NIDDK Conference Puts Pelvic Pain into New Perspective

As the Prostatitis Foundation celebrated its 10th anniversary in October, urologists, neurologists, pain management specialists, pharmacologists, psychologists, and infectious disease specialists came together to present the latest ideas and research on chronic pelvic pain. At the Chronic Pelvic Pain/Chronic Prostatitis Scientific Workshop in Baltimore, Maryland, sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), it became apparent that thinking about chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and interstitial cystitis (IC) is undergoing a major shift. Researchers’ attention is moving away from looking at the prostate and bladder alone as treatment targets and more toward treating pain itself in both conditions.

Are CP/CPPS and IC the same condition? Right now, the experts seem to see enough differences between them to keep them separate, especially in terms of symptoms and levels of antiproliferative factor (APF), the peptide specific to IC patients’ urine. But the question isn’t settled and won’t be until we know more about the genetics of each condition. What was clear, however, was that both sets of patients may benefit from looking at these syndromes as neuropathic pain conditions.

Focus Shifts to Nerve Pain

The first session of the conference, in fact, was focused on neuropathic pain. Researchers are trying to find out how pain is transmitted and especially how changes in the central nervous system can perpetuate pain when it may no longer have much to do with a noxious stimulus, say, inflammation of the prostate. John Loeser, MD, a neurologist from the University of Washington, Seattle, strongly urged the researchers and clinicians there to shift their focus to the nervous system.

Gerald Gebhart, PhD, a pharmacologist at the University of Iowa in Iowa City, is changing the way we think about how pelvic organs are innervated and how pain from them is transmitted. Each pelvic organ has input from at least two anatomically distinct nerves. And pain travels back to the spinal cord through both, which branch up and down the spinal cord. In addition, nearly every nerve root in the spinal cord gets input from skin and body wall nerves as well as pelvic organs. This could explain why it is difficult to tell where the pain is coming from and how pain gets referred from the organs to muscles and skin. In addition, sensory nerves in the organs that are usually quiet may be activated by inflammation and contribute to hypersensitivity because of the extra load of input. Sensitization of nerves may happen both at the organ and in the central nervous system, he said.

Ob/gyn and anesthesiologist John McDonald, MD, from the Harbor UCL Medical Center in Torrance, California, spoke from a practical standpoint about the relationship between pelvic pain and nerve pain. He has seen many women with pudendal neuralgia, whose pelvic pain had gone undiagnosed for years, similar to the experience of some urologists and neurologists with men. Typically, patients have pain when they sit that is relieved when they stand. To relieve pelvic pain caused by pudendal neuralgia, he uses injections of anesthetic around the pudendal nerve and also at the sacrum. He speculated that the local anesthetic somehow helps “reboot” the more central nerves in the spinal column to offer long-term relief, especially after repeat injections.

The neuropathic pain session also included reports of research that could lead to new drugs for pelvic pain. Some were being studied for their effects on bladder overactivity, but another, called macrophage migration inhibitory factor (MIF), is known for its effects in both the prostate and bladder. Pedro Vera, PhD, a research physiologist at the University of South Florida in Tampa, has been researching this substance, which plays a role in inflammation, especially by cells that line the lower urinary tract. It can also be found in the nerves that go to the pelvic organs and in the central nervous system. Dr. Vera found that putting antibodies that block MIF into the bladder reversed or prevented the inflammation that MIF can cause in the bladder and prostate.
Alan Cowan, PhD, a pharmacist from Temple University in Philadelphia, Pennsylvania, talked about more immediate drug options for pain control and how those are growing. On the horizon are new drugs that affect receptors for neurokinins, cannabinoids, NMDA, and TRPV1. A few new compounds have been successful for neuropathic pain, such as venlafaxine (Effexor), gabapentin (Neurontin), and pregabalin (Lyrica).

But, unfortunately, the pace of new drug development has been slow. Instead, drug companies have focused on developing newer forms of existing drugs and drug combinations that may have more effect that the drugs by themselves, such neuropathic pain drugs combined with opioids, and new ways of delivering old drugs, such as transdermal delivery of opioids. Dr. Cowan sees potential in the irritable bowel drug tegaserod (Zelnorm), which may have a role as a painkiller for visceral pain beyond its effects on gastrointestinal function.

**Genes, Sex Can Determine Pain Sensitivity**

What makes someone susceptible to pain? Two researchers had great insight on that question. Richard J. Bodnar, PhD, from Queens College, City University of New York in Flushing, is investigating how sex differences affect pain perception. He has confirmed that females do tend to feel more pain and that hormones make a difference in pain control with opioids. He also noted that, although men and women respond similarly to the mu family of opioids (morphine and its cousins), women respond better to kappa opioids.

Jeffrey Mogil, PhD, showed that both genes and sex play important roles in the response to pain and opioids. Genetic differences can explain some of the huge variations that people and animals have in responding to opioids. In humans, the response can be as much as 40 times greater in one person than in another. Although he is finding out exactly what genes control responses to different kinds of pain and to opioids in mice, he thinks the research may apply to people, too. In fact, he zeroed in on a gene responsible for higher response to kappa opioids in mice, but it happens to make a difference in pain in humans—and in females not males. It also happens to be a gene in which variants code for red hair. He found that, indeed, redheaded women with that variant respond better to those opioids and that they can withstand a certain type of pain better than any nonredhead or male redheads. In addition, he has found that different genes are very specific for different types of pain. For example, a gene may affect how an animal senses pain caused by extremes of temperature but not by inflammation. In the future, research of this kind might give clinicians tests to see which painkillers and how much of them you might need. It could also lead to new pain drugs. But for now, said Dr. Mogil, that tremendous genetic variability should at least destigmatize pain-sensitive patients, that is, doctors should recognize it’s not patients’ “fault” when they’re more sensitive to pain than others.

**New Approaches to Measuring Pain**

Pain is a complex phenomenon, so how should we measure it? Because experts are recognizing that pelvic pain is a neurologic disorder, neurologic tests can help with research and in the clinic, said Clare Yang, MD, a urologist at the University of Washington, Seattle. The tests she uses might show in an objective way how well pain therapy is working. And some of the tests she uses may even help show when the pain has become centralized—that is, perpetuated in the nervous system itself.

Dennis Turk, PhD, from the University of Washington, urged pelvic pain experts there to rethink how pain should be measured in clinical trials. He asked them to think about who decides what is important—the researchers or the patient. Just because an outcome, such as reduction in pain on a scale of 1 to 10, is statistically significant to the researchers doesn’t mean that it’s meaningful for the patients, so experts should try to find the measures that are, he said. Change should also be weighed from the patient’s perspective, for example, by finding out whether patients consider the extra cost of a new drug worth it for the amount of relief they get. Dr. Turk also recommended that researchers in this field get together to agree on what kinds of measurements should be used and to find out whether different treatments will be useful for different groups of patients.

**Psychological, Physical Therapies Being Integrated**

It was apparent at this workshop that pain management is becoming broader, focusing not just on medical therapy but also on mechanical, psychological, and social factors as well. Chronic pain isn’t always treatable with painkillers, and different explanations why
suggested different approaches. There was a significant focus on the types of psychological treatment that can help patients cope with and even reduce pain, although moderately. Also, use of physical therapy in treatment of both men and women was much more apparent at this conference than in the past.

Psychologist and neurophysiologist Catherine Bushnell, PhD, from McGill University in Montreal has looked—literally—at how attention and emotion affect pain by analyzing images of the brain. Distraction actually reduced pain intensity in the brain’s pain sensing areas. Negative emotion had more widespread effects in the brain. She said that she believes pain is seldom just created by our psychology, but psychological factors can have a strong influence on the perception of pain and pain-related activity in the nervous system.

Psychological research shows that depression, anxiety, and “catastrophizing” can contribute to pain, said clinical psychologist Jennifer Hathornwaite, PhD, from Johns Hopkins University. Psychological research is also showing that certain psychological therapies, such as cognitive behavioral therapy, that help patients cope can reduce pain, said Judith Turner, PhD, a psychologist from the University of Washington. The pain reduction seems to be real, although moderate.

Julia Heiman, PhD, who is director of the Kinsey Institute at Indiana University in Bloomington, said that psychologists have moved away from considering pain with sex to be psychological to recognize that it is, in fact, physical. Research is just beginning to teach us more about how chronic pelvic pain and, specifically, how pain with sex affect both relationships and daily living in men and women, she said.

David Wise, PhD’s presentation about the Stanford protocol for paradoxical relaxation and trigger point release showed the growing acceptance of physical therapy for pelvic pain syndromes and the idea that muscle tension and its detrimental effects on the nerves, muscles, and organs of the pelvis may be a major cause of pelvic pain. Dr. Wise is coauthor of A Headache in the Pelvis, which describes Stanford’s combination of pelvic floor physical therapy, breathing techniques to quiet anxiety, and relaxation training that focuses attention on the effortless acceptance of tension (thus paradoxical relaxation). Recently, Dr. Wise and his colleagues reported that this therapy achieved a 72 percent improvement in men with CP/CPPS who weren’t helped by other treatments.

Is CP/CPPS an Infection or Autoimmune Disease?

Even though those who still think CP/CPPS is an infection seem to be in the minority today, the debate continues. Bennett Lorber, MD, DSc, an infectious disease specialist from Temple University School of Medicine in Philadelphia, pointed out that many diseases thought not to be caused by infection before are being recognized as infections today, such as peptic ulcers caused by Helicobacter pylori. Bornaviruses have recently been implicated in mental illnesses, such as schizophrenia and autism, and herpes virus 8 in prostate cancer. Nanobacteria, very small bacteria thought to produce calcium salts and form stones, have also been held out to be an unculatable but bacterial cause of disease, but Dr. Lorber noted that the National Institutes of Health (NIH) concluded that the “bacteria” were, in fact, a contaminant of the chemicals used to detect them.

Dr. Lorber noted that, although infections may play a role in many diseases, the diseases may not be caused by active infection. Rather, infection may be a trigger. Guillain-Barré syndrome seems to be an example because many patients have evidence of active or previous Campylobacter infection. But in this case, the immune response to the bacteria produces antiganglioside antibodies—antibodies to nerve tissue—and the patient’s immune system then attacks his or her own nervous system.

Is there any evidence that CP/CPPS might be an autoimmune disease? Richard Alexander, MD, of the University of Maryland in Baltimore has been researching that very question and has interesting evidence that this might be so in some cases. Clinically, CP/CPPS acts like an autoimmune disease because it flares and remits. Some patients, indeed, have immune system cells that react to prostate antigens, unlike normal men. The men showed very abnormal prostate tissue, a condition known as granulomatous prostatitis, and also showed evidence of a type of white-cell antigen that is typical in patients with autoimmune diseases.

John Kreiger, MD, a urologist from the University of Washington, has looked for a
pathogen that’s not easy to culture that might be the cause of CP/CPPS. He found that about 20 percent of patients had levels of bacterial DNA in prostate tissue judged high enough to indicate an infection. That suggests, he said, that there are likely multiple causes of the syndrome and that some research ought to be directed to finding out why some men do, in fact, respond to antibiotic therapy.

Antibiotic therapy remains the gold standard of therapy, not because evidence supports it but because urologists “vote with their feet,” said Daniel Shoskes, MD, of the Cleveland Clinic in Cleveland, Ohio. He suggested a number of reasons antibiotic therapy might be helpful. First, patients may have an active infection that goes unrecognized, in part because urologists are reluctant to culture anything but urine. The antibiotics need to be selected for their ability to kill a wide spectrum of bacteria and their ability to penetrate prostate tissue, and they need to be administered for enough time—typically four to six weeks. After that, without evidence of bacteria, the therapy should be stopped, he said, pointing out the potential risks of long-term antibiotic therapy, such as diarrhea or tendon rupture with quinolones. He also suggested that when antibiotics combined with prostatic massage seem to help, it may be that the massage disrupts a biofilm that keeps the bacteria protected from the antibiotics. On the other hand, he noted, prostatic massage may in fact be massaging pelvic muscle trigger points.

When disease is in fact nonbacterial, antibiotics may still be helpful because of their properties that have nothing to do with killing bacteria, added Dr. Shoskes. Although the placebo effect and the flaring/remitting nature of CP/CPPS may sometimes be the reason they seem to help, antibiotics, especially the quinolones and macrolides, also have anti-inflammatory properties. Some even block the very inflammatory proteins known to be at high levels in the semen and expressed prostatic fluid of men with CP/CPPS.

Dr. Shoskes himself has studied a therapy for men with prostatic stones and apparent nanobacteria. “I don’t care if they’re microorganisms or not,” he said, noting that a therapy aimed at eliminating them seems to work for men when no other therapy does for men with CP/CPPS who have these stones. The treatment combines the antibiotic tetracycline with EDTA, intended to help dissolve the stones; and an oral neutraceutical thought to help the antibiotic penetrate into the stones.

What Works?
What works for CP/CPPS? “Everything,” joked Curtis Nickel, MD, from Queens University in Kingston, Ontario. He pointed out that in pilot or uncontrolled studies, nearly every therapy seems to do well. But each—antibiotics, alpha blockers, pentosan polysulfate (Elmiron)—has then fallen from grace in comparison with placebo. Some treatments that have seemed to fare well in uncontrolled studies haven’t yet been tested against placebo or sham treatment, such as saw palmetto, acupuncture, and physical therapy. He has hopes for physical therapy and acupuncture in particular, which produced responses of 80 percent in uncontrolled studies. But all these therapies need to be tested against placebo or sham treatment.

He also sees potential in some surgeries—incision of the bladder neck in patients with voiding symptoms or transurethral microwave thermotherapy (TUMT) of the prostate; tricyclic antidepressants, which have been shown helpful for interstitial cystitis in controlled studies; alpha blockers or antibiotics as early therapy (in patients who have had symptoms for four weeks or fewer); and the gabapentinoid drugs, which are used to treat neuropathic pain, such as gabapentin (Neurontin) and pregabalain (Lyrica). In fact, studies by the Chronic Prostatitis Clinical Research Network (CPCRN) of Lyrica for CP/CPPS are under way, and trials of alpha blockers for newly diagnosed patients are being planned.

For therapy today, said Dr. Nickel, multimodal therapy, that is, using more than one therapy at a time, seems to do best. In addition, when medical therapy fails, it may be because the biomedical model of disease just isn’t the best one, and it’s time for plan B—the biopsychosocial approach that integrates psychological with medical and physical therapy.

“One therapy doesn’t fit all,” said Dr. Nickel, emphasizing that researchers have to find ways to differentiate among types of pelvic pain in CP/CPPS patients, for example, inflammatory, neurogenic, or neuroendocrine, with biomarkers that could help clinicians target the right treatments to the right patients.
Opiate Argument Erupts
A mini “opiate war” erupted among some of the experts at the meeting. Dr. Nickel, for example, said he was against the use of any opioids in the treatment of pelvic pain. Last May, Christopher Payne, MD, from Stanford (California) University made a plea at the American Urological Association meeting for urologists to learn to use opioids to treat chronic pelvic pain, and the reaction against them by some at this meeting seemed to be in response to that speech. Dr. Nickel argued that long-term use of opioids provokes side effects, such as abnormally low testosterone levels, galactorrhea (discharge from the nipples), amenorrhea in women, and even hyperalgesia—abnormally large reactions to painful stimuli—working against pain control in the long run.

We asked a well known pain management researcher who treats pelvic pain, Daniel Carr, MD, to put that controversy in perspective. Dr. Carr warned against oversimplifying the issue into an “all-or-none, forever-or-never dichotomy.” His own meta-analysis of controlled studies of opioids has confirmed opioids’ effectiveness for chronic pain. As always, the side effects have to be weighed against the benefits, and few other types of drugs are effective for the worst levels of pain. The side effects can be treated directly or can be minimized by choosing the appropriate kinds of opioids, restricting opioids to treatment of flares, or by using effective drug combinations. Dr. Carr also pointed out that recent studies point to a synergistic effect between the neuropathic pain drugs, such as venlafaxine (Effexor), and opioids that may give better pain control than either type of drug alone with lower doses of each drug and, therefore, fewer side effects.

The Long View
The progress made so far in CP/CPPS research and treatment wouldn’t have been possible, noted Dr. Shoskes, without support from NIH and private foundations that patient and advocacy groups have helped bring about. Leroy Nyberg, MD, PhD, director of urology programs at NIDDK, pointed out that tax dollars come to NIDDK for research from Congress, and the way that Congress knows how to focus the tax dollar is through patient advocacy. “If it wasn’t for the patient advocacy of the Prostatitis Foundation and patients that are citizens who are interested in supporting that effort, I don’t think we’d be here today,” he said.

Prostatitis Foundation President Mike Hennenfent put the progress in perspective with his long view of clinical practice, research progress, and the activities of the foundation. He noted that, although CP/CPPS is a common problem, possibly affecting some 10 percent of men, it began to be a focus of research only 10 years ago, in part because of the efforts of the Prostatitis Foundation. The tide of professional awareness began to turn, Mike noted, at an American Urological Association meeting the May after the organization was founded, where Dr. Kreiger said that NIH now recognizes prostatitis as one of three major diseases of the prostate and remarked to his colleagues, “You can no longer tell these people it’s all in their head.” The research tide has turned too, said Mike, noting that Curtis Nickel at a prior meeting had said, “More has been published about CP/CPPS in the last 5 years than in the previous 50.”

The organization’s presence on the worldwide web has also helped raise awareness around the world. In fact, the foundation’s growth has paralleled that of the worldwide web, said Mike. When the foundation started, 45 percent of Americans had internet access, and that has grown to over 80 percent, with 50 percent of those having broadband access. Now, the foundation is providing much of its information through its website instead of mail.

The foundation plans to grow and meet the needs of more patients for information, counseling, and support. And, of course, the foundation will continue to support research. “We ask you to redouble your efforts,” Mike told the researchers. “Let’s not come back here in 10 more years and have to say the things we’re saying at this meeting.

The Prostatitis Foundation does not endorse any medicine, doctor or treatment protocol.

Meeting summary contributed by Penny Allen, who is a freelance medical writer in Cleveland, Ohio.
Smallest Bacteria Found in Chronic Prostatitis

Mycoplasmas, a type of bacteria, are some of the smallest free-living organisms. Various species are found in healthy people, especially in the mouth and genitourinary tract, but some have been associated with disease, including various urinary tract diseases and some immunodeficiency and autoimmune diseases. They are difficult to identify and culture, and a kit commonly used to detect them does not distinguish well among different species. These Estonian researchers looked for mycoplasmas in the semen of men with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and healthy controls. Using the kit first in 161 men, including healthy men and those with all categories of CP/CPPS (IIA, the inflammatory type with white blood cells in semen and IIb, the noninflammatory type, and IV, the inflammatory type with no symptoms). The kit detected mycoplasmas in all the groups of men, but a more precise method of identifying the bacterial species called polymerase chain reaction (PCR), used in 60 of these men, detected mycoplasmas more often in chronic prostatitis patients than healthy men. A quarter of the men with chronic prostatitis had mycoplasmas compared with about a fifth of the controls. In addition, the mycoplasmas occurred more frequently in the semen of men with category IIA disease than in the healthy men. No healthy man had either Ureaplasma parvum or Mycoplasma genitalium, but some men in all categories of CP/CPPS had U parvum, and some men with IIA disease had M genitalium. Although the numbers of patients in each group were very small, the differences between the CP/CPPS patients and controls for these two species were statistically significant. Further research has to be done to show whether these organisms may actually cause or trigger CP/CPPS.

CP/CPPS May Affect Fertility

There are a number of ways to check a man’s fertility. Traditionally, those have included sperm counts, sperm motility (the proportion of sperm that swim), and normal appearance. More recently, fertility experts have used the acrosome reaction to assess sperm quality. That reaction, in which the head of the sperm ruptures and releases enzymes, is the one that allows the sperm to penetrate the egg. Infertility is known to have a negative effect on sperm quality and fertility, and inflammation is thought to have a negative effect. These German researchers looked at traditional measures of sperm quality and measurements of the acrosome reaction in normal men and men with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), who often have evidence of inflammation (category IIA, with white blood cells in the semen), and found that men with CP/CPPS appear to have significantly lower sperm quality, fewer acrosome reactions, and lower acrosome-reaction potential. The researchers compared these measurements between 95 control men and 56 men with CP/CPPS, including 24 with type IIA and 32 with type IIB. They found that men with both types of CP/CPPS had significantly lower sperm counts, lower proportions of normal sperm, and lower levels of acrosome reactions, and lower acrosome reaction potential.

The NIH and the Prostatitis Foundation would like to have more input from patients. We have discussed the possibilities of regional meetings at different locations throughout the country. These would be patient meetings in a less scientific setting. We would discuss patient concerns instead of research protocols and could allow a few minutes for everyone who wanted to share their history and what they have learned from it, such as what worked for them and what did not help. We might discuss the latest information on what causes prostatitis/CPPS, latest on treatment options, and latest on what might be cures? The idea might be to have a short overnight meeting where we would meet in the late afternoon for a dinner and an evening speaker. Then another speaker or two the next day and plenty of opportunity to ask questions in each setting. We would adjourn in plenty of time for people to reach their return flights the next afternoon.
We are considering a thorough update on where we stand in the identification and conquest of this disease.

Dr. Nyberg from the NIH and a Prostatitis Foundation representative would be present. We would hope to have one or two doctors with experience treating prostatitis/CPPS patients. Perhaps this time we can get a health care reporter to address the group about public awareness and education through the effective use of the news media.

We will have a forum for everyone to discuss:
How do you feel about being public with this disease? Do you discuss it with your family, friends?
How long have you had it?
What was your age at onset?
What do you think brought it on?
Your most severe symptoms?
What remedies have you tried?
What did not help? What did help?
How do you prevent and handle a flare up?
Did you think it was a cause of infertility?
Do you have advice for new patients?
Have you had any experience with overseas doctors?
Do you have convictions about how we could prevent prostatitis in the first place?

Would you prefer Atlanta or Chicago for the first meeting? It will probably be the spring or summer of 2006. Please notify Mcapstone@aol.com about what would interest you and if you would attend.

"Nocturia, or nocturnal urination, is sometimes a symptom of sleep apnea," as explained by Patrick J. Strollo, Jr, MD who is the Medical Director of the Pulmonary Sleep Evaluation Laboratory at the University of Pittsburg Medical School. He writes the, Ask The Doctor, column that you can see in the August—September 1996 issue of WAKE-UP Call on sleepapnea.org: go to resources—publications and down to Health Issues for the complete article.

Chronic, recurrent Urinary Tract Infections
The December 2005 issue of Urology Times in an article on page 26-7 by MacOvermyer quotes Scott Hultgren, Helen L. Stover Professor of Molecular Microbiology, at Washington University School of Medicine as saying, "According to his research, recurrent infections are probably more accurately described as resurgent infections because they evolve from quiescent reservoirs established not on the surface of bladder lumen, but in colonies within the umbrella cells of the bladder."

It is important for every patient, their friends and family members write, fax or e-mail their senators and congressmen about the need for prostatitis research. It is important that you keep reminding them how prostatitis has affected your health, work, marriage and family relationships. A handwritten letter is the most effective.

Supporters of our website are Farr Labs, LLC, the makers of ProstaQ for chronic prostatitis. For more information visit ProstaQ.com or call 1-877-284-3976

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Enclosed is my tax deductible gift to support The Prostatitis Foundation, 1063 30th Street, Smithshire, Illinois 61478.

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