American Urological Association (AUA)
Report and IC-Related Abstract Summaries 2007:

2007 AUA Meeting Brings New Treatments, Clues to Cause, Posts Education Record

This year's American Urological Association (AUA) meeting showed we're entering a new era for IC in medicine. The focus wasn't just on research, which is as active as ever and may bring the first new treatment in years for severe IC using a currently available drug. This year there more courses than ever before to help teach urologists how to treat IC and related conditions, and the AUA put IC and ICA Founder and President Vicki Ratner, MD, in the history book of medicine.

Researchers presented more than 40 studies relevant to IC, not only in a poster session devoted to IC, but also in sessions on female urology, prostatitis, basic research, and pharmaceutical development. Some of the researchers are well known to the IC community, but this meeting brought fresh faces as well.

Among the most hopeful were three studies of the immunosuppressant cyclosporine for patients with severe IC. Two of these studies also looked at urine markers that might show whether the treatment is working or who might benefit from it. All the studies included patients with severe IC who weren't helped by other treatments. Their symptom scores dropped from top-of-the-charts levels to tolerable and even better levels, with some patients saying they finally felt normal. This immunosuppressant carries risks, however, such as susceptibility to infection, liver dysfunction, and hypercholesterolemia. Although the Brazilian researchers did not see any significant side effects, that wasn't the case in another study from Finland, where some patients had severe side effects. That study showed that urine markers related to bladder lining growth and inflammation changed with treatment, an indication it was truly working. A Swedish study of cyclosporine treatment measured levels of nitric oxide (NO), well known as a marker of inflammation, in IC patients' bladders as the patients got lower and lower doses. Cyclosporine knocked NO levels down, and they didn't rise until patients got the very lowest dose or stopped the drug. Low doses, or making sure patients don't have conditions that could be exacerbated by cyclosporine, may be keys to success. We should hear more in the future from these researchers who are continuing their research as well as from the Interstitial Cystitis Collaborative Research Network, which is now studying another immunosuppressive drug, mycophenolate mofetil (CellCept), for IC.

These and another marker study may revive the theory that IC has an autoimmune or immune system foundation. Researchers at Harvard Medical School found that IC patients had greater autoantibody reactions to 37 antigens compared with controls, with 25 of them showing up very often and looking like candidates for biomarkers of IC.

Two studies of botulinum toxin A (Botox) injections into the bladder of IC patients and another in patients with radiation and chemical cystitis also looked hopeful, showing long-term relief. The good results in IC patients contrast with some previous studies, and it's not clear what might have made the difference.

Again, clinical researchers warned physicians to be thorough when they have patients who may have IC. University of Missouri by urologists found a few bladder, vulvar, and cervical cancers and also kidney stones in patients diagnosed with IC. Most of the cancer patients had been under the care of doctors who should have caught the cancers. The number of cancers was small, but this shows that sometimes doctors jump too quickly to the IC conclusion or just assume most symptoms in their IC patients are caused by IC. It's important for physicians to consider all the possibilities and examine patients thoroughly.

Epidemiologic studies are confirming some things we have known about IC, but the studies are also changing our thinking about who has it. One of these studies confirmed that, indeed, IC doesn't travel alone, and patients often have other problems such as irritable bowel syndrome and fibromyalgia. Another study showed that symptoms of IC—pain, urgency, and frequency, are more common in men than urologists have been aware of.

Physiologic, pharmacologic, and genetic research at AUA hints at some new approaches to treating IC and progress in uncovering IC's cause or causes. A prostaglandin-like compound may help, and that fits with previous research indicating that nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit the prostaglandins, may do IC bladders more harm than good. An entirely new class of drugs is also being looked at for its positive effects on bladder contractions and capacity. Certain components of green tea were found to protect bladder cells from inflammation. Melatonin may enlarge the bladder and ease nocturia. Calcium channel blockers, which include some anesthetics and heart rhythm drugs, may help treat bladder pain.

Proteomics, which studies the different proteins genes express, has shown that chronic prostatitis patients have protein signatures that might serve as markers, and one of them may break down one of the body's natural painkillers. A drug in development may counteract that and help IC patients, too.

Research on processes in IC at the cellular level continue. The basic science of antiproliferative factor (APF) took a big step forward with discoveries about its role in cell growth and division and its relationship with a known regulator of cell function. In addition, research is moving closer to showing how IC patients' bladder lining may be "leaky."

These studies and more are summarized here. You can read the original abstracts at http://www.abstracts2view.com/aua and view posters at http://www.posters2view.com/aua07

TREATMENTS

Cyclosporine Yields Dramatic Results in Severe IC

Evaluation of Symptoms in Patients with Interstitial Cystitis treated with Cyclosporine A
Jamil Chade, Antonio M Lucon, Daher C Chade, Miguel Srougi, São Paulo, Brazil

This Brazilian team used the immunosuppressant cyclosporine to treat severe IC in 36 patients (34 women and 2 men) who had IC by the NIDDK research definition, had maximum scores (36) on the O'Leary-Sant Symptoms and Problem Indexes, and had had all other previous treatments fail. Patients received 1.5 mg/kg of cyclosporine twice a day for 12 months. They answered the O'Leary-Sant questionnaire and had their bladder capacity measured before treatment and at 6 and 12 months of treatment. The mean score dropped to 21.6 at 6 months and to 15.2 at 12 months, a dramatic result. Bladder capacity increased by an average of 92.9 mL at 6 months and 107.4 mL by 12 months. The patients didn't show any abnormalities in their liver and kidney function. (No patient with high blood pressure or kidney problems to start with was accepted for the study.) Cyclosporine is a new alternative for IC treatment with promising results and good tolerance and safety, said Dr. Chade.

Cyclosporine Works Well for Severe IC, Prompts Measurable Changes

Urinary IL-6 and EGF levels in patients with PBS/IC treated with cyclosporine or pentosan polysulfate sodium.
Jukka Sairanen, Kristina Hotakainen, Helsinki, Finland; Teuvo LJ Tammela, Tampere, Finland; Ulf-Håkan Stenman, Mirja Ruutu, Helsinki, Finland

This study compared the effects of low doses of cyclosporine with those of pentosan polysulfate (Elmiron) in IC patients with severe disease. Cyclosporine is known to affect inflammatory cells in autoimmune diseases. (The "control" patients received Elmiron because it would not have been appropriate to give them just a placebo.) The researchers also measured levels of two urine markers known to be high in IC patients, interleukin 6 (IL-6) and epidermal growth factor (EGF). IL-6 is a cytokine related to inflammation, and EGF is related to growth of the bladder lining. Of the 37 IC patients, 15 got the immunosuppressant (1.5 mg/kg twice a day), and 16 (14 women and 2 men) got Elmiron (100 mg three times a day). The markers were measured in urine at the start of the study and in the last week of the six months of treatment. Patients were counted as responders if they said they were "much better" or "cured." By that measure, 72 percent of the cyclosporine patients (13 out of 18) responded to treatment versus 6 percent (1 out of 16) of the Elmiron patients. In the groups as a whole, IL-6 didn't change, but EGF levels went down significantly with cyclosporine treatment. When the researchers divided patients by age, they found that older patients (55 to 75 years old) started out with high IL-6 levels, unlike the younger patients (22 to 52 years old). For the older patients, this inflammatory marker did drop significantly. This drug carries a risk of some strong side effects, and patients need to continue to take it, so Dr. Sairanen uses it only for patients with severe disease and generally only for patients over 40 years old.

Nitric Oxide May Tell Who Is Responding—and Who Can Respond—to Cyclosporine

Nitric oxide as a marker for evaluation of treatment efficacy of ciclosporin in patients with classic interstitial cystitis
Ingrid Ehrén, Margit Vrba, Pierre Lafolie, Stockholm, Sweden

Nitric oxide (NO) in urine is known to be a marker of inflammatory disorders in the bladder, and this team also found it to be a good marker for IC with Hunner's lesions. Now, they have measured NO levels with cyclosporine treatment. The six IC patients in the study started out getting the same dose as in the other two cyclosporine studies reported here—3 mg/kg for 12 weeks. But after that, the dose was stepped down every two weeks, first to 1.5 mg/kg, then to 0.75 mg/kg, and then to 0. With treatment, NO levels went down to nearly nothing and rose only moderately at the lowest cyclosporine dose. Then, when the drug was stopped, the NO levels shot up. The scores on the O'Leary-Sant Symptom and Problem Indexes followed suit, starting out at a very high average total of 30 (the highest is 36) and dropping to an average of 18 at 12 weeks, generally staying at that level until the very lowest dose and rising fast to an average of 25 when the drug was stopped. Dr. Ehrén said that other IC patients with similar symptoms don't show these high NO levels, so inflammation may not be the source of their symptoms, and they should be treated with something else.

Botox Gives Long-Term Relief

Treatment of Interstitial Cystitis with botulinum toxin A
Stefan Carl, Sebastian Laschke, Emmendingen, Germany

This team used botulinum toxin A (Botox) injections into the bladder wall to treat 29 patients with IC that met the NIDDK research criteria and who didn't get relief from standard treatments. The urologists injected Botox at 26 sites in the bladder wall, including the trigone (the area at the bottom), through a rigid cystoscope while the patients were under anesthesia or sedated. The researchers then assessed how patients were doing at the start and six weeks, three months, and six months later. At the six-week mark, 83 percent of the patients had improved, with their daytime frequency down 50 percent, their nocturia 75 percent, their urgency 43 percent, and their pain 81 percent. Their maximum bladder capacity increased from an average of 260 mL to 389 mL, and their bladder compliance (a measure of how well the bladder can stretch) from 13 mL/cm H_2O to 23 mL/cm H_2O. Those results lasted through the three-month mark. By six months, seven patients (24 percent) had pain recur and got reinjections. Two patients had temporary hematuria (blood in the urine), three patients had residual urine (that is, urine that doesn't come out with a void) of 100 mL, and one patient (a man) had urinary retention and had to learn intermittent self-catheterization. Why the results were so good in this study compared with some other studies in the past isn't clear, although technique may have had something to do with it.

Botox Cuts Pain for Some—Nerve Growth Factor Shows Who

Intravesical Botulinum Toxin A Injections Reduced Nerve Growth Factor Production and Bladder Pain in Chronic Interstitial Cystitis
Hann-Chorng Kuo, Hsin-Tzu Liu, Hualien, Taiwan

These researchers gave 19 patients with severe IC Botox injections of 100 or 200 units into the bladder wall and measured levels of nerve growth factor (NGF). After two weeks, the patients also underwent cystoscopy and hydrodistention under anesthesia. All had biopsies of bladder tissue before Botox injection and after hydrodistention. Three months later, 14 patients had symptom improvements, whereas 5 had no change. The overall satisfactory rate was 74 percent. Maximum and functional bladder capacity increased significantly. In the IC patients NGF levels were much higher at the start of the study than the levels in 12 control patients who had other types of lower urinary tract symptoms. Two weeks after Botox injection, NGF levels dropped 29 percent, a significant reduction. Pain scores dropped more than two points for 11 patients but less than two points in 8 patients. The patients who had the greater pain reductions were the only ones who also had significant drops in their NGF levels, which came down to normal. The NGF changes correlated with bladder pain reduction but not the increase in capacity.

Botox Helps Patients with Radiation and BCG Cystitis

Bladder botulinum toxin A injection can benefit patients with radiation and chemical cystitis
Yao-Chi Chuang, Yao-Chi Chuang, Kaohsiung Hsien, Taiwan; Dae Kyung Kim, Pittsburgh, PA; Po-Hui Chiang, Kaohsiung Hsien, Taiwan; Michael B Chancellor, Pittsburgh, PA

Another study of Botox showed benefits in patients with bladder pain and damage. These eight patients had cystitis induced by radiation therapy for prostate or cervical cancer or by Bacille Calmette-Guérin therapy for bladder cancer and didn't get relief from anticholinergic (overactive bladder) drugs. Under sedation or local anesthesia, patients got Botox injections at 20 places in the bladder trigone (the area at the bottom) and floor. Of the six patients with radiation cystitis, two had significant improvement, three had moderate improvement, and one had no improvement. Bladder capacity increased by 145 mL and their frequency decreased from 14 to 11. The amount of urine remaining in the bladder after voiding (residual urine) remained the same. Both patients with BCG cystitis had significant improvement, their bladder capacity went up 120 mL, their pain went from an 8 to a 2, their frequency went down from 16 to 12, and they had no residual urine after treatment. The authors urged researchers to do larger clinical trials.

Anesthetic Bladder Cocktail Eases Pain with Intercourse

Effect of therapeutic solution on dyspareunia and voiding symptoms in interstitial cystitis
Blayne K Welk, Joel M Teichman, Vancouver, BC, Canada

Up to 78 percent of IC/painful bladder syndrome (PBS) patients have pain with intercourse, called dyspareunia. These researchers looked at whether instillations of an anesthetic bladder cocktail (lidocaine, heparin, and bicarbonate), which is known to help bladder pain, could ease this pain as well. They treated 21 patients with the instillations three times a week for three weeks. The patients answered questionnaires on their symptoms overall, their IC symptoms, and sexual function and reported voided volumes and nocturia before treatment and three weeks later. The doctors also assessed how tender the patients were during a vaginal examination. Scores on the overall symptom questionnaire improved an average of 54 percent (but with a wide range), and 12 patients (57 percent) reported no dyspareunia after instillations. Improvements in tenderness were significant, dropping from an overall 73 percent to 27 percent. Pain scores went from an average of 4.4 to 2.7. In addition, although 10 patients (83 percent) said they had pain with intercourse before treatment, only 2 (22 percent) said they did after treatment. The patients that get the best help for intercourse pain from the bladder instillations were those who had point tenderness on the front wall of the vagina.

New Drug Class Shows Potential for Relaxing Bladder, Increasing Capacity

Therapeutic effects of type 4 phosphodiesterase inhibitor on detrusor overactivity in rats with bladder outlet obstruction

Yasuhiro Kaiho, Sendai, Japan; Jun Nishiguchi, Michael B Chancellor, Pittsburgh, PA; Yoichi Arai, Sendai, Japan; Peter B Snyder, Bothell, WA; Naoki Yoshimura, Pittsburgh, PA

A new class of drugs, inhibitors of phosphodiesterase 4, may help control inflammation and other immune system dysfunctions. These inhibitors have shown potential for inflammatory and airway disease and are also being looked at in nervous system and urinary tract disease. By inhibiting an enzyme, they elevate levels of cAMP in cells and relax smooth muscle. One of these drugs, IC485 (ICOS) is beginning to be investigated for its effect on the bladder. It decreased bladder contractions that had nothing to do with urination and also increased bladder capacity without affecting voiding function. Although the research was done on experimental bladder outlet obstruction and overactive bladder, these effects might also be helpful in IC.

Hydrodistention, Sodium Hyaluronate Work Together, Even After Failing Alone

Hydrodistension and intravesical instillation of sodium hyaluronate under general anaesthesia for treatment refractory interstitial cystitis
Imran Ahmad, Glasgow, United Kingdom; Nalagatla Sarath Krishna, Robert N Meddings, Ayr, United Kingdom

Hydrodistention together with sodium hyaluronate (eg, Cystistat) instillation seems to provide relief for patients with severe IC, even when either treatment alone has not. These clinicians recruited 23 IC patients (4 men, 29 women) who had had no success with previous therapy, which included antibiotics, anticholinergics (overactive bladder drugs), painkillers, and neuromodulating drugs. Fourteen of the patients had had hydrodistention with only minimal relief. Eighteen had undergone instillation under local anesthesia of sodium hyaluronate, which is thought to be a GAG layer replacer. But even with an average of 9 treatments (and as many as 33), three patients felt no effect, three couldn't tolerate the treatment, and 12 had a only short-lived relief. In this study, the 23 patients underwent cystoscopy, hydrodistention, and sodium hyaluronate instillation under general anesthesia monthly at first and then later depending on how long the relief lasted. Patients underwent an average of six treatments with an average 1.8-month interval in between, but some went as long as 12 months between treatments. Seventeen patients (74 percent) had symptoms improve immediately. Of the 18 patients who had had sodium hyaluronate alone before, 11 of those who had temporary relief, 1 who had no relief, and all those who couldn't withstand the treatment before had improvements. In all the patients who improved, ulcerations healed and inflammation resolved. Bladder capacity increased by an average of 223 mL. Hydrodistention and then instillation of sodium hyaluronate under general anaesthesia should be considered for resistant cases of IC, especially for patients who cannot tolerate sodium hyaluronate instillation under local anaesthesia, said these urologists.

Melatonin Might Make Bladder Bigger

Melatonin enlarges the bladder by the GABAA receptor in the brain, suggesting its efficaciousness against nocturia
Yosuke Matsuta, Aniwar Yusup, Masaharu Nakai, Kazuya Tanase, Yoshitaka Aoki, Nobuyuki Oyama, Yoshiji Miwa, Hironobu Akino, Osamu Yokoyama, Fukui, Japan

Sleep disturbance itself may contribute to nocturia, in addition to low bladder capacity, and pain. Because melatonin helps with sleep disturbance, these researchers speculated it might also influence urine production at night, so they looked at how melatonin and a derivative of it called TAK-375 might influence urine production. They gave melatonin and TAK-375 to rats who had a condition that causes sleep disturbance and measured urine production and levels of various hormones before and after the rats got the drugs. Melatonin significantly increased the bladder capacity of control animals by 63 percent. The effect could be inhibited by a blocker of $GABA_A$, a nervous system transmitter. TAK-375 did not increase the bladder capacity of rats that did not have the condition, but it had a huge effect on the rats that did have the condition, increasing their bladder capacity 98 percent. Melatonin also significantly decreased urine production, whereas TAK-375 did not. The pressure of bladder contractions did not change. Melatonin also reduced levels of the hormone vasopressin, which reduces urine production. These results imply that melatonin increases bladder capacity through $GABBA_A$ receptors in the brain and reduces urine production, but not by influencing the hormone vasopressin. That TAK-375 increased bladder capacity in the rats with sleep disturbance suggests some other underlying mechanism to enlarge the bladder in animals with the sleep disturbance, said the investigators.

Sodium Channel Blockers Show Potential for Bladder Pain

Effect of sodium channel blocker mexiletine on visceral nociception to urinary bladder distention
Xin Su, Erin S. Riedel, Lisa A. Leon, Nicholas J. Laping, GlaxoSmithKline Pharmaceuticals, King Of Prussia, PA

Could sodium channel blockers help ease the nerve hyperexcitability of lower urinary tract disorders such as IC? These researchers think so based on this proof-of-principle study. Sodium channel blockers include anesthetics such as lidocaine and ketamine and heart rhythm drugs such as mexiletine, which is also used for neuropathic pain. The researchers looked at the effect of mexiletine on the muscle reflexes and nerve responses to bladder irritation in rats under anesthesia. Mexiletine reduced the muscle responses to bladder irritation in a dose-dependent way (higher responses with higher doses). The drug also calmed the response of pelvic nerves to irritation. These results suggest that this type of drug could reduce bladder pain. The drug does have central

nervous system side effects, so it would be valuable to be able to restrict the drug to the bladder area or to find a drug of this type that would specifically target the bladder.

Green Tea Components May Protect Bladder from Inflammation

Green tea protects bladder cells from hydrogen peroxide-induced inflammation: potential of herbal agents to treat inflammatory bladder diseases
Shelby N Morrisroe, Christian H Coyle, Brian J Philips, William C de Groat, Naoki Yoshimura, Michael B Chancellor, Pittsburgh, PA

Previous studies have shown that green tea has potential antioxidant and anti-inflammatory effects, although not many studies have looked at the effects on the bladder. This team looked at the effect of a green tea extract that had two major catechins (a type of flavanoid) known as ECG and EGCG. ECGC did a good job of protecting bladder cells from damage and death caused by hydrogen peroxide. ECG also helped keep cells from dying off. Catechin compounds might be a way to treat bladder conditions such as IC, the researchers speculated. At the meeting, the presenter noted that whole green tea did not have this effect.

NSAID Opposite May Ease IC

The cyclopentenone prostaglandin, 15-deoxy-Δ12,14-PGJ2, attenuates the development of cyclophosphamide induced cystitis
Hitoshi Masuda, Kazunori Kihara, Bunkyo-ku, Tokyo, Japan; Michael B Chancellor, Naoki Yoshimura, Pittsburgh, PA

Some researchers think the painkillers known as nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, ibuprofen, and their relatives may have a negative effect on IC patients' bladder lining, so they recommend other types of painkillers. NSAIDs work by inhibiting production of biochemicals called prostaglandins. Now, it looks like a type of prostaglandin itself could help thwart cystitis. In this study, researchers tried a product of prostaglandin D2, known as 15d-PGJ2, to both prevent and calm irritation, in rat bladders irritated by cyclophosphamide (an anticancer drug). The investigators also tried a selective inducible nitric oxide synthase (iNOS) inhibitor, which cuts the production of nitric oxide, an indicator of inflammation. Both compounds helped thwart the decrease in bladder capacity cyclophosphamide can cause and they also reduced other biochemical evidence of inflammation. The researchers concluded that 15d-PGJ2 could help thwart development of cystitis by suppressing production of inflammatory cytokines and induction of iNOS.

New Nerve Stimulation Approach Shows Potential

Dorsal genital nerve stimulation for the treatment of refractory overactive bladder symptoms
Howard B Goldman, Jeffrey M Mangel, Cleveland, OH; Cindy L Amundsen, Durham, NC

Although this study was done on patients with overactive bladder and urge incontinence, it shows that nerve stimulation therapy for urinary problems is evolving and could produce new approaches for IC patients. In this study, urologists placed electrodes through the skin to stimulate the dorsal genital nerve, which is part of the pudendal nerve. The electrodes were connected to a pulse generator for a seven-day testing period and a three-day post-treatment period. Nearly half the patients had a 50 percent or better reduction in leaks, and 81 percent of patients who had severe urgency had a 50 percent or better improvement. Eight patients were completely dry.

Experience Outlines Expectations with Sacral Neuromodulation

Sacral neuromodulation: long term experience
Blake W Palmer, Gennady A Slobodov, Andrew D Schultz, Daniel J Culkin, Oklahoma City, OK

At this clinic, urologists have been implanting the InterStim sacral nerve modulator for some time for difficult cases of urge/frequency/pain syndrome, urge incontinence, and nonobstructive retention, so their experience can help urologists and patients know what to expect over the long term. Seventy-two of their patients, ranging from 28 to 77 years old (average 50) got the stimulator. Seventeen patients didn't go past the testing phase on to the permanent implant. Thirty-four patients either had the devices removed before 24 months had passed or had not yet had the device for 24 months. The 21 patients who did use the stimulators for 24 months or more included 13 (62 percent) who had refractory urge/frequency/pain syndrome, 4 (19 percent) who had urge incontinence, and 4 (19 percent) who had nonobstructive retention. Patients required an average of 2.3 reprograms per year, with six (29 percent) patients requiring more than three reprograms per year. Thirteen (62 percent) required a total of 25 reoperations, with a mean of 1.9 (1 to 5) per patient. Five (24 percent) units were removed on average at 42.2 (31 to 58) months, and batteries were changed after an average of 55.7 (46 to 70) months.

What to Do When Neuromodulator Leads Wander

Management strategies for the migration of percutaneous tined leads for sacral neuromodulation
Kristy M Borawski, George D Webster, Cindy L Amundsen, Durham, NC

The newer tined leads used in sacral neuromodulation were expected to reduce the problem of leads moving around after implantation, but it does happen. At this medical center, 49 patients had tined leads and a permanent implant. Seven of those patients had a total of 10 lead migrations. Leads stayed in place for an average of 250 days, but some shifted

immediately and some as late as 857 days. Two of the patients had three lead migrations within the first week. One lead was fixed with sutures. In the other patient, suturing didn't work. Six patients had delayed migrations at an average of 427 days. Causes of migration included falls in two patients and direct trauma in one. The cause was unknown in four. What alerted patients to lead migration was pain (in two patients) and loss of sensation in the vaginal area (in two patients). Insertion of another tined lead was a successful solution in all but one patient. The remaining patient had three lead migrations, and all the attempted fixes failed. When leads migrate early, they just don't have the support to adhere to, but suturing can solve the problem. Delayed lead migration may be caused by tension on a short lead, so sudden, jerky movements, such as a fall, displace the lead. The best solution for these is to insert another tined lead. Longer leads might prevent these, speculated the researchers.

Epinephrine Instillation Helps Stop Hemorrhaging

Intravesical instillation of epinephrine in patients with intractable hemorrhagic cystitis due to radiation cystitis
Yung C Chow, Jong M Hsu, Wen C Lin, Huang K Chang, Yuh C Yang, Hung J Shih, Stone Yang, Taipei, Taiwan

Although this study included patients with radiation-induced cystitis, treatments for this kind of cystitis have sometimes been helpful for patients with IC. Twenty patients who didn't respond to any other treatment and who were bleeding received a bladder instillation of epinephrine (also called adrenalin) and were closely monitored by an anesthesiologist. This treatment stopped their bleeding. While not a definite treatment for severe cystitis, this may be valuable for patients who are hemorrhaging.

DMSO Cuts Inflammation in Irritated Tissue, Promotes it in Healthy Tissue

DMSO effect on bladder inflammation and urinary glycosaminoglycans excretion after protamine sulfate induced cystitis
Roberto Soler, Homero Bruschini, Jose Carlos Truzzi, Niels Camara, Joao Roberto Martins, Juliana Dreyfuss, Maria Teresa Seixas, Helena Nader, Miguel Srougi, Valdemar Ortiz, São Paulo, Brazil

This study looked at the effects of DMSO on normal and irritated bladder tissue. DMSO reduced inflammation in irritated tissue but provoked inflammation in normal tissue, which might explain the initial symptom flare after treatment. Levels of hyaluronic acid seemed to correlate with infiltration of inflammatory white blood cells. DMSO influenced excretion of hyaluronic acid (associated with the glycosaminoglycan or GAG layer) only on the first day, when the infiltration of inflammatory white cells in irritated tissue was reduced. Healthy bladders had higher levels of hyaluronic acid and more infiltration of the inflammatory white cells. DMSO did not influence the excretion of a type of GAG called S-GAG.

Prostate Drug Helps with Frequency, Straining in Women

Terazosin therapy in the treatment of women with lower urinary tract symptoms: a randomized, placebo controlled trial
Bee Yean Low, Minden, Malaysia; Men Long Liong, Pulau Pinang, Malaysia; Kah Hay Yuen, Minden, Malaysia; Christopher Chee, Wing Seng Leong, Pulau Pinang, Malaysia; Wooi Loong Chong, Sungai Petani, Malaysia; Nurzalina Karim, Minden, Malaysia; Phaik Yeong Cheah, Oxford, United Kingdom

Terazosin (Hytrin) is an alpha blocker often given to men with lower urinary tract symptoms associated with prostate enlargement. These researchers tested the drug against a placebo in 80 women age 19 to 70 years old who had urinary symptom scores of 8 or above for at least a month on the International Prostate Symptom Score (IPSS) and no other medical conditions that could mimic the symptoms. Patients who took the drug started at 1 mg/day and increased the dose to 2 mg twice a day during 14 weeks of treatment. The women kept a voiding chart and had peak urine flow and urine remaining in the bladder after voiding measured and filled out quality-of-life and symptom questionnaires. Thirty-seven of 40 women (93 percent) scored less than 4 on the quality of life index, compared with 28 of 40 women (70%) taking the placebo. In the women taking the drug, 34 (85 percent) had a score less than 8 at the end of 14 weeks of treatment compared with 22 (55 percent) taking placebo. Most of the reduction of symptoms was in the frequency and straining scores. There were no differences in frequency and volume, peak flow rate, and postvoid residual urine. The placebo group actually reported more adverse reactions (58 percent) than the drug group (40 percent).

EPIDEMIOLOGY, SOCIOLOGY, AND ECONOMICS

Cancers, Stones Get Overlooked in Some IC Patients

Malignancy in an Interstitial Cystitis Referral Population
Durwood E Neal, Jr, Columbia, MO

Among 261 IC patients referred to this practice from 2001 to 2006, 6 patients (2 percent) had cancers, and 13 (5 percent) had undiagnosed kidney stones. One patient had cervical cancer, one had vulvar cancer, one had kidney cancer, and three had bladder cancers—one of them metastatic. The two patients with gynecologic cancers had been under the care of a gynecologic oncologists, and the three patients with bladder cancer had had a cystoscopy done by a urologist within the preceding year. Not all of these were just misdiagnoses of IC. Nevertheless, physicians should be careful about making the IC diagnosis and be sure to be thorough. "We should not be lulled into labeling patients who have been given this diagnosis

without a complete evaluation," said these referral clinicians. Physicians also need to be careful about just assuming symptoms in IC patients are always because of their IC.

Study Confirms IC Doesn't Travel Alone

A case-control study of medical co-morbidities in women with interstitial cystitis

J. Quentin Clemens, Chicago, IL; Richard T Meenan, Maureen C O'Keeffe Rosetti, Teresa M Kimes, Portland, OR; Elizabeth A Calhoun, Chicago, IL

What other conditions do IC patients have that are actually in their medical records? These researchers combed through the records of a health maintenance organization, Kaiser Permanente Northwest in Portland, Oregon, to find out. Women who had a diagnosis of IC in their records were matched with three control patients similar in age and time in the health plan to see what other diagnoses other were more typical of IC patients. Twenty-three other conditions came up as much more common in IC patients. Interestingly, after the top two, which were other problems with the bladder and urinary tract, was drug dependence. That doesn't mean street drugs, Dr. Clemens told the *ICA Update*. Rather, it indicates that many IC patients have severe enough pain to require opioid painkillers, which results in dependence but not often addiction. Gastritis and duodenitis, then endometriosis, followed. The diagnoses involved many different organ systems in the body, which hints that IC is part of a whole-body disease rather than being just a disease of the bladder. Many of the associated conditions, such as fibromyalgia, irritable bowel syndrome, back pain, and gastritis, indicate the presence of other unexplained physical symptoms. Although IC patients had a significantly higher rate of a history of child abuse, the vast majority of IC patients (96%) did not have that in their records.

Pain May Be Ignored in Both Men and Women with Urinary Symptoms

Overlap of lower urinary tract symptoms and pain in men and women

J. Quentin Clemens, Talar W. Markossian, Chicago, IL; Richard T. Meenan, Maureen C. O'Keeffe Rosetti, Portland, OR; Elizabeth A. Calhoun, Chicago, IL

No matter what you call the problem, men and women have similar lower urinary tract symptoms and pain associated with them, revealed this survey of 1,550 men and 1,954 women in an HMO. That means labeling people with diagnoses such as "lower urinary tract symptoms" or "overactive bladder" may be ignoring the pain, said the researchers. This might also imply that a higher proportion men may have IC or PBS than previously recognized. Of those who answered the survey 701 men (mean age 57) and 745 women (mean age 52) reported having symptoms, including urgency, frequency, nocturia, sense of incomplete emptying, intermittency, slow stream, straining to void, or pelvic pain. The researchers divided the symptoms in to storage symptoms (when the bladder fills or holds urine), voiding, and pain symptoms. There was great overlap in the symptom categories with little difference between men and women. In men and women who had moderate to severe symptoms, 57 percent of men and 63 percent of women said they had pain. In those who had pain, 90 percent of the men and 94 percent of the women also had voiding or storage symptoms, although more women (33.5 percent) were bothered by their symptoms, compared with 19.1 percent of men. The only statistically significant difference between men and women in terms of symptoms was that 27.1 percent of women had the combination of storage and pain (which might fit the picture of IC or PBS) compared with 18.8 percent of men.

Costs Are Similar—and high—for IC/PBS and CP/CPPS

Comparison of the economic impact of chronic prostatitis/ chronic pelvic pain syndrome and interstitial cystitis/ painful bladder syndrome

J. Quentin Clemens, Sheila O Brown, Elizabeth A Calhoun, Chicago, IL

The cost of IC/PBS and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) are similar and higher than the cost of many other chronic illnesses. These investigators estimated the direct and indirect costs based on records of 62 of their male patients with CP/CPPS and 43 female patients with IC/PBS. They used both Medicare and standard non-Medicare prices and standard prescription prices to estimate the total costs. For IC/PBS, the yearly medical costs were $3,632 at Medicare rates and $7,044 at non-Medicare rates. The indirect costs, based on the patients' income and lost work, were $4,216 a year. For CP/CPPS, the annual medical costs were $3,017 at Medicare rates and $6,534 at non-Medicare rates. Their indirect costs were $3,248 a year. These costs are much higher than the yearly costs reported for other chronic conditions, such as peripheral neuropathy ($917), low back pain ($2,144), fibromyalgia ($2,274), and rheumatoid arthritis ($2,533).

IC Patients Show Reactions Similar to PTSD Patients

Evidence for central hyperexitability in patients with interstitial cystitis

Christian Twiss, Lisa Kilpatrick, Veronica Triaca, Valerie Arboleda, Michelle Craske, Hana Ibrahimovic, Shlomo Raz, Emeran A. Mayer, Edward Ornitz, Larissa V. Rodriguez, Bruce D. Naliboff, Los Angeles, CA

Blinking when you are startled is a defensive, involuntary movement that is a response to sudden, intense stimuli and is used to indicate whether people are having an emotional response to a situation. This reflex is modulated in a part of the brain that modulates emotional states and physical sensations. Increases in this reaction are taken to be a measure of the

emotional response to a stimulus, such as the threat of pain. These investigators measured the reflex in 6 women with IC and 19 healthy women when the bladder was stimulated with an unpleasant sensation (from a TENS unit) and during safe situations when there was no possibility of unpleasant stimulation. Both groups of patients had an increase in this reflex when they were uncomfortable, but the IC patients had an increase in this reflex even when they were totally safe from pain, similar to people with post-traumatic stress disorder or anxiety disorder. IC patients may have increased responses of the limbic system in the brain involved in anxiety and stress that may change their perception and processing of pain, said the researchers. They added that more research is needed to determine if this is a cause of the IC disease process or a secondary effect.

Women Urology Patients Highest Users of Herbal Remedies

The prevalence of herbal remedy use in the urological outpatient clinic.
Mischel G Neill, Gina A Lockwood, Toronto, ON, Canada; Michael Holmes, Hamilton, New Zealand

One-third of urology patients surveyed in outpatient clinics in Canada and New Zealand reported using herbal remedies. Users tended to be middle-aged women. Ethnicity, domicile, and education level were no different among uses and nonusers. The average cost was $5.43 (US dollars) a week. Herb users didn't report problems with them, and 23 percent said they would have under-reported their use of herbs. The patients tended not to have a good understanding of the potential problems related to use of herbals, said the researchers.

MARKERS AND SIGNS

IC Markers Don't Change over Long Term with Neuromodulation

Changes in symptoms and urinary HB-EGF, EGF, and Antiproliferative Factor during chronic neuromodulation for refractory interstitial cystitis
Kenneth M Peters, Richard C Bennett, Ibrahim Ibrahim, Royal Oak, MI; Kristopher Koch, Chen-Ou Zhang, Susan Keay, Baltimore, MD

Previous studies showed that after five days of sacral neuromodulation, levels of the urinary markers APF and HB-EGF changed and frequency and urgency improved in patients with severe IC. This team measured the symptoms and the markers in 11 similar patients at two weeks and at one, three, and six months of neuromodulation . Ten of the 11 patients had at least a 50 percent reduction in symptoms during the test phase and got the permanent implant., and 10 of 11 showed APF activity at the beginning but also throughout the study. After two weeks, levels of the marker EGF increased, but there were no significant changes in APF or HB-EGF levels. The researchers concluded that urinary markers for IC do not generally change long-term with neuromodulation. More research is needed to clarify what effects neuromodulation has on these markers.

Autoantibodies Could Be IC Markers, Hint at Autoimmune Process

Identification of autoantibodies as biomarkers of interstitial cystitis using the "reverse capture" autoantibody microarray
Robert J Caiazzo, Jr, Oliver W Tassinari, Joshua R Ehrlich, Daniel W Cramer, Michael P O'Leary, Brian C.-S. Liu, Boston, MA

Using a novel "reverse capture" autoantibody microarray platform that these researchers developed, they searched the serum of IC patients and compared the autoantibody profile with that of healthy people to see if IC patients had a profile that distinguished them from people who don't have IC. The investigators compared immune system globulins from 6 IC patients and 20 controls and found 37 autoantigens (that is, antigens to one's own tissues) that were different in IC patients and narrowed that down to 25 that stood out the most. The autoantigens are responsible for a variety of functions in cells that fall into the categories of protein kinases, cancer growth factors, cell cycle regulators, neurobiology, mediators of programmed cell death, and other functions. One of the autoantigens was IL-6, discussed in the Finnish cyclosporine and other IC studies. Further refinements could not only develop a test for IC but could also point to new avenues for research, since many of these cellular functions have not been associated with IC before.

Marker Promising for Nonulcerative IC

Uroplakin III-delta4 messenger RNA as a promising marker to identify nonulcerative interstitial cystitis
Yu Zeng, Yoshiyuki Kakehi, Xiu Xian Wu, Kagawa, Japan; Yukio Homma, Tokyo, Japan; Naoki Yoshimura, Pittsburgh, PA; Hideaki Iwaki, Susumu Kageyama, Tatsuhiro Yoshiki, Otsu, Japan

Uroplakins are the major barrier proteins on the top surface cells of the bladder lining. These investigators looked at how these proteins are expressed in IC patients and measured the levels of mRNA, the genetic messenger that helps build the protein, in 29 IC patients (13 with ulcers and 16 without) and in healthy controls. The levels of mRNA related to a particular uroplakin protein called UP III-delta4 were much higher in IC patients than controls, and the levels of mRNA for the uroplakin UP III and UP III-delta4 were higher in IC patients who did not have ulcerative changes than in IC patients who did. The difference was most pronounced with UPIII-delta4. Although the clinical implications of these findings aren't clear,

it looks like the mRNA for UP III-delta4 is a promising marker for identifying nonulcerative IC.

Glomerulations Don't Affect BPH Treatment Outcome

Is glomerulation observed during TURP for LUTS/BPH a predictor of clinical outcome?
Ryoji Furuya, Seiji Furuya, Kitami, Japan; Naoya Masumori, Toshiro Oda, Sapporo, Japan; Hiroshi Ogura, Kitami, Japan; Satoshi Takahashi, Sapporo, Japan

Glomerulations—pinpoint bleeding—are often seen in the bladder wall of IC patients, and sometimes they appear in men with symptoms typical of prostate enlargement (benign prostatic hyperplasia or BPH). These urologists did the typical surgery on 197 men along with hydrodistention, measured their bladder capacity, and looked for glomerulations. Forty of the men (20 percent) had them. The urologists also had the men complete prostate symptom and O'Leary-Sant and quality-of-life questionnaires and measured the men's urine flow rates, total voided urine volume, and amount of urine remaining in the bladder after voiding. There was no difference in bladder capacity and in other measurements before and at 3 and 12 months after the surgery between the men who had glomerulations and those who didn't. The only differences were that the men with glomerulations were younger and had somewhat smaller prostates and higher scores on the O'Leary-Sant Problem Index. In general, whether the men had glomerulations or not, they had the same amount of improvement from the procedures.

Older Men with Glomerulations Have More Pain, Less Bladder Capacity

Painful symptoms and decreased bladder capacity are significant predictors of cystoscopic glomerulation suggestive of interstitial cystitis in elderly male patients with lower urinary tract symptoms
Munekado Kojima, Yasufumi Yada, Yosimasa Hayase, Nagoya, Japan

Unlike the study from Sapporo, Japan, this study found some significant differences between those who do and don't have glomerulations among older men with lower urinary tract symptoms. In this study, 110 men who came to this urology clinic complaining of symptoms underwent cystoscopy and hydrodistention under anesthesia. Twelve of the patients (11 percent) had glomerulations. The men completed Chronic Prostatitis Symptom Index and IPSS questionnaires. There was no difference in age, prostate volume, PSA levels, or IPSS scores between patients with and without glomerulation. But there was a significant difference between them in their pain scores on the CPSI. The men with glomerulations had an average pain score of 5 versus 1.7 for those who didn't have glomerulations. In addition, the frequency of glomerulation increased as the painful scores did, from 6 percent (5 out of 90) in patients with pain scores of 0 to 4 to 35 percent (7 out of 20) in those with pain scores of 5 or more. Moreover, pain and lower bladder capacity—two hallmarks of IC—were independent predictors of having glomerulations.

BASIC RESEARCH

Research Reveals How APF Works

P53 as a downstream mediator of signaling by antiproliferative factor (APF)
Jayoung Kim, Boston, MA; Susan K Keay, Baltimore, MD; Jordan D Dimitrakov, Michael R Freeman, Boston, MA

The basic science of APF and its role in IC took a big step forward with this study that showed where APF fits in the process of cell growth and division. APF is known to decrease proliferation of bladder lining cells—both normal and cancerous ones. Now, researchers have discovered that APF increases the levels of a well-known protein, p53, that is a key regulator of normal cell function. The investigators artificially reduced production of p53 and found that diminished the effects of APF. On the other hand, forcing production of p53 mimicked the effects of APF. That indicates, said the investigators, that p53 is likely a mediator of the biological effects of APF. APF seems to regulate a control point in the growth and division of cells. The results imply that p53 may be involved in a cellular signaling pathway that might result in defects in IC patients' bladder lining.

APF, ATP Signaling Now Linked

Anti-proliferative factor's (APF) effect on purinergic signaling in normal human bladder urothelial cells
Yan Sun, Susan Keay, Toby Chai, Baltimore, MD

Cells from the bladder lining of IC patients are known to produce APF. They also release adenosine triphosphate (ATP) when they're stimulated by that same biochemical and increase their number of ATP-type receptors, a process thought to be involved in nerve-like transmission of pain signals in the bladder. Now, researchers have found a link between these two biochemicals and their actions. APF changes the way IC bladder lining cells send signals through this ATP mechanism. The researchers also found that this activity can be blocked by the drug suramin (used outside the United States to treat African sleeping sickness). That means researchers might consider investigating suramin as an IC treatment.

Top Layer Fails to Form in IC Bladder Lining

An altered differentiation program in the urothelium of interstitial cystitis patients
Robert E Hurst, Paul J. Hauser, Gennady Slobodov, Daniel J. Culkin, Oklahoma City, OK

Differentiation is the process cells go through to mature, take specialized shapes, and perform specific functions. Researchers theorize that this process might not be normal in the bladder lining of IC patients. To find out whether that is true and how, these investigators took cells from 28 IC patients and 5 controls and looked at them under the microscope after the cells had been stained with antibodies to certain types of biochemicals called cytokeratins. Cytokeratins are contained in the most specialized cells in the lining. In normal bladder lining cells, two types of cytokeratins occurred only in the very top layer of cells that form the barrier to urine, but only 10 of 25 IC patients had normal distribution of one cytokeratin, called KRT18. It was ether absent entirely or contained in cells other than the top layer. The situation was similar with another cytokeratin, KRT20, which was normal in only 11 of 25 patients. IC patients' specimens fell into two main groups—those with mostly normal results, and those with mostly abnormal results, but some patients had both normal and abnormal areas. These findings demonstrate that the cell differentiation program is not normal in IC patients and that the top barrier layer of cells, called umbrella cells, fail to form normally. So, then, does the barrier to urine and the irritating substances in it. What causes that abnormal program and how to restore it is still something we need to understand.

Proteins Preventing Leaky Lining Low in IC

Decreased expression of claudins 1, 4 and 8 in bladder epithelial cell explants from interstitial cystitis patients as compared to normal controls

Chen-Ou Zhang, Li Guo, Susan K Keay, Baltimore, MD

Proteins called claudins are known to be involved in the tight junctions between cells—the points where they link together tightly to form a barrier to fluid. Recently, some of these proteins have been found in bladder lining cells and some specifically in the cells that form the very top barrier layer of the bladder lining. These researchers grew bladder lining cells from three IC patients and three healthy controls and looked for claudin proteins in the cultures. The IC patients had much less of three different claudins than the healthy controls. This may contribute to the "leakiness" of the bladder lining in IC.

Pain Sensitization, Inflammation in Cystitis May Depend on Genes

Bacterial cystitis in c57bl/6n mice increases sensitivity to thermal stimuli

Dale E Bjorling, DVM, Wade Bushman, MD, PhD, Kyle Boldon, BS, Zun-Yi Wang, MD, PhD. University of Wisconsin, Madison, WI; University of Wisconsin-Madison, Madison, WI

These investigators found that bacterial bladder infection in three strains of mice made one strain more sensitive to pain (judged by how quickly they lift their paws from a hot surface). Another strain had much less inflammation. The mice that did not have as much inflammation lacked the toll-like 4 (Tlr4) receptor that is thought to play a crucial role in the cellular response to a bacterial toxin. The increased overall sensitivity to pain that can result from inflammation of internal organs may depend on genetic background.

Prostatitis Markers Point to Potential Pelvic Pain Therapy

A panel of potential diagnostic biomarkers for chronic prostatitis/ chronic pelvic pain syndrome

Jordan D Dimitrakov, Boston, MA; Jayoung Kim, Jaeseop Lee, John Quackenbush, Boston, MA; Weidong Zhou, Lance Liotta, Emanuel Petricoin, III, Manassas, VA; David Zurakowski, Michael R Freeman, Boston, MA; J. Curtis Nickel, Kingston, ON, Canada

A profile of proteins in the urine of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) patients showed these men have 177 unique proteins, with six top candidates as markers of the disease. One of the proteins is neprilysin, whicht neutralizes enkephalin, one of the body's own painkillers. An experimental drug that inhibits this protein is already being studied in neuropathic pain and may have potential for pelvic pain.

Blood Vessel Growth Abnormality May Cause Glomerulations in IC

Abnormalities in pericyte coverage on blood vessels induce glomerulations in patients with interstitial cystitis

Hiroshi Kiuchi, MD, Testuya Takao, Jiro Nakayama, Toshiaki Hirai, Tomohoro Ueda, Kazuhiko Komori, Yasuhiro Matsuoka, MD, Yasushi Miyagawa, Shingo Takada, Tsujimura Akira, Keisuke Yamamoto, MD, Masami Takeyama, MD, Akihiko Okuyama. Osaka Graduate School, Osaka, Japan; Osaka Central Hospital, Osaka, Japan

Many patients with IC show glomerulations—pinpoint bleeding—in their bladders during hydrodistention, but it isn't well understood why and how this happens. This research team has discovered that it may be because IC patients have fewer of a type of cell that supports blood vessels and a high proportion of immature blood vessels in the bladder. Cells called pericytes support the walls of small blood vessels and are known to be abnormal in other conditions where blood leaks from vessels, as in diseased retinas in patients with diabetes. The researchers looked at the density of these cells, the levels of the factor that promotes blood vessel proliferation, counted small vessels, and assessed vessel maturity in IC patients' bladder tissue compared with normal bladder tissue. The coverage of pericytes in blood vessels was significantly lower in IC patients than in controls in the layer of cells just under the bladder lining. Also, in the layer below the lining, IC patients had more of the growth factor but no more microvessels than controls. The researchers concluded that IC patients' high level of this growth factor does not promote growth of more blood vessels, but it does promote formation of

immature microvessels, which might play a role in glomerulation.

Abnormal Urine Protein May Be Key to Bladder Damage in IC

Sialic acid content of urinary Tamm-Horsfall protein is reduced in interstitial cystitis patients
C. Lowell Parsons, Mahadevan Rajasekaran, Marianne Chenoweth, Paul Stein, San Diego, CA

Tamm-Horsfall protein is thought to neutralize chemicals in urine that can damage bladder lining, but IC patients apparently don't make a normal version of this protein, so this may be a reason that IC bladders sustain damage. The difference seems to be in the sialic acid content of the protein, which makes the protein electrochemically abnormal and prevents it from neutralizing positively charged, damaging chemicals. To test that idea, the investigators compared the sialic acid content and electrostatic potential if the protein from 28 IC patients and 29 healthy controls. The Tamm-Horsfall protein from IC patients did, indeed, have a lower sialic acid content and a lower electrostatic potential than controls. There was no difference, however, between the quantity of Tamm-Horsfall protein in urine between the IC patients and controls. This research might help us understand the cause of IC, concluded the investigators.

More Evidence that IC Bladder Cells are Different from Normal Cells

Increased efficacy and potency of carbachol in inducing increases in intracellular calcium ([Ca2+]i) and outward potassium currents (I0) in interstitial cystitis (IC) bladder urothelial cells (BUC): Evidence of persistent phenotypic alteration of cultured human IC BUC
Gopal N Gupta, Mingkai Li, Yan Sun, Michael Gold, Marc Simard, Toby C Chai, Baltimore, MD

Basic research on bladder lining cells in IC has already shown that they may release neurotransmitters and produce APF, unlike normal cells. To find more differences, these researchers used electrophysiologic measurements and techniques that measure calcium ions. (Calcium ions play a role in transmitting nerve signals.) The researchers added a stimulator called carbachol to the cells and found that IC cells reacted very differently from normal cells. IC cells had much greater electrical activity and more calcium ions. Taking away calcium from the cells' environment and adding the drug tolterodine (Detrol), an overactive bladder drug, erased the differences. Based on these results, this research team concurs that bladder lining cells play a central role in the IC disease process.

Nerve Stimulation, Not Anticipation, Affects Sensation, Pain Brain Areas

Effects of sacral neuromodulation on the central nervous system
Nasim Zabihi, Daniel Silverman, Veronica Triaca, Christian Twiss, Cheri Geist, Shlomo Raz, Larissa V Rodriguez, Los Angeles, CA

Using the brain scanning technique positron emission tomography (PET), these investigators looked at whether and how sacral neuromodulation affects the brain. They assessed the reactions to high stimulation, no stimulation, stimulation too low to be felt, and just anticipating the stimulation. Certain areas of the brain did light up with stimulation that was high enough for patients to feel, including the pons, hippocampus, and perigenual anterior cingulate cortex. High stimulation also showed decreased activity in the left dorsal anterior cingulate compared with no stimulation or just expecting stimulation. The brain changes were a direct result of stimulation and not just thinking about it, noted the researchers. The anterior cingulate cortex, where activity decreased with stimulation, is associated with sensory and motor functions of the body. Increased activity there is associated with sensation and motor functions of the internal organs, especially inhibition of pain.

COURSES FOR CLINICIANS VERY POPULAR

AUA put on three courses specifically about IC for doctors who wanted to learn more about IC treatment. That's a record number, with a record number of participants. But even more courses helped attendees learn about treating IC and related problems.

One teaching team included three ICA Medical Advisory Board members, urologists Robert Moldwin, MD, from Long Island Jewish Medical Center, New Hyde Park, New York, and Ragi Doggweiler, MD, from the University of Tennessee, Knoxville, and gynecologist Fred Howard, MD, from the University of Rochester, Rochester, New York. Their course gave attendees a practical approach to treatment of chronic pelvic pain, including IC, pelvic floor dysfunction, pelvic congestion, vulvodynia, endometriosis, irritable bowel syndrome, and chronic prostatitis/chronic pelvic pain syndrome in men. They emphasized that treatment needs to be interdisciplinary and may need to include urologists, gynecologists, physical therapists, psychologists, pain specialists, nutritionists, rheumatologists, and acupuncturists. Dr. Moldwin's approach to IC includes using anesthetics in the bladder rather than potassium to help make the diagnosis, using a laser to treat Hunner's ulcers, and other practical approaches. Dr. Howard helped urologists understand when the pain may be gynecologic, how endometriosis and pelvic congestion are treated, and how to manage pain medically, including the use of opioids and neuropathic pain drugs. Dr. Doggweiler spoke about pelvic floor muscle dysfunction and neuropathic pain. Calling myofascial and trigger point physical therapy the "best kept secret in pain management," she outlined these treatments and others that emphasize the mind-body connection, including deep relaxation."

Another course was taught by two other ICA Medical Advisory Board Members, Philip Hanno, MD, from the University of Pennsylvania, Philadelphia, and David Burks, MD, from the Henry Ford Health System, Detroit. Their class was both a primer and an update. They spoke about diagnosis, pointing out that the potassium sensitivity test is not sensitive and specific enough for diagnosis and that glomerulations are also not diagnostic. Doctors can suspect IC when patients have pain, frequency, and urgency and don't have evidence of infection and other urologic and gynecologic problems. Dr. Hanno and Dr. Burks also outlined all the current therapies as well ones that are being tested in clinical trials, including mycophenolate mofetil (CellCept), physical therapy, a leukotriene antagonist that is also an antiasthma drug, an IgE inhibitor used for asthma in Japan, botulinum toxin A (Botox), an alpha agonist (in the family of drugs for treating blood pressure and prostate enlargement), intravesical chondroitin, a cannabinoid, and an anesthetic cocktail.

John Forrest, MD, and nurse Saundra Seidel taught a course that helped urologists learn, not only how to diagnose and treat IC, but also how urologists can organize IC treatment in their practices. Dr. Forrest made the important point that urologists don't have to shy away from treating IC patients because it's not cost effective. IC treatment is an important and positive part of his business because of the way he works with Ms. Seidel and the nursing staff. IC patients who need help with flares, need to get their urine checked for UTIs, or anything else can walk into the clinic any weekday from 8 AM to 5 PM and get help and can even come in on the weekends in emergencies.

IC was an important part of a course on female urology, led by David Staskin, MD, from Weill-Cornell Medical College in New York City. In this course, Toby Chai, MD, from the University of Maryland, Baltimore, and Kenneth Peters, MD, from William Beaumont Hospital in Royal Oak, Michigan, spoke about the different and sometimes competing theories on where the disease IC actually is based—in the bladder, in the nervous system, in the pelvic floor, or all of those. Susan Kellog-Spadt, PhD, who works with Kristene Whitmore, MD, at the Pelvic and Sexual Health Institute in Philadelphia, Pennsylvania and is Director of Sexual Medicine there was a faculty member in a course on sexual dysfunction. Dr. Kellog-Spadt lectured on sexual pain, especially vulvodynia and vulvar vestibulitis and their treatment, including pelvic floor muscle therapy and innovative medications in creams and injections, neuropathic pain drugs, nerve blocks, and more. Her participation in this course helped emphasize to urologists that serious pelvic pain problems contribute to sexual dysfunction and deserve treatment so that women with pelvic pain can reclaim their sexual selves.

IN THE HISTORY BOOKS

In the exhibit hall, a large central display festooned with pink bunting stood out from the rest. Here, the AUA's William P. Didusch Center for Urologic History honored women healers, with descriptions and photos on the walls and artifacts in displays tracing the history of women in medicine. They have always been there, as a quote a wall from 19th century physician Eliza Flagg Young, MD, reminded viewers: "Every woman is born a doctor. Men have to study to become one."

But formal recognition and acceptance have not always been there. Women healers and physicians were prominent in ancient times, but their role diminished, reaching a terrible low as "witch" burning began during the Inquisition. After the Renaissance, women didn't break into formal medicine again until the 18th century in Europe and the 19th century in the United States when Elizabeth Blackwell became the first American woman to be granted a medical degree in 1849.

In urology, women are still pioneers, and the AUA recognized eight MDs and PhDs who work in the field today. Only one, Dr. Ratner, is not a urologist or a urology researcher. She was recognized for her accomplishments in raising awareness of IC, stimulating and guiding research, and supporting patients. Two other honorees in the exhibit are also IC heroines: pioneer IC clinician and researcher Kristene Whitmore, MD, who won the ICA Advocate of the Year Award in 2005, and research advocate Monica Liebert, PhD, who won the award in 2006.

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