



# Chronic Pelvic Pain and the Overlap of Chronic Pelvic Pain Disorders

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*Dr. Pezzone is the 2005 recipient of the IFFGD Basic Science Research Award to a Junior Investigator. He is also the recipient of a Research Excellence in GI and Liver (REGAL) Award for Lower GI Research. Dr. Pezzone is the principle investigator of an NIH study looking at the pathways of neurogenic cross-sensitization of pelvic viscera and its implications for the overlap of irritable bowel syndrome, interstitial cystitis, and other chronic pelvic pain disorders.*

Chronic pelvic pain (CPP) is the key element comprising several CPP disorders that are all characterized by intermittent or continuous pain of at least 6 months duration localized to the pelvic area, the lower part of the abdominal cavity. Bowel, lower urinary tract, sexual, and/or gynecologic function are often affected. Chronic pelvic pain disorders affect 15% of both men and women, and include disorders such as irritable bowel syndrome (IBS); interstitial cystitis (IC); chronic prostatitis (an infection or inflammation of the prostate gland); levator ani syndrome (characterized by a dull ache in the rectum that lasts for hours or even days); and vulvodynia (chronic discomfort or pain in the female genitalia).

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Chronic pelvic pain disorders can develop following acute or chronic irritation of individual pelvic visceral organs (internal organs such as the colon or bladder), their sphincters, the internal muscular support structures of the pelvic floor itself, the nerves that supply and stimulate the pelvis, and/or the external muscular or cutaneous (skin) components of the pelvic abdominal wall and/or perineum, the area between the anus and the genitals. Considering that the colorectum and urinary bladder function as an integral part of daily, physiological pelvic activity, it is not surprising that IBS and interstitial cystitis, analogous disorders of pelvic visceral pain and hypersensitivity, account for half of all cases of chronic pelvic pain.

## **Cross-sensitization**

Because bowel, lower urinary tract, sexual, and gynecologic

function are all inter-related, the pelvic organs and structures require an integrated neural control mechanism to permit cross-organ communication or “cross-talk.” In other words, the pelvic organs and structures communicate through nerve connections or reflexes either directly or via convergent pathways (pathways that meet in control areas such as the lumbosacral or lower spinal cord). Such reflexes require no conscious input and are important for normal pelvic physiologic function including urination, defecation, sexual intercourse, and the maintenance of fecal and urinary continence.

We propose that through these same pathways, which are important for carrying out normal pelvic physiologic function, “cross-sensitization” can develop whereby acute or chronic irritation of one pelvic organ can lead to abnormal activity, sensitivity, or even neurogenic (nerve-mediated) inflammation in another, non-irritated organ or structure. This hypothesis could help explain the common overlap of chronic pelvic pain disorders.

## **Frequency of Overlap**

IBS, an intestinal disorder characterized by chronic or recurrent lower abdominal pain or discomfort associated with altered stool consistency and frequency, is the most common gastrointestinal cause of chronic pelvic pain, affecting 50% of such women presenting to gynecologic clinics. Interstitial cystitis, or painful bladder syndrome, is a chronic pelvic pain disorder characterized by unpleasant urinary symptoms such as urinary frequency, urgency, waking at night to urinate (nocturia), and, most notably, pain in the pelvic area and perineum related to bladder filling in the absence of active infection or organic disease. As many as 40–60% of patients diagnosed with IBS also experience bladder symptoms of urinary urgency, while correspondingly, 38–50% of patients diagnosed with interstitial cystitis also have symptoms of IBS. Furthermore, 26% of patients diagnosed with interstitial cystitis were also found to have concurrent pain of the vulva, or vulvodynia, and 45% of males with chronic prostatitis or male chronic pelvic pain exhibited pain with bladder filling, a classic feature of interstitial cystitis. The high concurrence rate of IBS, interstitial cystitis, and other chronic pelvic pain

disorders and the role of cross-sensitization of pelvic organs has become the focus of my laboratory research as well as others.

### **Study Findings**

Recently, we were one of the first groups to describe an animal model of bowel-bladder cross-sensitization. In our novel experimental model, we provided compelling evidence of neural cross-talk and bidirectional cross-sensitization in the pelvis. The ability to measure concurrently lower urinary tract and lower (distal) colonic sensory function and associated sphincter muscle activity in response to cross-organ, non-irritative and irritative stimulation substantiated the importance of this model in studying pelvic pain and the overlap of chronic pelvic pain disorders such as IBS and interstitial cystitis.

In our initial experiments, we first showed that colorectal distension inhibited urination (colon-to-bladder cross inhibition), and that during urination, colonic motor activity was inhibited (bladder-to-colon cross inhibition). We then showed that colorectal sensory thresholds to distension were dramatically decreased (implying colonic sensitivity as seen in IBS) after acute irritation of the bladder. Likewise, acute colonic irritation led to irritative urination patterns as seen in interstitial cystitis or acute cystitis (bladder irritation).

We then extended our studies to more long-term irritation and found that following chronic colonic irritation, not only was there evidence of chronic cystitis (increased frequency of urination and decreased volume) as seen in interstitial cystitis, but there was also evidence of neurogenic (nerve-mediated) bladder infection or inflammation (cystitis) as evidenced by increased numbers and activation of bladder immune (mast) cells in the absence of any observable bladder injury. Growth factors for mast cells were also increased. Mast cells have been implicated in IBS, interstitial cystitis, and other pain disorders as they can release chemical mediators that can cause pain, increase motor activity, and make pain nerves (afferent nerves) more sensitive.

Subsequently, to test our hypothesis further, we directly recorded from bladder afferent C-fibers (type of neurons involved in the perception of pain) traveling in the pelvic nerve. Following acute and chronic colonic irritation, we found that bladder afferent nerves were directly sensitized to both mechanical and chemical stimulation. In other words, after colonic irritation, the very nerves that carry signals for uncomfortable bladder sensation (e.g., over distension, or chemical irritation) had become hypersensitive, or overly sensitive.

Such visceral sensitization is thought to occur in the spinal cord via the convergence of both bladder and colon sensory nerves

onto spinal interneurons. [Interneurons are nerves confined wholly within the spinal cord – as compared with sensory and motor neurons whose fibers project outside the cord; they help integrate sensory information and coordinate muscle activity.] By injecting special tracers into the bowel and bladder, we sought to examine these afferent sensory pathways in greater detail. To our surprise, we actually found double-labeled cells in the bundle of cell bodies (dorsal root ganglia) where the nerves supplying such pelvic organs converge. In other words, the tracer from the bladder and the tracer from the colon were found in some of the same cells implying that the two organs are connected by one pain nerve in some instances. These findings suggest that such pelvic organs as the bladder and colorectum may have a population of pain fibers that directly supply both organs. This would be another means of explaining the clinical overlap of IBS and interstitial cystitis and could account for our experimental findings as we have described above.

### **Conclusion**

In conclusion, IBS and other chronic pelvic pain disorders often co-exist, and in many cases, treatments are similar (e.g., antispasmodics, tricyclic antidepressants, stress-reduction techniques, etc.) As we learn more about the origin and development of these disorders, including their overlap and the role of mechanisms involved with disturbances of sensory afferent nerves, we may be able to treat these disorders more holistically and more effectively.

### **References**

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