

Semen and Urine Culture in the Diagnosis of Chronic Bacterial Prostatitis

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ABSTRACT

Objective: To assess the diagnostic accuracy of semen and urine culture in the diagnosis of chronic bacterial prostatitis (CBP).

Materials and Methods: In 70 consecutive men suspected of having chronic bacterial prostatitis along with 17 asymptomatic controls, we obtained urine and semen cultures followed 1 week later by the Meares and Stamey test, our reference standard. The interpretation of each of the cultures was blind to the results of other tests.

Results: 139 men were referred for evaluation of chronic bacterial prostatitis and 70 received all tests. Additionally, 17 control men volunteered to participate. The Meares and Stamey Test was positive in 69 (79%) patients. The semen culture had a sensitivity of 45% and a specificity of 94%. The likelihood ratio associated with a positive semen culture was 8.1 (95% confidence interval (CI) 1.2 to 55.3); the likelihood ratio associated with a negative semen culture was 0.6 (95% CI 0.5 to 0.7). The urine culture had a sensitivity of 4% and a specificity of 100%. The likelihood ratio of a positive urine culture was infinity and of a negative urine culture was 0.96 (95% CI 0.9 to 1).

Conclusions: While a positive semen culture in a symptomatic patient may suffice to select and start antibiotic treatment against chronic bacterial prostatitis, a negative culture does not rule out the condition. Urine cultures alone are not useful for diagnosing CBP. The Meares and Stamey test remains important for the diagnosis of CBP in practice.

Key words: urinary tract infections; prostate; prostatitis; diagnosis; laboratory techniques and procedures
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INTRODUCTION

Chronic prostatitis (CP) is a very common urologic diagnosis in men (1, 2), with 50% of men having this condition at some point in their life (3). Men with chronic prostatitis experience a similar loss in quality of life that survivors of recent acute coronary syndromes do (4).

Chronic bacterial prostatitis (CBP) or chronic prostatitis category II (5) is defined in men with documented recurrent urinary tract infections (UTI)

who may be asymptomatic between episodes, or may present chronic genitourinary pain for more than 3 months in association with bacterial isolation from the prostate (6-8). About 10% of cases of CP have a bacterial etiology. *Escherichia coli* accounts for up to 80% of cases of (CBP) (6).

In 1968, Meares and Stamey described the four-glass test, which continues to be the reference standard test for CBP. This test localizes the inflammatory and bacteriologic focus along the lower urinary tract and prostate (9). The cost, inconvenience

and discomfort to patients, however, decrease its feasibility in practice: a survey of U.S. urologists found that 80% hardly ever used the Meares and Stamey test to diagnose CBP (10). Simpler tests including modifications of the original technique such as the pre and post massage test (11), expressed prostatic secretion culture, semen culture, and urine culture, while more feasible, convenient, or inexpensive, seem unsatisfactory alternatives. The reported sensitivity of semen culture to the diagnosis of CBP varies between 10 and 100% (12 - 14), and that of urine culture is 10% (13).

In our urology referral service, we have noticed that patients referred with the tentative diagnosis of chronic bacterial prostatitis that were ultimately found to have a positive Meares and Stamey test had a prior negative semen and urine culture. Therefore, we sought to determine the diagnostic accuracy of the semen and urine cultures compared to the Meares and Stamey test in the diagnosis of CBP.

MATERIALS AND METHODS

This is a prospective test performance study. The institutional ethics committee approved the protocol and consent procedures used in this study.

We enrolled consecutively 70 adult men attending the Urology and Oncology Service of Cayetano Heredia National Hospital, in Lima, Peru from September 2003 to October 2004 who had clinical suspicion of CBP on the basis of recurrent episodes of UTI and/or symptoms of chronic genitourinary pain within the last 3 months localized in the perineum, suprapubic area, penis, testes, groin, low back, or pain during or after ejaculation. Patients gave written informed consent to participate in this study.

In order to assess the discriminatory capacity of the semen and urine cultures, we additionally enrolled 17 asymptomatic adult men who volunteered to participate in this study and who did not have any history of previous UTI or chronic genitourinary pain.

Ineligible patients showed evidence of other infections received antibiotic treatment within the month prior to the study, used urinary catheters or

other urological devices, had undergone prostatectomy, or had prostate cancer. After a complete physical and urological examination, the participants completed the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) (15, 16).

In order to evaluate the diagnostic performance of semen and urine cultures, we developed an Alternative test based on the Meares and Stamey test. Table 1 describes how the samples were collected for our alternative test.

The samples were examined directly and cultured. For the Alternative test, we considered the test positive when: 1) there were bacteria in the semen sample; and 2a) no bacteria was found in the VB1 and VB2 samples or 2b) the bacterial colony count in the semen sample was ≥ 10 times that in the VB1 and VB2 specimens. The VB3 sample was not considered in the analysis of the results of the semen culture. VB2 cultures were the urine cultures for this study. Positive urine cultures had colony counts $\geq 10^5$ UFC/mL.

The Meares and Stamey test was taken as our standard. It was performed according to the standard procedure (Table-1) (9) and one week after the Alternative test to avoid contamination of the semen sample by the prostatic secretion. None of the patients received any antibiotic therapy during this week. For the Meares and Stamey test, we considered the test positive if there was a 10-fold increase in bacteria in the expressed prostatic secretion (EPS) or in VB3 samples compared with the VB1 and VB2 specimens.

All the samples of this study were centrifuged and seeded on blood agar and McConkey media with standard biochemical tests to characterize bacteria. Additionally, the presence of over 10 leukocytes per high-power field (X40) in the expressed prostatic secretion sample indicated prostatitis (17, 18).

All the processing and reading of the samples of this study were performed by the same expert microbiologist who was blinded to the patient's history and results of previous tests. Samples from the Alternative test received a different codification from those of the Meares and Stamey test in order to guarantee the independent interpretation of the results.

Finally, we defined CBP as the presence of 1) a positive result in the Meares and Stamey test and 2a) the presence of recurrent episodes of UTI

Table 1 – Procedures for obtaining the samples for our Alternative Test and the Meares and Stamey reference test.

Alternative Test	Meares and Stamey Test
1. Urethral urine - the first 10 cc urine (voided bladder 1 or VB1)	1. Urethral urine - the first 10 cc urine (voided bladder 1 or VB1)
2. Mid-stream urine – 10 cc of urine after the man voids 150 cc (voided bladder 2 or VB2)	2. Mid-stream urine - 10 cc of urine after the man voids 150 cc (voided bladder 2 or VB2)
3. Semen sample obtained by masturbation	3. Expressed prostatic secretion sample post prostatic massage
4. Post-ejaculation urine – collected immediately after ejaculation (voided bladder 3 or VB3)	4. Urine post prostatic massage - 10 cc urine post massage (voided bladder 3 or VB3)

or 2b) symptoms of already described chronic genitourinary pain.

Statistical data were gathered into a Microsoft Excel XP database and transferred to the version 9STATA software. We use descriptive statistics to characterize the study population, and we compare the characteristics of those with and without documented chronic bacterial prostatitis using either the chi square test (for proportions) or the independent sample t-test (for continuous variables). We also estimated the sensitivity and specificity of each test (and their corresponding 95% confidence intervals) compared with the reference standard, and calculated the likelihood ratios associated with a positive and a negative semen culture. The likelihood ratio of a test result is the ratio of the proportion of patients with CBP who had the test result to the proportion of patients without CBP who had the same result (19).

We used likelihood ratios because of their advantages in the assessment of diagnostic tests, i.e., they are less likely to change with the prevalence of the disease, they can be calculated for several levels of symptoms, signs or tests, and they can be used to calculate post-test probability for a target disorder (20).

RESULTS

We assessed 139 consecutive men referred for symptoms consistent with chronic prostatitis, but

only 70 of them completed all the tests and were considered in the study. We additionally enrolled 17 asymptomatic patients that volunteered to participate. The mean age of the population was 37.5 years (\pm 9.7). Table-2 describes the population by their clinical presentation. The means and standard deviations of the NIH-CPSI scores are also shown.

The Meares and Stamey test was positive in 69 patients. Forty-four had gram-negative bacteria, and 25 had gram-positive bacteria. The isolated bacteria were *Escherichia coli* in 32, *Enterococcus* sp. in 13, *Staphylococcus aureus* in 10, *Klebsiella* sp. in 7, *Enterobacter* sp. 4, *Streptococcus* Group D in 1, coagulase-negative *Staphylococcus* in 1 and *Proteus vulgaris* in 1. The results of the gold standard and semen cultures in the symptomatic and asymptomatic patients are shown in Table-3. There was coincidence in the bacteria isolated in the Alternative test and their corresponding isolates in the reference standard, except for one patient who presented *S. aureus* in the semen culture and *E. coli* in the Meares and Stamey test. Although we performed a VB3 sample as part of our Alternative test, we did not consider it in the analysis of the semen cultures. It was found positive only in 9 of the 32 patients with positive semen cultures, with a bacteriologic correlation of 100%.

Table-4 describes the performance of the semen culture in comparison to the reference standard. It shows a semen culture sensitivity of 45% (95% CI

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Table 2 – Clinical and demographic differences among symptomatic and asymptomatic patients.

	Symptomatic Patients		Asymptomatic Patients		p Value
	N = 70		N = 17		
Age in years (SD)	36.6		41.1		0.08
	N	%	N	%	p Value
More than one sexual partner	8	11.59	2	11.6	0.98
Background of UTI	61	87.1	0	0	<0.001
Partner with leucorrhea	20	28.6	8	47	0.15
Total NIH-CPSI score(SD)	19.9 (7.97)		6.8 (5.6)		<0.001
	N	%	N	%	p Value
Physical exam					
Abdominal pain	11	15.7	0	0	0.08
Pain in the penis	9	12.9	0	0	0.12
Right testis pain	4	5.7	3	17.6	0.1
Left testis pain	9	12.9	2	12	0.1
Pain in the prostate	8	11.4	3	17.6	0.5

SD = standard deviation, UTI = urinary tract infections, NIH-CPSI = National Institute of Health – Chronic Prostatitis Symptom Index.

33.8% to 56.6%), specificity of 94% (95% CI 74.2% to 99%), a likelihood ratio associated with a positive semen culture of 8.1 (95% CI 1.2 to 55.3), and likelihood ratio associated with a negative semen culture of 0.6 (95% CI 0.5 to 0.7).

Figures-1 and 2 show how the post-test probability of having CBP varies compared to the different pre-test probabilities (clinical suspicion) according to the likelihood ratios.

The performance of the urine culture in relation to the Meares and Stamey test is shown in Table -5. We found a sensitivity of 4.3% (95% CI 1.5% to 12%), a specificity of 100% (CI 82.4% to 100%), an infinite likelihood ratio of a positive urine culture and a 0.96 (95% CI 0.9 to 1) likelihood of a negative urine culture.

Finally, the leukocyte count per high power field in expressed prostatic secretions showed that 64

Table 3 – Laboratory results in symptomatic and asymptomatic patients.

Laboratory Results	Symptomatic Patients		Asymptomatic Patients		p Value
	N = 70		N = 17		
Meares and Stamey test	N	%	N	%	p Value
Positive	67	95.7	2	11.8	< 0.001
Negative	3	4.3	15	88.2	< 0.001
Leukocyte count (SD)	24.9 (11.3)		6.2 (8.4)		p Value
Semen culture	N	%	N	%	
Positive	31	44.3	1	5.9	< 0.001
Negative	39	55.7	16	94.1	0.01
Leukocyte count (SD)	6.44(7.34)	1.8(2.83)			

Table 4 – Semen culture results vs. Meares and Stamey test.

Semen Culture	Meares and Stamey		Total
	Positive	Negative	
Positive	31	1	32
Negative	38	17	55
Total	69	18	87

Sensitivity: 45% (33.8% - 56.6%), Specificity: 94% (74.2% - 99%), LR (+): 8.1 (1.2 - 55.3), LR (-): 0.6 (0.5 - 0.7). LR: Likelihood ratio, LR (+): Is the ratio of the proportion of patients with chronic bacterial prostatitis (CBP) with a positive semen culture, to the proportion of non-diseased males who also had a positive result., LR (-): Is the ratio of the proportion of patients with CBP with a negative semen culture, to the proportion of non-diseased males who also had a negative result.

(91.4%) of the symptomatic males and only 2 (11.7%) of the controls had prostatic inflammation according to our criteria ($p < 0.001$). When we changed our parameters to 5 or more leukocytes per high power field, the number of patients with inflammation increased to 67 (95.7%) and 7 (41.1%) respectively (p

< 0.001). The leukocyte count mean in the EPS sample from the symptomatic patients was significantly higher than in asymptomatic males; $24.9 (\pm 11.3)$ vs. $6.2 (\pm 8.4)$, $p < 0.001$. No other significant difference was seen at the time we compared the leukocyte counts in the other samples obtained in this study.

COMMENTS

In our sample, 77% of patients had CBP according to their symptoms and results in the Meares and Stamey test. The semen and urine cultures revealed limited diagnostic properties. Our results argue that a negative semen culture is not an adequate test to rule out CBP, particularly in patients with high pre-test probability (i.e., men with classic symptoms). On the other hand, a positive semen culture greatly increases the post-test probability of CBP and may orient the choice of antibiotic therapy obviating the need for the cumbersome reference standard test.

Figures-1 and 2 help the clinician determine how the likelihood ratios associated with the semen culture results determine the post-test probability of

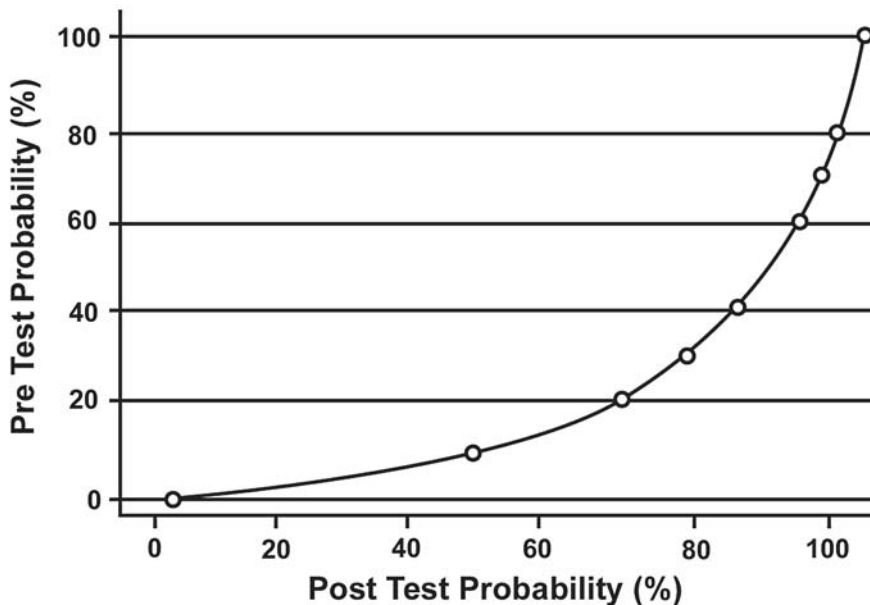


Figure 1 – Post-test probability determined by the Likelihood ratio of a positive semen culture (8.1), in patients with varying pre-test probabilities.

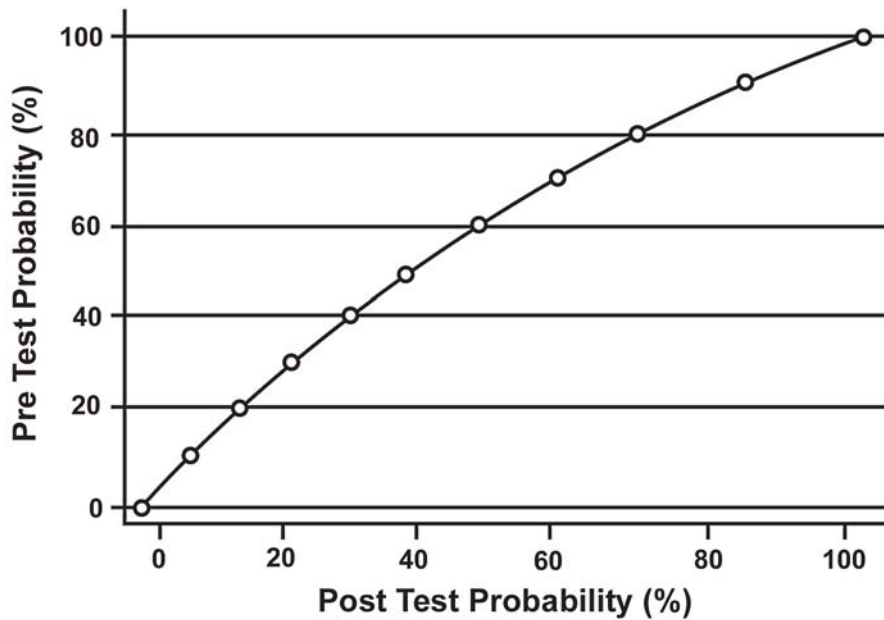


Figure 2 – Post-test probability determined by the Likelihood ratio of a negative semen culture (0.6), in patients with varying pre-test probabilities.

having CBP in patients with varying pre-test probabilities.

The performance of the urine culture is poor when used alone to diagnose CBP. In our opinion, its utility in CBP is only in determining the presence of an active UTI, and then must have negative or very low counts in order to correctly interpret the results of the Meares and Stamey tests.

Table 5 – Urine culture results vs. Meares and Stamey test.

Urine Culture	Meares and Stamey		Total
	Positive	Negative	
Positive	3	0	3
Negative	66	18	84
Total	69	18	87

Sensitivity: 4.3% (1.5% - 12%), Specificity: 100% (82.4% - 100%), LR (+) Undefined LR (-) 0.96 (0.9 - 1), LR: Likelihood ratio, LR (+): Is the ratio of the proportion of patients with chronic bacterial prostatitis (CBP) with a positive urine culture, to the proportion of non-diseased males who also had a positive result. LR (-): Is the ratio of the proportion of patients with CBP with a negative urine culture, to the proportion of non-diseased males who also had a negative result.

With respect to the presence of prostatic inflammation, it was found that out of a total of 69 patients with positive Meares and Stamey test, 66 patients suffered from prostate inflammation. Of the 3 patients who did not present inflammation according to our definition, 2 had low growth cultures in the EPS samples (5000 and 10000 ufc/cc), which reflects a good correlation between the microbiological results and the presence of prostatitis (17, 18).

Our study applies to the urological referral population in a South American country. The extent to which these results apply to other patients depends on the extent to which they share similar clinical presentations, referral patterns, and bacteriology. On the other hand, our study is strengthened by the evaluation of both alternative and reference standard tests in patients where there was suspicion of CBP as well as in asymptomatic patients, with blind interpretation of the results. Establishing the timing of the samples so that the Meares and Stamey test always followed the alternative test prevented contamination of the samples for the alternative test from expressed prostatic secretions.

The semen culture sensitivity in our study was 44%, which is lower than the sensitivity described by

Budia et al of 100% (14). One explanation is that the semen culture in Budia et al was obtained after the Meares and Stamey test and could have been “contaminated” by expressed prostatic secretions. This would decrease the independence between the test and the reference standard, a known cause of bias (21).

A previous study has shown no differences in the rates of localization of bacterial cultures for men with chronic prostatitis/chronic pelvic pain syndrome or CP category III compared to control men (22), but in our study, 95.7% of the symptomatic males and only 11.8% of the controls had bacterial growth in the Meares and Stamey test. The underlying explanations for these findings could be that we included a different set of patients with a higher possibility of having CBP due to their history of recurrent episodes of UTI and that our controls were healthy asymptomatic men with no urological complaints or previous UTI. Only two of our patients with CBP had EPS cultures with the so-called non-uro pathogens (Streptococcus group D in 1 and coagulase-negative Staphylococcus in 1) (23), and could be labeled as contaminated samples – a category that we would disagree with due to their corresponding leukocyte count which was significant for inflammation.

Although one of our limitations is not having followed the response of our symptomatic patients to their antibiotic treatment, we consider that our results still reflect the pathogenic role of these organisms in the development of CBP.

A significant difference was also found in the leukocyte count of the EPS and semen samples between the symptomatic and asymptomatic patients – results that differed from the ones reported in association with CP category III (22), but otherwise consistent with the isolation of bacteria in our patients with chronic bacterial prostatitis. Using our definition of more than 10 leukocyte per high power field as a parameter of prostatic inflammation, we found prostatitis in 91.4% of our symptomatic patients, and when we changed the cut-off to more than 5 leukocytes per high power field, the frequency increased to 95.7% – a prevalence that differs from the 31% and 49% previously reported by the NIH

chronic prostatitis cohort study (23), and can be related to the presence of pathogenic bacteria and CBP in almost all our symptomatic patients.

CONCLUSIONS

While a negative semen culture does not rule out CBP, a positive test in a patient with high pre-test probability of CBP may be sufficient to select and start antibiotic treatment. Urine culture cannot be used alone in the diagnosis of CBP. The Meares and Stamey test, in spite of its difficulty and discomfort for the patient, remains the reference standard for diagnosing CBP in clinical practice.

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CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

This interesting study follows the traditional viewpoint that bacteria found in semen have clinical relevance in the generation of symptoms in men. The well conducted study from the NIH collaborative group showed that both symptomatic and asymptomatic men had similar bacterial counts in their semen, suggesting that these bacterial commensals have nothing to do with the generation of symptoms seen in these men.

This study basically attempts to reproduce the traditional belief, but adds the wrinkle of comparing the Meares and Stamey test with their own modifications.

Although the study is of interest, one weakness should be mentioned: i.e. the semen bacteria may have nothing to do with the disease process.

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EDITORIAL COMMENT

Prostatitis is a very challenging disease. The causes are not known and diagnostic methods are difficult to apply. The survey of U.S. urologist found that 80% hardly ever used the Meares & Stamey test to diagnose chronic bacterial prostatitis. In this issue, the article by Zegarra Montes et al. addresses an important issue regarding finding more feasible methods to diagnose chronic bacterial inflammation. Semen sample was used instead of expressed prostatic secretion sample. The alternative test did not outdo the Meares & Stamey test in the sensitivity. While a positive semen culture in a symptomatic patient may justify the treatment with antibiotics, a negative culture does not rule out the condition. Relatively small and regional study population and selection of the samples may account for the differences with previous studies showing higher sensitivity for the use of semen. It is obvious that carefully conducted large cohort studies are required in order to assess the accuracy of traditional methods vs. urine and semen cultures to establish the significance of acute or chronic prostatitis. Careful localization cultures of urine, expressed prostatic secretion, and semen along with the antimicrobial susceptibility combined with clinical symptoms remain

clinically important in management of prostatic infections. Follow up of anti-microbial or anti-inflammatory therapies would also be important when correlated with the diagnosis.

Only a small percentage of all prostatitis cases involve proven bacterial infection. Prostatitis is a much wider diagnostic and therapeutic problem. The classification of National Institutes of Health (NIH) divides prostatitis into four categories. The differentiation between the categories is based on the presence or absence of bacteria, leukocytes, and clinical symptoms. Category I (acute bacterial prostatitis) and Category II (chronic/recurrent bacterial prostatitis) have infectious etiologies. Category III refers to chronic nonbacterial prostatitis/chronic pelvic pain syndrome (CP/CPPS). The differentiation between IIIa and IIIb is based on the finding of inflammatory cells in EPS or voided specimen 3. Category IV refers to asymptomatic inflammatory prostatitis that is diagnosed incidentally during evaluation of the patient for other purposes.

Recent studies have presented problems with this classification system (1,2). Prostate biopsies from patients with non-inflammatory CPPS (category IIIb) display a low-grade inflammation with diffuse

distribution of lymphocytes into the stroma and periglandular space. Inflammation appears to be common in both forms of category III. The traditional marker of inflammation, leukocytes in the prostatic fluid, does not correlate with the predominant symptom of pelvic pain. Schaeffer et al. (3) assessed the relationship between leukocytes and bacteria and symptom severity in men with CP/CPPS. They observed no association between inflammation in any of the specimen sites and symptoms. Further, no association between bacterial colonization and symptoms were observed. Tsuboi et al. (4) found no correlation between the aggressiveness and extent of inflammation and leukocyte count in prostatic fluid. Neither a correlation was found between the number of leukocytes in EPS and the histopathology of the prostate. The study by True et al. (5) examined correlations between the symptoms and histology of prostatitis and suggested that histologic inflammation may not be a significant factor in the process of CP/CPPS. This findings extended by the large scale REDUCE trial data which suggest that presence of chronic prostatitis-like symptoms did not provide any discriminative value for a histologic diagnosis of either acute or chronic inflammation (6). One has to conclude that leukocytes and bacteria in the prostatic fluid do not distinguish between symptomatic and asymptomatic individuals. Moreover, the lack of or weak correlation between inflammation and infection with severity of symptoms implies that factors other than inflammation and infection contribute to symptoms associated with CP/CPPS (3).

Histologic inflammation may not be important for the development of chronic pelvic pain but it may bear other significances. There is emerging evidence that inflammation in the prostate gland may be associated with BPH, voiding dysfunctions and prostate cancer. Chronic inflammatory infiltrates have been associated with human BPH nodules, and it is likely that gradual infiltration of the prostate by lymphocytes leads to BPH (7). Results from the REDUCE trial confirmed the important role of inflammation in BPH (6). A statistically significant correlation was found between histological grade of chronic prostatic inflammation and lower urinary tract symptoms (8). The correlation was weak but did not

preclude the possibility that histopathological inflammation may be strongly correlated with changes over time. Patients with chronic prostatitis may be more likely to develop bladder dysfunction, bladder outlet obstruction or urinary retention than men without inflammation. Finally, accumulating evidence indicates the significance of inflammation in human prostate carcinogenesis. Chronic or recurrent acute inflammation, a product of infectious agents or other sources, has potential promotional roles in the development of prostate cancer (9).

There is evidence predominantly from animal studies that the nonbacterial prostatic inflammation results from an autoimmune process (10). The onset of autoimmune reaction may be triggered by an infection through antigen mimicry. Although no microorganisms are detectable, it has been suspected that an infection (occult, unculturable, or regarded as non-pathogen) may be responsible for the changes in immunological parameters (11). The infectious and autoimmune etiologies would thus be compatible. Further, the possible autoimmune process may be under the hormonal control. Findings in preclinical models indicate that the balance between immunosuppressive androgens and pro-inflammatory estrogens may be of particular importance (12,13). Finally, intraprostatic reflux of urine or semen may produce a chemical injury to the epithelium that initiates the immunological reaction. There may be several triggers of inflammation, which act in concert simultaneously or sequentially.

If inflammation is indeed in causal relationship with BPH and prostate cancer, anti-inflammatory agents should be investigated as drug candidates for the treatment and prevention of BPH and prostate cancer (6,9).

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