Theories of Prostatitis Etiology

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Prostatitis reflects a broad spectrum of prostatic infections, both acute and chronic. Chronic prostatitis, known as National Institutes of Health category III or chronic pelvic pain syndrome, broadly defines a disease that is still poorly understood, and as a consequence, difficult to treat. Typical symptoms include pelvic pain and voiding dysfunction. Infection is often cited as the cause of this condition, despite frequent negative cultures. A close look at the local prostatic microenvironment may yield clues. The role of inflammatory mediators and what stimulates them can point to potential sites of prevention. A genetic link or relationship to other diseases may prove to be part of the cause. Furthermore, a neurologic source, whether anatomic or psychologic, has been strongly debated. Ultimately, it may become clear that chronic prostatitis represents the final common result of a disease that originates from a cascade of multiple stimuli.

Introduction

There is continuing debate among researchers as to the cause or causes of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). Is it an infectious, autoimmune, or some other inflammatory agent that mediates a process, perhaps with resultant neuropathic damage, that leads to a final common pathway of pain? Nickel [2•] has proposed a concise but "inter-related, multifactorial cascade" that begins with an inciting event and may, but not must, end in pain (Fig. 1). This concept provides a conceptual framework for what is likely a complex process. Other modulating factors must also be examined in considering the origin of this condition, such as endocrine function, psychiatric state, and the local environment of the prostate gland.

Bacteria and Prostatitis

The symptoms of pelvic pain and voiding dysfunction that characterize CPPS are similar to those that occur with a true bacterial infection. Therefore, it is not surprising that one of the most common theories of CPPS etiology is that of an occult infection. This idea has been bolstered by the discovery of fastidious microbes as the cause of other previously poorly characterized conditions such as *Helicobacter pylori* for stomach ulcers and *Tropheryma whippelii* for Whipple's disease [3]. One limitation to isolating organisms in patients with prostatitis may be the culture method itself. Shoskes *et al.* [4] suggested that increasing culture time from 2 to 5 days yields 7.5% more positive cultures, and that these cultures correlate with inflammation secondary to gram-positive bacteria. Longer culture time seemed to make the biggest difference in cultures of semen and expressed prostatic secretions (EPS), indicating that there may be local environmental factors in these fluids that may inhibit their growth initially, but are eventually overcome by longer incubation time. Could there be a relation between infection and sexual activity? A Finnish population-based study headed by Mehik *et al.* [5] reported on 1832 (75%) respondents to a non–National Institutes of Health (NIH) questionnaire of men in the two most northern provinces of Finland. Interestingly, divorced and single men had a lower risk of infection than married men, independent of age. The authors speculated that this difference might be due to the exposure of married men to potential pathogens from their wives' genital tract.

Newer studies have also increasingly used molecular techniques to try to answer the question of infection in these patients. Several unusual organisms were identified in a recent study using polymerase chain reaction (PCR) [6]. Using PCR on the pellet samples from patients with CPPS and control patients, Canadian investigators found that the most common species discovered were from the genera *Paenibacillus* species and *Proteobacterium*. These organisms were much more common in men with CPPS. Shoskes and Shahed [7] found that performing PCR on EPS detected the presence of bacterial DNA in patients with category IIIa disease in 23 (70%) of 33 specimens, whereas culture was positive (for gram-positive bacteria) in only 17 (51%) of 33 patients. Only two of 14 patients with category III disease had bacterial DNA. Nevertheless, 13 (57%) of the total patients with bacterial DNA improved with antibiotics, while patients who lacked bacterial DNA by PCR did not improve with antibiotics. This negative predictive value of 100% is important because it directs against giving unnecessary antibiotics in lieu of other treatment options, while predicting which patients would benefit most from antibiotics. Interestingly, 56% of the bacterial DNA-negative patients improved after antioxidant/α-blocker therapy.

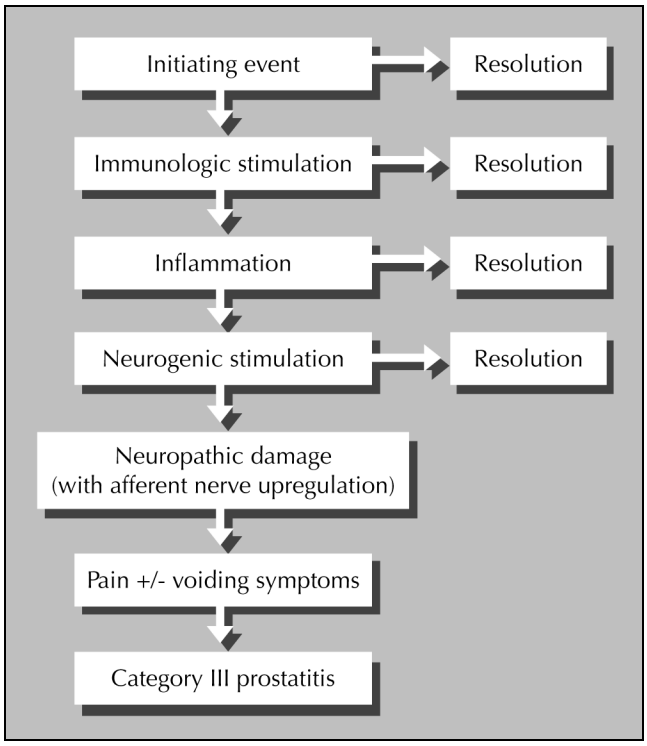

Figure 1. Pathogenesis of pain in patients with National Institutes of Health (NIH) category III disease. (*From* Nickel [2•]; with permission.)

One of the ways to determine whether or not prostatic bacteria are pathogenic is by evaluating men without pelvic pain for prostatic flora. Are bacteria normally present in the prostate? Hochreiter *et al.* [8] compared PCR results of prostatic tissue samples searching for bacterial DNA from radical or open prostatectomy specimens versus samples from (healthy) organ donor prostates. In the former group, they found samples with inflammation that correlated with the presence of bacterial DNA by PCR, while a negative PCR result was seen in the healthy group that lacked inflammation. They concluded that healthy prostate glands contain no flora. Another study also found that bacterial RNA in the prostate is not specific for men with prostatitis and was also found in men undergoing implantation of radioactive seeds for prostate cancer [9]. A recent study by Krieger *et al.* [10••] supports the association between bacterial DNA and inflammation. Sterile prostate biopsies were retrieved from radical prostatectomy specimens and compared with sterile perineal biopsies from patients with category III disease. Bacterial DNA was detected by PCR in 20% of the cancerous prostates and in 46% of prostates with chronic prostatitis. DNA sequences from typical and atypical uropathogenic bacteria were found. This finding was contrary to the authors' hypothesis that older men, *ie*, older prostates, would have higher bacterial rates because they may have been catheterized or contracted urinary tract infections in the past. They concluded that bacteria may be associated with prostate disorders, but are not necessarily a reflection of medical history.

Another consideration regarding the role of bacteria in prostatitis is the local environment of bacteria in the prostate. If bacteria are present but protected by a biofilm, they may be inaccessible for culture or treatment by antibiotics. It is widely accepted that bacterial biofilms that coat artificial implants or organ linings create favorable conditions for protection from host immunity and promote colony propagation. Previous reports have noted that various proteins [11] can be laid down into a matrix that inhibits chemotaxis and phagocytosis of neutrophils [12]. As described by Choong and Whitfield [13], bacteria in biofilms behave differently from and are phenotypically different from free-floating bacteria. Free-floating bacteria can be cleared by antimicrobials while biofilm bacteria are protected within the matrix, may grow slower, and also may be genetically resistant to antibiotics, especially after multiple courses or by way of plasmids. If free-floating bacteria are left untreated or undertreated they can form biofilms and lead to chronic inflammation and persistent immunologic stimulation [14], and thus, persistent pain as hypothesized by Nickel [2•]. Treatment must therefore ideally be instituted prior to biofilm formation. Determining when this window of intervention occurs is the difficult but crucial step. Also, it is possible to speculate that the lack of inflammation seen in patients with category IIIb disease may be merely a defective immune response secondary to inhibition by biofilm. Nevertheless, it is worth consideration that even this group of patients may have a microbial source as an immuno/pain syndrome stimulator.

Inflammation and Prostatitis

Whether or not there is an ongoing infection or a remote infection, patients with CPPS commonly have chronic inflammation. Several groups of researchers have measured the levels of inflammatory mediators in the EPS of men with chronic prostatitis. Hochreiter *et al.* [15] reported that levels of interleukin (IL)-8 and epithelial neutrophil activating factor-78 were significantly elevated in patients with categories IIIa, IV, and I disease over controls and patients with category IIIb disease. These cytokines are direct mediators of leukocytic chemotaxis and activation. An association was shown between leukocytes and levels of IL-8, but not between cytokines and pelvic pain. The ultimate role these agents play in causing pain is questioned by the authors because they were unable to document increased cytokine levels in patients with IIIb disease, and also because it is not conclusively known if these cytokines are released after leukocyte activation or precede and stimulate leukocyte arrival. In another study, Nadler *et al.* [16] found elevated levels of IL-1β and tumor necrosis factor (TNF)-α in EPS samples from patients with category IIIa disease, as opposed to patients with IIIb disease and control subjects. No correlation was noted between these cytokines and leukocytes. The authors proposed that such cytokines may be used a clinical markers

and are more reliable than leukocyte-only detection. Elevated levels of TNF-α and IL1-β have also been reported in the seminal plasma of men with chronic prostatitis, when compared with asymptomatic control patients [17].

Another marker of inflammation is the presence of free radicals, specifically reactive oxygen species (ROS) in EPS. Neutrophils release ROS in response to antigenic stimulation. Release of ROS ($O_2\cdot$, $HO\cdot$, H_2O_2), or oxidative stress, within prostatic fluid of patients with category III disease is a hot topic of investigation. Oxidative stress in EPS was studied by Shahed and Shoskes [18] as a marker of tissue injury secondary to pathogenic bacterial infection. They proposed that infection by gram-positive bacteria in category IIIa disease (as opposed to prostatic colonization) results in oxidative stress, because by definition tissue injury follows infection and not colonization. Thus, after antibiotic treatment for infection oxidative stress would be reduced, proving gram-positive bacteria to be the true pathogens. The presence of fewer ROS minimizes tissue injury and ultimately, causes less pain. Shahed and Shoskes' [18] patients with category IIIa disease had significantly higher levels of oxidative stress than did their patients with category IIIb disease. Oxidative stress levels, however, were independent of leukocyte count in the EPS, and therefore not a marker per se of leukocytes, but rather a marker of tissue injury. Less oxidative stress was subsequently detected in the EPS after clinically successful treatment with oral antibiotics or antioxidants. Increased ROS levels and low antioxidant levels were also reported by Pasqualotto *et al.* [19] in seminal plasma from men with CPPS, compared with controls. Thus, the concept of nonleukocyte inflammation must be considered in future models of prostatitis.

Whatever the mechanism of inflammation, mucosal disruption with concomitant irritant exposure was found to cause prostatitis in rats [20]. Significant inflammation with generation of IL-1β resulted only when ethanol, used to disrupt mucosal integrity, was injected in conjunction with dinitrobenzenesulfonic acid (DNBS) (an irritant). This outcome was not observed when these agents were injected individually.

Autoimmune-induced Prostatitis

The possibility of an autoimmune basis for prostatic inflammation has been examined in both human and animal models. Shahed and Shoskes [18] found markers for cytotoxic T cells in their patients' EPS. This cell type is not typical of antimicrobial immunity but more consistent with autoimmune inflammation or secondary remodeling of injured tissue. Prostate-specific antigen (PSA) was proposed as a candidate self-antigen by Ponniah *et al.* [21]. CD4 T cells from patients with category III disease had an observed proliferative response to PSA more than double that seen in controls, yet no response was found to two other seminal proteins, prostatic acid phosphatase and β-microseminoprotein. Possible autoimmunity may, in part, explain the chronic and relapsing nature of chronic prostatitis that resembles other relapsing autoimmune disorders such as multiple sclerosis and lupus.

One important modulating factor in the development of prostatitis may be sex hormones, which have especially been linked to the autoimmune process. The aging process heralds waning immunity as a result of decreased thymic function from defective T-cell activity. Morón and *et al.* [22] proposed that aging may also contribute to thymic dysregulation in the rat model of autoimmune prostatitis, but potentially could be modulated by manipulation of male hormone levels. Early castration improved thymic function and decreased the development of autoimmune prostatitis as the rats aged. The authors referred to a recent pilot study that showed significant pain relief in patients with category III disease treated with finasteride and hypothesized a novel drug effect on the thymus [23].

The male Wistar rat model has been used to study experimentally induced prostatitis (by hormone manipulation) or to define the nature of its unique characteristic of developing spontaneous autoimmune prostatitis with age. Harris *et al.* [24] implanted estradiol (E_2)-17β capsules into rat models and noted that there was extensive infiltration and inflammation of the lateral lobes of the prostate 4 weeks after implantation. This inflammatory response was not observed in control rats. Using PCR, they noted dramatic upregulation of cytokines IL-6, macrophage inflammatory protein-2, and inducible nitric oxide synthase (iNOS), and smaller but consistent upregulation of IL-1β and TNF-α. IL-6 is a key pro-inflammatory cytokine. iNOS suggests the role of nitric oxide (NO) production, an agent required for vascular permeability. These cytokines were first detected by day 4, before any observed histologic inflammation was noted. As inflammation developed over time, infiltrates were first detected within the prostatic stroma and later in the ascini. Prior studies [25,26] have noted that co-administration of testosterone with E_2 prevented estrogen-induced prostatitis, while it was not true for co-administered dyhydrotestosterone (DHT). This suggests that testosterone must exert an independent role on the prostate gland aside from conversion to DHT and its effects. What role this implies for finasteride is still undetermined. The proinflammatory effect of E_2 had been shown previously [25] to be blocked by bromocriptine, suggesting a role for prolactin in prostatic inflammation. Similarly, Kwon *et al.* [27] were able to induce prostatitis in rats administered the estrogenic bioflavinoid, isoflavone, that contains genistein and daidzein. Mean body weight and inflammation were significantly lower and higher, respectively, in the experimental group. These investigators suggested that estrogenic effects may be dose-dependent, so that elevated exogenous estrogen levels may induce inflammation, while in lower doses they can act as an antagonist by saturating estrogen-receptor binding sites [28]. Moreover, isoflavone itself has

been shown to induce an inhibitory effect on 5-α reductase activity [29].

An interesting finding on the genetics of patients with CPPS bolsters the theory that this condition may be the result of an underlying problem with the regulation of sex hormones. Krieger and Riley [30] found allele frequency differences of the *PGK1* gene between patients with CPPS and control subjects. The phophoglycerate kinase gene differed in the number of STRs or short tandem repeats. The *PGK1* gene in the assessed region has been found to be associated with familial prostate cancer, hypospadias, and androgen insensitivity. Another gene in the same region of the X chromosome, Xq11-Xq13, is the androgen receptor. This finding raises the possibility of androgen insensitivity or dysfunction in the pathogenesis of CPPS.

The Etiology of Prostatitis Pain

The defining symptom in patients with CPPS is pain, indicating some neurologic involvement either on a local level or in the central nervous system (CNS). Inflammation itself may alter the local environment. It is known that immune cells produce β-endorphin, an endogenous opioid, at sites of inflammation or tissue injury to decrease pain, and that the inflammatory marker prostaglandin E_2 (PGE_2) is known to inhibit β-endorphin [31]. Shahed and Shoskes [32•] proposed that oxidative stress in patients with category III disease raises PGE_2 levels, which in turn lowers β-endorphin levels, thereby contributing to the pain of prostatitis. PGE_2 levels in their patients were four to six times higher than in their asymptomatic control subjects. Although not significant, a trend to lower levels was seen in IIIb versus IIIa disease, which itself is important as it lends further credence to the final common pathway of pain, again, as hypothesized by Nickel [2•]. After treatment with either an antibiotic or antioxidant, β-endorphin levels were significantly higher and PGE_2 levels were significantly lower.

Another local factor contributing to pain could be elevated intraprostatic pressure. Intraprostatic tissue pressure was measured in 42 patients with chronic abacterial prostatitis under spinal anesthesia [33]. After an injection of 1 mL of saline, significantly higher intraprostatic pressures were recorded at all time points in these patients versus control subjects. The investigators felt this reflected increased tissue resistance and possibly poor tissue microcirculation. Whether this was secondary to intrinsic prostatic changes or increased sympathetic or pelvic floor activity is unknown. They speculated that poor flow may contribute to tissue rigidity and fibrosis.

Inducible nitric oxide synthase levels are upregulated during prostatic inflammation, with a consequent increase in NO, and therefore, in vascular dilatation and permeability. Cho *et al.* [34] used color Doppler ultrasonography to show marked increases in flow to the prostatic capsule and parenchyma in patients with category IIIa and IIIb disease, compared with control subjects. This again may support the notion of a common denominator leading to pain in these different subsets. Is it vascular congestion itself or the delivery of inflammatory cells (resulting from vascular congestion) with their resultant cytokine production that generates the pain experienced by patients with CPPS?

Several researchers believe the etiology of the pain in patients with category III disease lies with heightened pelvic floor tension that may or may not be related to pudendal nerve entrapment. Potts [35] believes that "biofeedback and progressive muscle relaxation, strengthening and stretching of the back and pelvic floor show much promise" for relieving pain, reporting a response rate of 38%. Even better results have been reported with biofeedback, with a decrease in median pain scores from 5.0 to 1.0 on a 10-point scale ($P = 0.001$) [36]. Antolak [37] proposed that pain and erectile/voiding dysfunction may all originate from pudendal nerve entrapment, either between the sacrotuberous and sacrospinous ligaments or from outright fibrosis within Alcock's canal. Electromyography (EMG) may show neuropathic changes, and if special sitting pads or avoidance of provocative actions (cycling) don't help then neurolysis and transposition may be beneficial. Shafik [38] uses pudendal canal fasciotomy for decompression of the nerve. Nerve transposition is then performed after documentation of perineal hypoesthesia or decreased EMG of the external sphincter. He believes entrapment results from lateral traction and subluxation of the levator muscles caused by high intra-abdominal pressures generated by chronic constipation. The sagging levator muscles stretch the nerve, leading to progressive damage with each episode of defecation.

The pain of chronic prostatitis has been likened to that of interstitial cystitis (IC) in women. Some say prostatitis may, in fact, be undiagnosed IC in men [39] or simply a condition which generates pain along similar anatomic pathways. Keith *et al.* [40] found increased density of nerve fibers and sensory neuropeptide calcitonin gene-related peptide at progressive time points in the Wistar rat model. In addition, he also found evidence of progressive mast cell degranulation. Any initiating stimulus may recruit sensory fibers if stimulation is persistent. The authors [40] cite previous research where mast cells were shown as antigen presenting cells [41] that degranulate after contact with T cells, thereby activating nearby nerve fibers. Furthermore, Ishigooka *et al.* [42••] found that chemical irritation of the rat prostate and bladder caused plasma extravasation and c-fos protein expression at identical spinal cord levels (L6 and S1) with referred pain to the corresponding dermatomes, underscoring the overlap of afferent nerve fiber distribution.

Data to further support a neurologic hypothesis are given by Zermann *et al.* [43•]. They found significant abnormalities in the coordination of voiding and activity in the pelvic floor/external urethral sphincter in over 80% of their men with symptoms of pelvic pain. This kind of dysfunction is classically found in patients with suprasacral spinal cord lesions, such as patients with a full spinal cord

injury, or men with spinal cord plaques from multiple sclerosis. This raises the question as to whether these men have a subclinical neural injury in the spinal cord that would contribute to such dyssynergy, and thus, pelvic pain. Also, some patients with CPPS respond to sacral neurostimulation [44], supporting the idea that there is a common pathway to nerve dysfunction in these patients, whatever the inciting insult may have been.

Although pain is the prevalent symptom experienced by these patients, there may be psychological and even environmental factors effecting how the patient perceives his pain. Mehik *et al.* [5] reported that men over 50 years of age had a threefold greater risk of experiencing pain than their younger cohort. Sixty-three percent of affected patients had their worst symptoms during the winter months between November and March, while very few (3%) had their worst symptoms in the summer. The authors concluded that the higher prevalence they reported might be, in part, due to cold climate. The same authors reported [45•] that psychological stress is a common finding among the same patient population. Personality self-assessment results demonstrated that these men reported being more nervous and busy than healthy control subjects. Less significantly, these same patients also expressed fear of having a sexually transmitted disease (STD) and higher incidence of suicidal thinking than healthy controls. A Korean study [46] also found increased exposure to sunlight to be protective against developing symptoms of CPPS and that a lower education level was associated with a higher incidence of CPPS. Overall, the psychological health of men with CPPS appears to be inferior to those of other groups. In a large cohort of CPPS patients, McNaughton-Collins *et al.* [47] used the SF-12 to evaluate the mental and physical health of patients. The mental component summary score for CPPS patients was lower than that observed in the most severe subgroups of congestive heart failure and diabetes. Although it is unlikely that depression is a cause of the original pain symptoms, depression itself may arise as a reaction to chronic pain and disability, thereby worsening the patient's perception of his symptoms.

Chronic Pelvic Pain Syndrome: A Possible Functional Somatic Syndrome?

Among physicians there is a growing perception that CPPS may be one manifestation of a series of disorders labeled functional somatic syndromes [48]. Compared with the general population, functional somatic syndromes and psychological disorders were significantly more prevalent among men with CPPS. Functional somatic syndrome symptoms include irritable bowel syndrome, chronic headache, fibromyalgia, and nonspecific dermatologic and rheumatologic symptoms. These symptoms are also observed in patients with IC [49], who were found to be 100 times more likely to have inflammatory bowel disease and 30 times more likely to have lupus than the general population. This again raises the question of whether the two entities (CPPS and IC) are either related or results of the same physiologic process.

Conclusions

Chronic prostatitis likely represents a multifactorial syndrome that arises from multiple causes. There is probably some initial injury to the genitourinary tract, be it infection or trauma, that then sets up a perpetuating inflammatory process. This could be an autoimmune process or the result of a particular individual predisposition, such as an hormonal abnormality. Whereas in most cases there is a normal inflammatory response, inflammation persists in patients with CPPS leading to local irritation or neurogenic inflammation, ultimately producing pain in other areas along the same dermatomal distribution. Another possibility is that an insult to the sacral portion of the spinal cord, caused by disc disease, trauma, or infection, can produce inflammation and pain in the terminal organ. The common endpoint is pain. How the patient perceives the pain can be affected by his environment, and also, by his psychological state. Pain can also probably contribute to depression, which can make patient discomfort more severe. Although it is unlikely that one root cause will be discovered to account for all men with CPPS, research leading to effective therapies targeting any of the processes in the cascade would be welcome to these patients.

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