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Chronic Prostatitis: An Infectious Disease?

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Chronic prostatitis is a common clinical entity. The only known etiology is related to microbial infection of the prostate gland. The majority of patients with chronic prostatitis are treated with long courses of multiple antibiotics, despite conflicting culture results (if cultures are done at all). Have we established the role of microorganisms in this disease entity? Historically, it was believed that all cases of prostatitis were related to bacterial infection. Traditional dogma states that only a small percentage of patients have prostatitis with a bacterial etiology, while basic and clinical research reported over the last 3 decades can be used to substantiate claims that either all or none of these conditions are related to microbial infection of the prostate. Is prostatitis an infectious disease?

Is chronic prostatitis an infectious disease? There is no doubt that prostatitis is a commonly diagnosed disease. Prostatitis results in more than 2 million office visits per year: 8% of total urologic visits and 1% of family physician visits.[1] Its prevalence among men at risk is believed to be between 5% and 8%.[2,3] Despite negative bacterial cultures (and in many cases no cultures at all), the majority of patients are treated with antibiotics.[1,4,5] There is no doubt that acute bacterial prostatitis is a bacterial infection of the lower male urinary tract.[6] There has never been an established relationship between acute bacterial prostatitis and the chronic form of the diagnosed syndrome. There is also no doubt that uropathogenic bacteria can be cultured in the rare patient with a chronic prostatitis syndrome. Many researchers feel that the majority of patients with prostatitis do, in fact, have a microbial etiology for their disease, but that we are just not culturing the correct organism. Others feel that the majority of cases of prostatitis, especially those in patients with no demonstrable inflammation, do not have a microbial etiology. To complicate things further, many asymptomatic patients in whom a diagnosis of chronic prostatitis has not been made have had both inflammation and microorganisms identified in prostate-specific specimens.

This confusion has led to the development of a new classification system by the NIH workshop on chronic prostatitis that was convened in Bethesda, Md, in 1995 (Table 1).[7] This new classification recognizes that, for the majority of patients, we do not really know if they have an infectious basis for their symptoms. The majority of patients with this syndrome would be classified as having chronic pelvic pain syndrome. These patients complain of genitourinary pain with variable voiding and sexual dysfunction problems and have no uropathogenic organisms cultured or identified on prostate specimens employing standard or traditional techniques. This classification is further divided into inflammatory and noninflammatory categories, based on the presence or absence of inflammatory cells in the prostate-specific specimens. The classification also identifies a category of asymptomatic prostatitis: inflammation and/or microorganisms identified in prostate-specific specimens, including biopsy, in asymptomatic men who would not have a diagnosis of prostatitis. Three years later, the International Prostatitis Collaborative Network, which met in Bethesda in November 1998,[8] confirmed the usefulness of this classification system in scientific studies and clinical use. The question remains, however: *Is chronic prostatitis an infectious disease?*

In the late 1800s, many investigators were studying bacteria within the normal and infected urethra, and it was generally recognized that bacteria normally inhabit the urethra in both health and disease. It was recognized early on that gonococci associated with urethritis could also be present in prostatitis.[9] The first definitive microscopic analyses of prostatic fluid were being performed by 1906,[10] and cultures of prostatic fluid from patients with prostatitis were being done by 1913.[11] In 1926, Nickel[12] focused attention on the important role of bacteria found in various focal infections, including those of the prostate gland, and in chronic inflammatory processes. Causal relationships between the organisms and the inflammatory lesions produced were established by isolation of bacteria from the lesions, whereas the blood and other tissues proved sterile. This was an important observation at the time and led Nickel,[12] Von Lackum,[13,14] and others to study bacterial localization in chronic prostatitis.

In a landmark 1930 study, Nickel[15] described the results of 3,500 cultures of prostate glands and seminal vesicles obtained from patients who had some ailment that might be attributable to prostatitis. He also examined 100 cultures

of tissue from the prostate glands of healthy males. The majority of cultures grew streptococci, staphylococci, bacilli, and diphtheroid organisms. These findings were confirmed by studies previously reported by Von Lackum[13] in 1927. In elaborate microbiologic analyses, other investigators identified *Staphylococcus* as the most important causative organism.[16] By the mid-1940s, it was generally accepted that prostatitis was an infectious disease.[17,18] However, by the 1950s, doubts and controversy erupted about the significance of leukocytes and bacteria in the prostate secretions.[19,20] It was becoming generally recognized that perhaps inflammation of the prostatic parenchyma may exist as a nonbacterial congested process.[21]

In the 1960s, many investigators found it difficult to correlate evidence for infection with chronic symptomatology. In 1968, Meares and Stamey[22] published their landmark paper in *Investigative Urology* and heralded what was thought to be a new age for the understanding of the prostatitis syndrome. These authors concluded that chronic bacterial prostatitis was rare and could only be diagnosed when uropathogenic bacteria were identified in greater numbers in the prostate-specific specimens (expressed prostatic secretion [EPS] or urine obtained after prostatic massage) than in cultures of urine from an initial stream and midstream. It is interesting to note that this conclusion was based solely on longitudinal studies of the bacteria localization patterns in only four patients with chronic prostatitis.[22,23] This concept was not really challenged for almost 3 decades.

Historically, prostatitis has been classified into four clinical entities:

- Acute bacterial prostatitis.
- Chronic bacterial prostatitis.
- Nonbacterial or abacterial prostatitis.
- Prostatodynia.[24]

Traditional dogma accepts that the first three types of prostatitis have an inflammatory origin, the first two have an infectious microbiologic origin, and the fourth (prostatodynia), despite similar clinical symptoms, is neither related to inflammation nor infection. The distinction between a so-called noninfectious abacterial prostatitis and noninflammatory, noninfectious prostatodynia was based on a belief that men with prostatic inflammation would demonstrate microscopic findings in the EPS with numerous leukocytes (and perhaps lipid-laden macrophages), whereas healthy men would not show this finding. However, no clinician or researcher was sure of what cutoff for white blood cells per high-power field should be suggested for inflammatory disease versus noninflammatory diease.

[25,26]

The traditional category of chronic bacterial prostatitis is much easier to accept. For patients in this category, the most important clue is a history of recurrent urinary tract infections (UTIs) with variable symptoms between these symptomatic infections. These patients traditionally show leukocytosis and uropathogenic bacteria in the EPS. In one of the largest recent prospective studies, Weidner and colleagues[27] found significant bacteria counts in prostate specimens in 4.4% of patients with symptoms of chronic prostatitis. Most researchers accept the finding that chronic bacterial prostatitis (prostatitis as an infectious disease) is an important but uncommon disease. The most common causes of bacterial prostatitis are gram-negative pathogens, predominantly strains of *Escherichia coli* that have been identified in 65% to 80% of infections.[27,28] *Pseudomonas aeruginosa, Serratia* species, *Klebsiella* species, and *Enterobacter* species are identified in the remainder. Although infections are commonly caused by a single organism, there have been reports of infections caused by up to four pathogens at the same time.[29] Traditional dogma states that most gram-positive bacteria identified in prostate-specific secretions do not represent pathogens that cause bacterial prostatitis,[30] whereas enterococci are accepted by many as a cause of bacterial prostatitis[31] and the UTIs associated with it. The traditional dogma is that *Staphylococcus saprophyticus, Staphylococcus epidermidis,* hemolytic streptococci, diphtheroids, *Mycobacterium,* and *Chlamydia* are doubtful candidates for causative agents.[26,32] Many researchers, however, remain unsure about the role of these organisms.[33-35]

If the majority of patients presenting with a chronic prostatitis syndrome do not have a microbiologic etiology for their disease, what is the cause of the patient's symptoms and/or inflammation? The following are various hypotheses put forward by researchers over the last several decades to explain the etiology and pathogenesis of this large group:

- Dysfunctional high pressure voiding[36-41] plus or minus intraprostatic ductal reflux.[36,37,42]
- Autoimmune or immunologic pathogenesis.[43-45]
- Chemical problems.[46]
- Neuromuscular problems.[47-49]

A number of related and unrelated clinical and research observations provide empiric support for the concept that all or at least the majority of patients with prostatitis may have a microbiologic cause for their syndrome.

The pattern of practice in North America is to treat patients presenting with chronic prostatitis with antibiotics.[1,4,5] This practice continues despite the fact that almost all standard localization cultures are negative (in most cases, cultures are never formally performed). The reason for this therapeutic paradox must be that the average practicing clinician feels that any antimicrobial therapy benefits many patients with prostatitis. In fact, clinical trials tend to confirm that as many patients with demonstrable infection (ie, chronic bacterial prostatitis) as without respond to antibiotics.[50] The successful culture of microorganisms in prostate-specific specimens is complicated by the presence of inhibitory substances known to exist in prostate secretions[51] and by the history in most patients of multiple previous courses of antibiotics.[50] Then there is the almost insurmountable problem of interpreting the microbiologic findings of EPS and semen in the presence of contaminating, indigenous flora of the urethra. The prostate-specific specimen, EPS, ejaculate, and postprostatic-massage urine must be cultured after passage through the contaminated urethra.

Repetitive prostate massage, the traditional and standard therapy for prostatitis for decades (abandoned after 1968), has become repopularized. This is, in part, because of the failure of traditional medical therapy to improve the symptoms of most patients with prostatitis, but also because of a belief that chronic bacterial infection exists in the prostate gland in blocked ducts or microabscesses.[52] In fact, more bacteria are identified in specimens of prostatic fluid expressed after repetitive prostate massage than are identified in an initial single localization study.[53]

Gram-positive organisms, particularly gram-positive cocci, are identified in prostate-specific specimens in patients with prostatitis syndromes. Traditionalists will argue that these patients usually do not have a history or documentation of bladder infection with these organisms. It is also argued that these organisms are picked up as prostatic fluid passes through the urethra. The significance of gram-positive cocci in patients with chronic prostatitis has been debated for most of the 20th century. As described above, gram-positive cocci were accepted as etiologic agents for most of the century. However, over the last 3 decades, the consensus was that these organisms are seldom, if ever, causative. However, it is now generally agreed that *Enterococcus faecalis* may cause chronic bacterial prostatitis and related recurrent enterococcal bacteriuria.[31,33] In our 1992 study,[54] we isolated coagulase-negative bacteria in cultures of EPS as well as identified similar organisms in sparse and focal microcolonies in prostate biopsy specimens. Others have also implicated coagulase-negative *Staphylococcus* in this disease.[55,56]

Chlamydia trachomatis has been identified as a possible causative agent in many cases of chronic prostatitis, yet the evidence is confusing. Mardh and Colleen[57] found that one third of men with chronic prostatitis had antibodies to *C trachomatis,* compared with 3% of controls. Shortliffe and associates[58] found that 20% of patients with nonbacterial prostatitis had antichlamydial antibody titers in the prostatic fluid. Bruce and co-workers[59] found that 56% of patients with subacute or chronic prostatitis were infected with *C trachomatis* (identified from early morning urine, prostatic fluid, or semen). In a follow-up study, Bruce and Reid[60] found that 6 of 55 men with abacterial prostatitis, including 31 believed to have chlamydial prostatitis, met strict criteria for positive diagnosis of chlamydial prostatitis based on identification of the organisms by culture or immunofluorescence. Kuroda and colleagues[61] identified *C trachomatis* in the urethras of 20% of men with prostatitis.

Other investigators have reached similar conclusions.[62,63] Poletti and associates[64] isolated *C trachomatis* from prostate cells obtained by transrectal aspiration biopsy of the prostates of men with nonacute abacterial prostatitis. Abdelatif and co-workers[65] identified intracellular *Chlamydia* employing in situ hybridization techniques in transurethral prostate chips from 30% of men with histologic evidence of chronic abacterial prostatitis. Shurbaji and associates[66] identified *C trachomatis* in paraffin-embedded sections from 31% of men with histologic evidence of prostatitis, compared with none of patients with benign prostatic hyperplasia (BPH) without inflammation. Koroku and colleagues[67] detected *C trachomatis*- specific IgA in 29% of men with chronic nonbacterial prostatitis. All these studies suggest that *Chlamydia* may invade the prostate, that chlamydial antigen can be detectable in prostate-specific specimens, and that the presence of *Chlamydia* may be related to the development of chronic prostatitis.

Many investigators have suggested that *Ureaplasma urealyticum* may be an important cause of chronic prostatitis. Weidner and associates[68] found high *U urealyticum* concentration in prostate-specific specimens in patients with signs and symptoms of abacterial prostatitis. Fish and Danziger[69] found significant *U urealyticum* concentrations in 13% of patients with prostatitis. Treatment with specific antimicrobial therapy cleared the organisms in all cases and resolved the symptoms of prostatitis in 75%. Isaacs[70] cultured *U urealyticum* from prostate secretions in 8% of patients with chronic nonbacterial prostatitis.

A number of observations support an association between *Trichomonas vaginalis* and prostatitis.[71-74] In one study, the prevalence of *Trichomonas* exceeded 85% in men who had symptoms of prostatitis that persisted despite their receiving antibacterial therapy.[75]

Anaerobic bacteria,[76] yeast such as *Candida,*[77-79] and viruses[80,81] have also been implicated in prostatic inflammation. Similarly, diphtheroids and *Corynebacterium* species,[82,83] usually acknowledged as prostate nonpathogens, have also been suggested as potential etiologic agents in this disease. Domingue and colleagues[82] suggest that the difficult-to-culture coryneforms could be missed by routine culture of EPS. Direct Gram's staining of the EPS showed gram-variable pleomorphic coccobacillary rods that do not grow on routine media. The presence of these pleomorphic swollen rods was also shown by fluorescent acridine orange staining. Biochemical identification of these organisms indicated two different species of *Corynebacterium.* Employing an rRNA-based molecular phylogenetic approach to the identification of bacteria in prostatic fluids from patients with prostatitis, Tanner and co-workers[84] noted positive bacterial signals, primarily related to *Corynebacterium,* in 65%. We may also not be culturing the bacteria because cell wall-deficient microorganisms[85] may be implicated in this disease.

It has also been suggested that we may not be growing the bacteria because they exist in aggregated "biofilms" adherent to the prostatic ductal walls or within obstructed ducts in the prostate.[86,87] Nickel and Costerton[86] reported that 60% of patients with previously diagnosed chronic bacterial prostatitis who progressed to having sterile EPS cultures but had continued symptoms despite antimicrobial therapy had positive cultures (similar to the initial organism) from prostate biopsy specimens. Berger and associates[88] cultured urethral, urine, and transperineal prostate biopsy specimens specifically for commensal and fastidious organisms. These investigators demonstrated that men with EPS indicating inflammation were more likely to have bacterial isolation, positive cultures for anaerobic bacteria, higher total bacteria counts, and more bacterial species isolated in prostate biopsy cultures than men without EPS indicating inflammation. These observations support the concept of bacterial colonization/invasion of the prostate and may be associated with negative EPS cultures.

Krieger and co-workers[89] used a combination of clinical, culture, and molecular biologic methods (polymerase chain reaction [PCR]) to evaluate a well-defined population of men with chronic idiopathic prostatitis. Prostate biopsy tissue was obtained using a double-needle technique to limit potential contamination and evaluated using PCRs for *C trachomatis, T vaginalis, Mycoplasma,* herpes simplex viruses, and cytomegaloviruses, as well as broad-spectrum PCRs for both tetracycline-resistant and 16S rRNA. Of the 135 subjects this group evaluated, 8% had positive PCR assays for one or more specific microorganisms. The broad-spectrum PCRs demonstrated tetracycline-resistant and coding sequences in 25% of subjects and 16S rRNAs in 77% of the patients.

The results of these two PCR techniques were highly correlated. The investigators also found a strong correlation between inflammation and EPS and detection of 16S rRNA and prostate tissue. These findings further suggest that the fastidious and nonculturable microorganisms might be important in the etiology of chronic inflammatory prostatitis.

It has been estimated that less than 10% of all environmental bacteria have been identified, so it is inevitable that we have not yet identified potential prostate-specific pathogens.[85] The evidence presented here strongly suggests that chronic idiopathic prostatitis may in many, most, or even all cases represent an infectious disease (Table II).

While much of the evidence discussed in the previous section is provocative and certainly can lead one to the conclusion that prostatitis is an infectious disease, substantial evidence exists that points to exactly the opposite conclusion: prostatitis is not an infectious disease.

Numerous studies have pointed out that antibiotic therapy for prostatitis associated with a cultured uropathogen produces dismal long-term results.[50] Although eradication of bacteria is successful in 40% to 80% of cases, the long-term resolution of symptoms and the effect on long-term relapse rates is questionable (in most cases, unknown). In fact, numerous studies have demonstrated that patients with chronic nonbacterial prostatitis have the same symptom improvement rate as those patients treated for cultured pathogens (ie, chronic bacterial prostatitis).[50,90] It could be suggested that this response rate of 30% to 40% in both categories may represent the placebo response, such as seen in other benign prostatic diseases.[91]

Most patients with a diagnosis of chronic bacterial prostatitis have a history of recurrent bacterial cystitis.[92-94] However, these patients are usually asymptomatic between episodes of UTIs. During UTIs, cystitis can be cleared with an antibiotic such as nitrofurantoin, and the bacteria will be cultured subsequently in prostate-specific specimens. In patients who are not suffering from an acute UTI episode, the bacteria can also be cultured from the prostate-specific specimens. The inference, then, is that the bacteria associated with chronic bacterial prostatitis persist in the prostate gland without producing symptoms and really only act as a reservoir for recurrent lower UTIs in the bladder. The majority (95% at least) of patients with prostatitis syndrome do not have uropathogenic bacteria localized to their prostate-specific specimens, nor do they suffer from recurrent lower UTIs.

In the previous section, evidence that a variety of microorganisms might be implicated in prostatitis was presented. The other conclusion that can be drawn from the same data is that these organisms are indeed present in the prostate gland in patients with prostatitis but that they might just be innocent bystanders. Perhaps control patients without evidence of prostatitis also have similar colonization of the prostate gland. There might indeed be a normal flora (as there is in the urethra) within the prostate gland. Is there any evidence to suggest this?

Histologic evidence of prostatic inflammation is often present in biopsy, surgical, or autopsy material. Inflammation in autopsy series is reported between 5% and 15% in patients over 60 years of age,[95] while McNeal[96] found inflammation in 44% of sampled adult prostates obtained at autopsy. Evidence of prostatic inflammation was noted in 45% of aspiration biopsy specimens taken because of suspicion of carcinoma.[97] Kohnen and Drach[98] discovered that up to 98% of surgically resected prostates removed for BPH contained at least some foci of significant prostatic inflammation. This finding has been confirmed by other researchers.[99] Bacteria, uropathogenic or otherwise, have also been documented in BPH without symptoms of prostatitis. Gorelick and associates[100] discovered that 21% of patients undergoing prostatectomy yielded positive, single-organism bacterial growth in prostate tissue. In a study recently completed in our institution, we noted that 100% of specimens demonstrated some degree of prostatic inflammation, while 44% of the prostate specimens demonstrated bacterial growth.[101] Eighty-seven percent of the organisms cultured from the deep prostatic chips were potentially uropathogenic. These findings suggest that inflammation and bacteria (uropathogenic and nonuropathogenic) are routinely associated in the prostate glands of asymptomatic men.

Although Mardh and Colleen[57] suggested that *C trachomatis* may be implicated in as many as one third of men with chronic prostatitis, their follow-up studies using cultures and serology could not confirm *C trachomatis* as a causative agent in idiopathic prostatitis.[102-104] Berger and colleagues[105] could not culture *C trachomatis* from the urethra in

men with chronic prostatitis nor did they find a serologic or local immune response to *C trachomatis* in such patients. Shortliffe and co-workers[45] came to a similar conclusion when they evaluated antichlamydial antibody titers in prostatic fluid. Twelve percent of controls (compared with 20% of patients with nonbacterial prostatitis) had detectable antibodies.

Doble and associates[106] were not able to culture or detect *Chlamydia* by immunofluorescence in transperitoneal biopsies of abnormal areas of the prostates of men with chronic abacterial prostatitis. Although in the previous section evidence was presented that *Chlamydia* may be related to the development of chronic prostatitis, many of these studies had absent or inappropriate controls, did not control for urethral contamination, and employed many different techniques of variable sensitivity and specificity to detect *Chlamydia.* Krieger and colleagues[89] were only able to find *Chlamydia* in 1% of prostate tissue biopsy specimens from men with chronic prostatitis.

Similarly, the data on *U urealyticum* as a causative agent in chronic prostatitis are suspect. Other investigators were unable to implicate *U urealyticum* in patients with nonbacterial prostatitis.[107,108]

T vaginalis has also been suggested (see previous section) as a possible cause of prostatitis.[71-73] While it is accepted that this microorganism can cause urethritis, Krieger and Egan[35] seldom isolated *T vaginalis* from the urethras of men with chronic prostatitis syndrome. The precise role of *T vaginalis* in nonbacterial prostatitis remains undefined.

Most investigators believe that coagulase-negative staphylococci localized to prostate-specific specimens, including those from prostate biopsies, represent only colonization. Some investigators found that staphylococci (in this case, *S saprophyticus*) disappeared from the male genital tract without any treatment at all.[55]

The study suggesting that anaerobic bacteria caused prostatitis[76] has been criticized because the investigators employed outdated bacteriologic methods.

In the previous section, the provocative work employing molecular biologic techniques by Krieger and co-workers[89] suggested that fastidious or nonculturable microorganisms might be important in chronic abacterial prostatitis. However, it may be that these findings represent contaminants. The method of PCR testing done in the study is extremely sensitive to contamination, although the investigators did control for it as much as possible. More important is the fact that just finding 16S rRNA or DNA sequences in prostate biopsy specimens from patients with chronic prostatitis does not establish an etiologic basis for these microorganisms. Keay and colleagues[109] have repeated similar studies in patients with prostate cancer without evidence of prostatitis and found very similar results. A conflicting study by Hochreiter and associates,[110] employing similar PCR methods, failed to duplicate these results, and these authors feel there is not a normal bacterial flora in the prostate gland.

These studies, therefore, suggest that the normal prostate in asymptomatic men may have a commensal population of bacteria and that focal prostatic inflammation is a ubiquitous finding (if one looks for it) in all or most men. In some patients who have prostate colonization by uropathogenic organisms (very rare), the bacteria act as a silent reservoir for recurrent UTIs. If this is the case, then we must look elsewhere to explain the symptom complex we observe in patients presenting with a "chronic prostatitis syndrome."

Is chronic prostatitis an infectious disease? It can be appreciated that the etiologic basis of chronic prostatitis symptoms has been poorly understood. Unfortunately, the field still remains confusing. Evidence can be found in the research literature to support the traditional dogma (that approximately 5% of chronic prostatitis is an infectious disease), or the hypothesis that chronic prostatitis is an infectious disease (but we are just not culturing or identifying the organisms in the majority of cases), or the theory that chronic prostatitis does not represent an infectious disease at all (and any microorganisms we may identify are innocent bystanders or normal flora and are not associated with the symptomatology). Is chronic prostatitis an infectious disease? As we enter the 21st century, that question remains unanswered.

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