the perineum or genitalia, voiding symptoms, such as dysuria or frequency, and sexual dysfunction…"

The NIH-CPSI measures 4 domains: 1. Pain; 2. Urination; 3. Impact of Symptoms; 4. Quality of Life. The female homolog of each male anatomical term was substituted in questions 1 a, b, c, d, in the Pain or Discomfort domain. Because we find that rectal pain is common in females we added Question 1 e; "In the last week have your experienced any pain or discomfort… or rectal area." The Urination, Impact of Symptoms, and Quality of Life domains remain unchanged. Score totals 44. Symptom scores completed during therapy are the basis for the present report. The simplicity permits weekly use. In this preliminary study, case reports demonstrate the variation of symptom scores correlating with clinical status.

MATERIALS AND METHODS

69 females were evaluated in 2004 for typical symptoms of pudendal neuralgia; pelvic pains that are aggravated by sitting, reduced standing or recumbent, and, relieved sitting on a toilet seat. They each completed 3 symptom indices; the Female Modification of the NIH-CPSI (f-NIH-CPSI), the American Urological Association Symptom Index, and the Female Sexual Function Index. All patients had a thorough pelvic examination and MRI of the lumbosacral spine and lumbosacral plexus.

A focused pudendal neurological evaluation includes sensory evaluation bilaterally, compression of the pudendal nerve at the Alcock Canal and medial to the ischial spine

to reproduce pain (Valleix phenomenon), and observation of the skin over the coccyx for evidence of autonomic stimulation. Warm detection threshold test and pudendal nerve terminal motor latency test are performed to confirm neuropathy. Treatment uses a sequential program of self-care (i.e. no sitting, exercise, cycling), bilateral pudendal nerve blocks (bupivacaine and Kenalog), and, if necessary, surgical decompression of the pudendal nerve as outlined by Robert.

RESULTS

The f-NIH-CPSI score of cases selected for demonstration purposes indicate success or failure of treatment. The weekly variations in scores correlate with symptom recall or diaries. Women rarely object to completing the f-NIH-CPSI. The simplicity permits weekly use. The brevity is not emotionally intrusive for most females with sexual dysfunction as a component of their pudendal neuralgia. A research protocol for validation of the f-NIH-CPSI is in developmental stages.

Leukocytes in Men with Category III Chronic Prostatitis/Chronic Pelvic Pain Syndrome

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OBJECTIVE

Diagnostics and therapy of category III chronic prostatitis (CP) or chronic pelvic pain syndrome (CPPS) according to the NIH classification raise multiple problems. Category III chronic prostatitis/chronic pelvic pain syndrome (CPPS) is a common debilitating condition of unclear ethiology. Difficulties are related with the fact that, after patient examination, it is not always possible to differentiate correctly whether it is inflammatory (category IIIa) CP or non-inflammatory (category IIIb) CP. Methods used in practice are based on results of tests of expressed prostatic secretions (EPS) and /or the four-glass test (voided bladder urine (VB)) when the count of white blood cells (WBCs) is determined and category IIIa or IIIb CP/CPPS is diagnosed accordingly.

MATERIALS AND METHODS

During initial investigation including medical history and physical examination, prostate per rectum − digital examination was performed with evaluation of prostate consistence, seizing of infiltrations or softening, determination of sensitiveness and painfulness; prostate ultrasound examination; EPS and/or VB tests including microbiological analysis; and category III CP/ CPPS was diagnosed in 632 patients. The *average* age of males was 38 years, the age varied from 18 to 70. Inflammatory (category IIIa) CP/CPPS made 554 (88%) of all cases and non-inflammatory (category IIIb) CP/CPPS 79 (12%). Further observation and treatment of 79 patients having category IIIb CP/CPPS showed that inflammatory processes of prostate appeared in 23 patients (26%) 2–4 weeks later, their EPS and /or VB tests showed appearance of WBCs (>10) and uropathogene microorganisms *were determined in no case*. EPS tests were performed for 15 patients of those 23 and significant increase in lecithin granules was found in 13 patients during repeatedly made EPS tests, after 2–4 weeks.

Only 56 patients (8%) with a diagnosed category IIIb CP/CPPS remained of the whole number of 632 category III CP/CPPS patients during the course of treatment. No prostate changes were found in these patients using per rectum—digital examination except for patients of older age with symptoms of benign prostate hyperplasia. It was assumed that symptoms of CP/CPPS in these 56 patients were conditioned not by prostate, but other causes (interstitial cystitis, neuropathy of the pudendal nerve, muscular dysfunction of the pelvic floor). WBCs were not found during initial EPS and/or VB tests because excretory ducts of prostate were damaged and obstructed by chronic inflammatory process; they got unblocked during the

course of therapy and, after massage of prostate, inflammatory content with white blood cells ran out through them and a higher number of lecithin granules appeared.

CONCLUSIONS

It is impossible to differentiate whether category III CP/CPPS is inflammatory (IIIa) or non-inflammatory (IIIb) during initial examination because ESP and/or VB tests performed after 2–4 weeks of treatment indicate no WBCs >10 in 26% of patients with previously diagnosed category IIIb CP; the diagnosis is therefore changed into category IIIa CP/CPPS and therapy is to be adjusted respectively.

The Effects of Foods, Beverages and Supplements on the Symptoms of Interstitial Cystitis

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INTRODUCTION AND OBJECTIVE

The etiology of interstitial cystitis (IC), a debilitating, multifactorial syndrome of the bladder, eludes doctors. Various causes have been speculated. Consequently IC is a complex condition to treat. Among the non-traditional approaches used for IC, dietary changes seem to improve symptoms in some individuals. Most of the data gathered on diet as it affects IC symptoms is anecdotal. We developed a questionnaire in order to determine if certain foods, beverages and/or dietary supplements are perceived as increasing or decreasing symptoms of IC.

METHODS

A questionnaire designed to detect whether food, beverages and/or supplements have an effect on bladder symptoms was developed and administered to patients meeting NIDDK criteria for IC (n=37). In addition to answering general questions about the effect of comestibles on IC symptoms, subjects were asked to indicate whether each of over 150 individual items worsens symptoms, slightly worsens symptoms, has no effect, slightly improves symptoms, improves symptoms, or the item is not eaten by the subject; responses were recorded as −2, -1, 0, +1, +2, DE, respectively, and a mean value for each item was generated.

RESULTS

Nearly three quarters (73%) of the IC patients surveyed indicated that consumption of certain foods or beverages caused exacerbation of symptoms; 5% indicated that foods or beverages did not exacerbate symptoms and 22% didn't know. 18% of the subjects indicated that consumption of certain foods or beverages reduced symptoms of IC. Greater than 75% of subjects reported exacerbation of IC symptoms after ingestion of coffee, cola, grapefruit and vinegar; 50-75% reported exacerbation of IC symptoms after ingestion of spicy foods, pizza, alcoholic beverages, strawberries, tomatoes. Subjects tended to avoid the most bothersome foods, indicating that they did not eat chili (50%), orange juice (41%), lemons (41%), spicy foods (41%), pineapple (36%), decaffeinated coffee (36%), grapefruit (32%), alcoholic beverages (32%), coffee (27%), oranges (27%), cola (27%), vinegar (27%). The rank order of specific comestibles which exacerbated symptoms are coffee, grapefruit, cola, vinegar, alcoholic beverages>tomatoes, tomato products>lemons, orange juice, chili> strawberries, pineapple, oranges, onions, pizza>chocolate>decaffeinated coffee, apples; coffee ranked as the most bothersome with a mean value of −1.85.

CONCLUSIONS

There is a large cohort of IC patients whose symptoms are exacerbated by ingestion of specific comestibles. The most frequently reported and the most bothersome comestibles include items containing caffeine, citrus fruits and juices, tomatoes and tomato products, items containing vinegar, and alcoholic beverages.

Corynebacteria in Semen of Chronic Prostatitis Patients

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Coryneform bacteria are frequently found in genital tract of both diseased and healthy men. At the same time there is scarce knowledge about their species composition and properties as well as their role in infections.

OBJECTIVE:

To identify corynebacteria isolated form seminal fluid of prostatitis patients and controls and to evaluate their antibiotic susceptibility.

MATERIAL AND METHODS

Altogether 115 men were investigated, 49 with inflammatory chronic prostatitis syndromes (NIH IIIA, NIH IV) and 66 controls. Corynebacteria were isolated from freshly prepared blood agar medium by characteristic morphology and positive catalase reaction. *Corynebacterium seminale* was identified by beta-glucuronidase activity, other corynebacteria with commercial kit API Coryne (bioMérieux). Susceptibility of 23 strains was tested against 8 antibacterial agents using E test method.

RESULTS

Coryneform bacteria were found from 37 (76%) prostatitis patients and 57 (86%) controls (P>0.05). One patient had 0…6 (mean 1.3) different corynebacteria. Further analysis included 114 strains. Of them, 70 appeared to be *Corynebacterium seminale*. The strains identified by API Coryne belonged to 12 species, including *Corynebacterium* group G (9 strains), *Corynebacterium striatum* (8), *Cellulomonas sp.* (6), *Corynebacterium jeikeium* (6), *Arthrobacter sp.* (4), *Dermabacter hominis* (4) and others. The prostatitis patients with serious inflammation (>1 M WBC/ml of semen) harboured significantly more frequently *Corynebacterium* group G (39% vs 1%, P=0.00005) and *Arthrobacter sp.* (17% vs 1%, P=0.03) than the controls.

All strains tested were susceptible to amoxicillin/clavulanic acid. Single strains were resistant to trimethoprim/sulphamethoxazole and erythromycin, one fifth of the strains were resistant to doxycycline, nitrofurantoin and norfloxacin, one third to benzylpenicillin and nearly half to clindamycin.

CONCLUSIONS

Most of men harbour coryneform bacteria in their genital tract. Corynebacterium group G and Arthrobacter sp. appear more frequently in prostatitis patients than in controls.

Mycoplasmas in Semen of Chronic Prostatitis Patients

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The vast majority of studies investigating etiology of chronic prostatitis use only aerobic culture detection in prostate specific specimens though several fastidious or non-culturable micro-organisms might be important as well. In recent years mycoplasmas, the smallest free-living organisms have been associated with prostatitis syndromes.

OBJECTIVE

To evaluate the occurrence of mycoplasmas in the semen of chronic prostatitis patients using two study methods.

MATERIAL AND METHODS

The semen of 121 chronic prostatitis (38 NIH IIIa, 59 NIH IIIb and 24 NIH IV category) patients and 40 controls was evaluated for genital mycoplasmas. The commercial kit Mycoplasma IST (bioMerieux) was applied to all 161 specimens for detecting ureaplasmas and *M. hominis*. Polymerase chain reaction (PCR) method was additionally used in 60 randomly selected men for investigating *M. genitalium*, *U. parvum* and *U. urealyticum*.

RESULTS

By Mycoplasma IST test, ureaplasmas were found in all study groups (21% in NIH IIIa, 17% in NIH IIIb, 25% in NIH IV, 12% in controls) but *M. hominis* was found only in one IIIb category patient in low count.

By PCR method, majority of ureaplasmas were identified as *U. parvum*. They were seen in all prostatitis groups (18% in NIH IIIa, 15% in NIH IIIb, 25% in NIH IV) but not in the controls. *M. genitalium* appeared only in NIH IIIa category patients (18%, P=0.032 in comparison with controls). The occurrence of any of the mycoplasmas was significantly higher in prostatitis patients than in controls (26% vs 4%, P=0.026) as well as in NIH IIIa patients than in controls (36% vs 4%, P=0.023).

Though we found substantial agreement between the two methods used for detecting genus *Ureaplasma* (Cohen's kappa coefficient _=0.69, P=0.0007), the IST test does not enable to differentiate between *U. urealyticum* and *U. parvum*. Since most of the ureaplasmas in our study appeared to be *U. parvum*, and the latter was present in prostatitis patients only, the PCR method would be preferred.

CONCLUSION

Mycoplasmas appear more frequently in the semen of prostatitis patients than in healthy controls, with *Ureaplasma parvum* being the most frequent species.

Acute and Chronic Cyclophosphamide-Induced Cystitis Upregulate Macrophage Migration Inhibitory Factor (MIF) in the Rat Bladder and Prostate: Further Evidence for a Viscero-Visceral Interaction Mediating Prostatic Inflammation.

Hugo L. Fernandez, PhD, Katherine L. Meyer-Siegler, PhD and Pedro L. Vera, PhD

INTRODUCTION

We have shown that acute bladder inflammation produces intraluminal release of MIF (a pro-inflammatory cytokine) and upregulation of MIF in the bladder. Since intravesical antibodies to MIF prevented or reduced inflammation, MIF may be involved in the development and/or maintenance of bladder inflammation. We investigated the effect of acute (24 hour) and chronic (8 days) administration of cyclophosphamide (CYP) on bladder MIF levels. In addition, since we previously documented a viscero-visceral interaction where bladder inflammation produced inflammatory changes in the prostate and vice versa, we also examined the prostate of CYP-treated animals for inflammatory changes.

METHODS

Male Sprague-Dawley rats (250-300 gm) were anesthetized with halothane. In acute experiments (24 hour), rats received CYP 150 mg/kg (i.p.; n=5) or saline (n=5). In chronic experiments, rats received CYP in doses of 75 (n=6), 60 (n=3), 40 (n=3) or 20 (n=3) mg/kg i.p. every 3rd day for 8 days while control rats received saline injections. Rats were allowed to recover from anesthesia and placed in metabolic cages. At the appropriate survival times, the rats were reanesthetized; bladder and prostate were removed and processed for MIF and other cytokine determination and for histology and immunohistochemistry.

RESULTS

In acute experiments, CYP resulted in marked epithelial denudation and hemorrhagic cystitis. MIF levels increased in the urine while decreasing in the bladder. MIF and cox-2 mRNA were upregulated in the bladder. Bladder weight was significantly increased, indicating bladder edema (confirmed histologically). Interesting, in CYP-treated animals prostate weight also was significantly increased indicating edema (confirmed histologically) with upregulation of MIF and cox-2. In chronic experiments, CYP caused a dose-dependent decrease in the MIF levels in the bladder and the prostate with upregulation of MIF in the bladder. The higher doses of CYP tested caused significant hemorrhagic cystitis, weight loss and unexpected death of some animals.

CONCLUSIONS

CYP-induced cystitis, a commonly accepted model of producing chronic cystitis in rodents, resulted in bladder excretion of MIF and upregulation of MIF in the bladder. These findings extend our findings in acute models of experimental cystitis. In addition, we again observed prostatic changes in response to a restricted insult to the bladder indicating that a viscero-visceral response may elicit prostatic inflammation. Strain and/or sex differences in the tolerability of CYP led us to titrate the effective dose. CYP-induced cystitis is a potential model to study viscero-visceral interactions that mediate inflammation in other pelvic viscera.

Supported by: VA Merit Review and Bay Pines Foundation

Substance P-Induced Upregulation of Glucose Regulated Protein (GRP78) in the Urothelium: Binding of GRP78 to Released Macrophage Migration Inhibitory Factor (MIF) Complexes as a Possible Mechanism for MIF's Pro-Inflammatory Effects in the Bladder

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INTRODUCTION

GRP78 (an endoplasmic reticulum stress protein) can also be located on the surface of cells where it activates MAPK signal transduction pathways upon binding of α2-macroglobulin or α1-inhibitor 3 (α1-I3; a rodent member of the α2-macroglobulin family). Therefore, GRP78 is a receptor for α1-I3-mediated signal transduction. MIF-α1-I3 complexes are released from the bladder after inflammation. Moreover, they localize to umbrella cells in the urothelium after inflammation. The presence and/or location of GRP78 had not been investigated in the bladder. Therefore, based on our findings, we examined the location and extent of this protein in the bladder and the effects of bladder inflammation.

METHODS

Fifteen (15) male Sprague-Dawley rats (250-300 gm) were anesthetized with sodium pentobarbital and divided into three groups: (1) Intact: bladders removed; (2) Saline: bladders isolated from kidneys by cutting ureters; bladders emptied and replaced with 0.3 ml saline; saline treatment (s.c.); (3) Substance P (SP): bladders treated as in group (2) with SP treatment (40 ug/kg; s.c.). After 1 hour, the intraluminal fluid (ILF) was collected; the bladder and prostate were excised and processed for MIF and GRP78 determination (using ELISA and Western blotting analysis). Co-immunoprecipitation studies examined the association of MIF and α1-I3 with GRP78. Sections of bladders and prostates were also processed for immunohistochemistry.

RESULTS

Bladders from intact or saline-treated animals showed no GRP78 urothelial staining. SP treatment caused marked immunostaining the umbrella cells. Western blotting demonstrated increased GRP78 in bladder homogenates after SP. Co-immunoprecipitation studies of bladder homogenates pulled down α1-I3 (as expected) and MIF. In particular, 130 and 80 kDa MIF-α1-I3 complexes were associated with GRP78. Finally, double immunofluorescence demonstrated co-localization of GRP78 and MIF in umbrella cells of SP-treated rats.

CONCLUSIONS

This is the first report to show GRP78 is activated during neurogenic inflammation in the rat bladder. In addition, GRP78 localizes to the umbrella cells that also contain demonstrable amounts of α1-I3 and MIF. This study shows an association between GRP78, α1-I3 and MIF in the bladder. During inflammation, α1-I3-MIF complexes are released into the lumen, bind to GRP78 and may activate signal transduction pathways that mediate MIF's pro-inflammatory effects on the bladder.

Supported by: VA Merit Review and Bay Pines Foundation

MIF-Alpha1-Inhibitor 3 (α1-I3) Complexes in the Rat Bladder: Substance P-Induced Localization to Umbrella Cells.

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INTRODUCTION

MIF is a pro-inflammatory cytokine founds constitutively expressed in the urothelium. We established that inflammation causes luminal MIF release as a high molecular weight complex with α1-I3 (a rodent α2-macroglobulin family protein). Although α1-I3 is synthesized in the liver, it can also reside in tissues where it may act as a proteinase inhibitor. In order to understand the changes in intraluminal levels of MIF-α1-I3 complexes caused by inflammation, we examined α1-I3 and MIF-α1-I3 in the bladder and changes produced by our model of neurogenic inflammation.

METHODS

Fifteen (15) male Sprague-Dawley rats (250-300 gm) were anesthetized with sodium pentobarbital and divided into three groups: (1) Intact: bladders removed; (2) Saline: bladders isolated from kidneys by cutting ureters; bladders emptied and replaced with 0.3 ml saline; saline treatment (s.c.); (3) Substance P (SP): bladders treated as in group (2) with SP treatment (40 ug/kg; s.c.). After 1 hour, the intraluminal fluid (ILF) was collected; the bladder and prostate were excised and processed for MIF and α1-I3 determination (using ELISA and Western blotting analysis). Sections of bladders and prostates were immersion fixed and processed for histology and immunohistochemistry.

RESULTS

ILF showed two high-molecular weight MIF-α1-I3 complexes (200 and 130 k Da), and also 12 kDa monomeric MIF. SP increased the two high-molecular weight MIF complexes in the ILF, in agreement with our earlier findings. In the bladder, 3 high-molecular weight MIF-α1-I3 complexes were identified: 200 and 130 (as in the ILF) and a 75 k Da complex (not found in the ILF or in the urine) in addition to 12 kDa (monomeric) MIF. SP induced a marked decreased in the 200 kDa complex in the bladder. Immunohistochemistry showed that in control bladders, α1-I3 is localized to subepithelial fibroblasts in the lamina propria and interstitial spaces in the bladder. SP treatment induced in pericellular α1-I3 in the urothelium and marked umbrella cell immunostaining. Dual immunofluorescence showed that MIF and α1-I3 localize to umbrella cells in SP-treated animals. In addition, SP treatment caused marked phospho-ERK immunostaining in the umbrella cells.

CONCLUSIONS

α1-I3 is found in the lamina propria in normal bladders and not in the urothelium. Specific MIF-α1-I3 complexes are released from the bladder during inflammation and bind to umbrella cells in the urothelium. Binding of MIF-α1-I3 complexes to umbrella cells may activate signal transduction pathways, possibly involving ERK phosphorylation that mediate MIF's pro-inflammatory effects during neurogenic inflammation.

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