Changing concepts on prostatitis

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Abstract

Comparatively little research has been directed to the pathogenesis and treatment of prostatitis, an infectious, inflammatory disabling condition that can cause considerable pelvic pain, with a range of associated symptoms that can influence 50% of all men at some period in their lives, often in their earlier adult years. This review considers the impact of prostatitis on patients and highlights the clear need for clinical research to enhance our understanding of the underlying biology of this ubiquitous disease. New insights into the molecular events that may be implicated in its pathogenesis, suggest that more rational treatment options could well be developed, but throughout, there is the recognition that prostatitis still remains an enigma.

Key words: prostatitis, inflammation, pathogenesis, prevention, treatment.

Some introductory issues

Prostatitis, a relatively common disease associated with the prostate, is an infectious, inflammatory disabling condition that can cause considerable pelvic pain. In comparison to research on BPH and prostate cancer, prostatitis remains the poor cousin, despite symptoms influencing nearly 50% of all men at some period of life [1]. It is the most commonly diagnosed urological disorder in men younger than 50 [2]. Surprisingly, it is stated in the report [3], that there can be more physician visits by patients suffering from prostatitis, than for either BPH or cancer. It seems appropriate, therefore, to re-kindle interest in prostatitis as molecular biology uncovers fresh insights into its biology. Furthermore, a renewed interest in patients presenting with prostatitis could further enhance the shared-care concept between the urologist and primary healthcare clinician and highlight the need for more clinical research into this ubiquitous condition.

The prostate gland: some anatomical reflections

A younger adult man's prostate, the size of a large 20 gm. walnut, is located just below the bladder and in front of the rectum, with the urethra passing urine directly through its centre. This is not the case with other animals and possibly only in man and dog [4], does the urethra pass directly

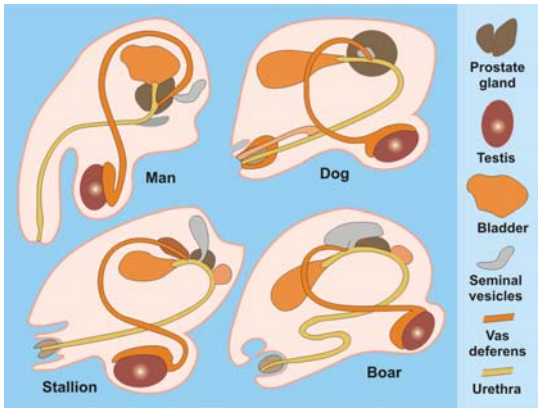

Figure 1. Schematic representation of the genital tracts of various animals to illustrate the passage of the ductus deferens through the prostate of man and dog [4]

through the centre (Figure 1). Whether this intimate relationship between the urethra and the prostate, impinges on the aetiology of prostate disease, remains open to conjecture. Interesting, however, is that both man and dog seem alone in their susceptibility to prostate hypertrophy [5] and species in which the vas deferentia pass through the prostate to reach the urethra. Attention was directed [4] to a link between the canine testis and prostate by the excurrent duct system, seminiferous tubules, rete testis, vas efferentia, epididymal ducts and vas deferentia, whereby testosterone reaches the prostate without entering the general circulation, the epididymis exercising a direct and unilateral influence over the prostate [4]. Testosterone levels in the deferential and testicular veins were comparable and higher than those in peripheral blood. Moreover, radio-opaque material can be transferred from the deferential vein directly to the prostate.

Sperm is conveyed to the central region of the prostate by the vas deferens, from where they are propelled into the prostatic urethra through the ejaculatory ducts, part of the sensual process of orgasm. The fluid from the seminal vesicles, sac-like structures at the base of the bladder, is also transmitted through the ejaculatory ducts. Importantly, the fluid secreted by glandular prostate epithelial cells is also propelled into the urethra by

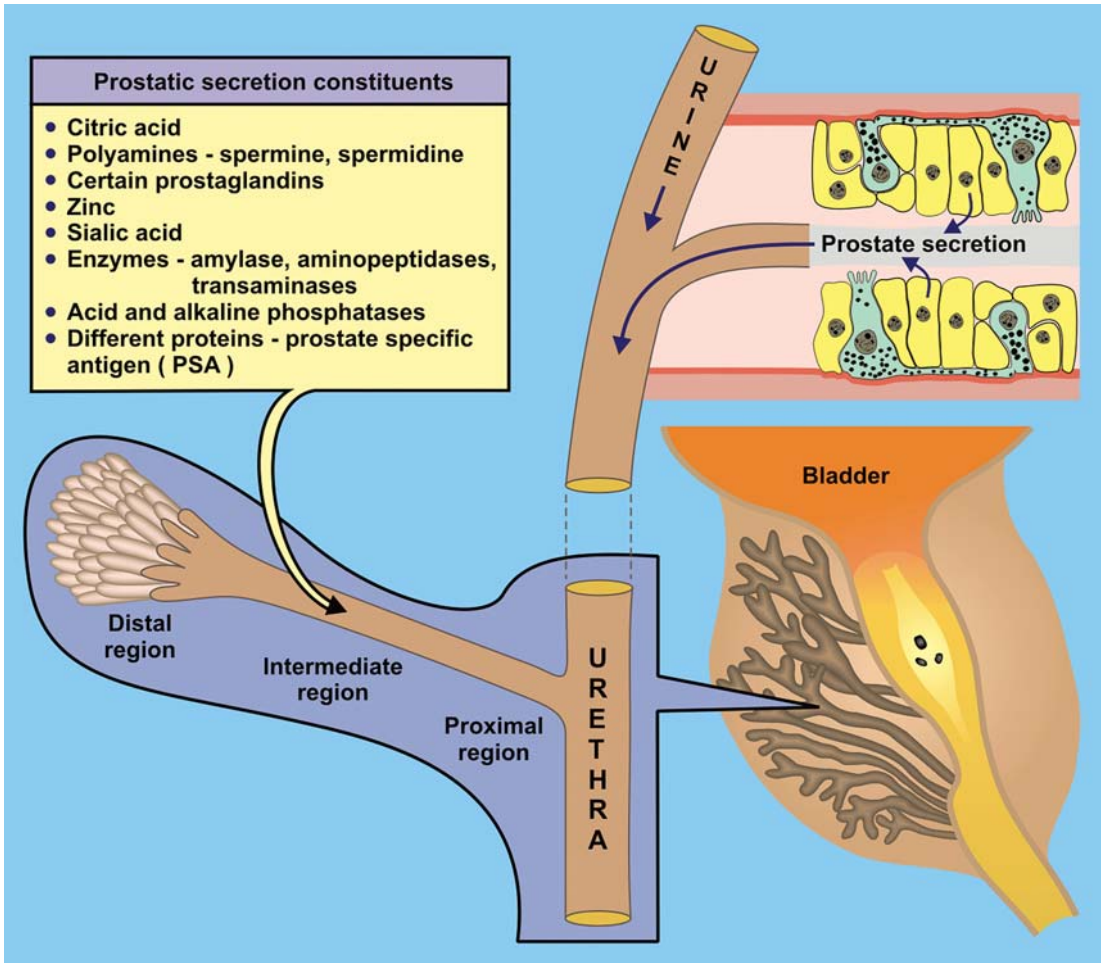

Figure 2. A simple representation of the ductal system of the prostate gland. The epithelial component is depicted as secretory cells interspersed with neuroendocrine cells, embedded in the supporting stromal elements. Shown are some of the constituents of prostate secretory fluid

Table I. Some somatic disorders associated with CP or CPPS [8]

Chronic prostatitis (C)/Chronic pelvic pain syndrome (CPPS): A functional somatic syndrome?	
• Irritable bowel syndrome	35%
• Chronic headaches	36%
• Fibromyalgia	5%
• Non-specific rheumatological symptoms	21%
• Psychological factors: anxiety, depression, sleep disorders, alcoholism	48%
• Sexual dysfunction	23%

the gland's muscular tissue and then expressed in the ejaculate. The seminal fluid is ejaculated through urethral muscular contractions. It is from secretory cells lining the 40-50 ducts of the prostate (Figure 2), that the prostate fluid originates.

Although the prostate fluid conveys spermatozoa to the exterior, it also provides certain constituents important in regulating the pH of semen and sustaining sperm motility and viability. These include citric acid, the polyamines, spermine and spermidine, certain prostaglandins, zinc, sialic acid, enzymes such as amylase, aminopeptidases, transaminases, acid and alkaline phosphatases and different proteinases such as the prostate specific antigen (PSA). Also secreted from the neuroendocrine cells are particular neuropeptides (Figure 3).

PSA receives attention with regard to prostate cancer screening [6]. Very simply, as proliferating cancer cells disrupt the anatomical structure of the prostate, PSA can then escape into the blood. Normally PSA, a proteinase, is secreted into the prostatic ducts.

Prostate awareness

Undoubtedly, the prostate generates considerable misunderstanding than most other organs and causes more clinical problems than any other organ. It is, however, its relationship to sexual activity, that promotes understandable concern, in particular, that a diseased prostate and its treatment, will inevitably lead to impotence. It is not unreasonable, therefore, that a male is reluctant to seek reassurance about the medical status of his prostate.

Men rarely experience prostate problems during their early life. Indeed, the gland is generally trouble-free until around 50 years of age, although in the 40s, certain 'bothersome symptoms' are not uncommon [7], often problematic symptoms generally stoically endured as a sign of ageing. Although prostate cancer provides the ultimate challenge, nonetheless, prostatitis remains a relatively common urological disorder in men below 50 [2], a problematic, sometimes serious challenge which impacts on their quality of life.

The enigma of prostatitis: can it be classified?

The clinical entity classically referred to as 'prostatitis', implies an inflammatory prostate disease, with patients suffering from symptoms that include voiding frequency, reduced urinary flow, perineal pain and often, severe pelvic discomfort and pain. It is noteworthy that patients may also suffer from other symptoms (Table I) and it is reasonable to suppose that the symptoms of chronic prostatitis (CP) / chronic pelvic pain syndrome (CPPS), could be the consequence of a more general functional somatic syndrome, a concept well highlighted by Potts [8]. Approximately 65% of CP / CPPS patients express somatic disorders, compared to only 0.5% of the general population.

It is particularly surprising that only 5-10% of patients presenting with such symptoms, have a recognisable bacterial infection of the prostate, a condition that is termed acute, or chronic bacterial prostatitis [9]. It is generally accepted, however, that the treatment and clinical management of patients with bacterial prostatitis, is successful.

Nevertheless, a bacterial infection cannot be identified in the majority of patients, who present with symptoms, referred to as either nonbacterial

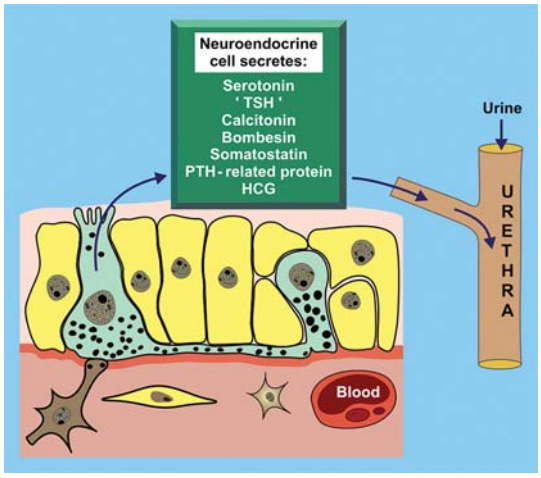

Figure 3. Some of the products secreted by the neuroendocrine cells

Table II. The re-classification of prostatitis and pelvic pain syndromes [11]

Classification of USA National Institutes of Health (NIH)
I. Acute bacterial prostatitis (An acute prostate infection)
II. Chronic bacterial prostatitis (A recurrent prostate infection)
III. Chronic pelvic pain syndrome (CPPS): No demonstrable infection. a) Inflammatory CPPS: formerly chronic non-bacterial prostatitis. In such patients, leucocytes are found in either expressed prostatic secretion (EPS), urine, after prostatic massage (voided bladder urine – 3, VB – 3, or in semen) b) Non-inflammatory CPPS (formerly prostatodynia). In such patients, there is no evidence of inflammation in the EPS, VB – 3 or semen)
IV. Asymptomatic inflammatory prostatitis (AIP). Such patients have no subjective symptoms, although white blood cells are found in either prostatic secretions, or prostate tissue, during an evaluation of other disorders

prostatitis, or as 'prostatodynia'. They suffer from severe chronic pelvic pain, apparently nonbacterial prostatitis resulting from either an infectious inflammatory disease due to an unidentified pathogen, or a non-infectious prostate inflammatory condition [10]. Patients with 'prostatodynia' also experience pain in the region of the prostate, but neither inflammation, nor infection, can be readily identified, nor is any other prostate dysfunction evident. Simply, therefore, patients with either prostatodynia, or with nonbacterial prostatitis, experience severe, disabling pelvic pain, although only the latter condition is associated with the presence of inflammatory cells in expressed prostate fluid (EPF), or in semen.

In 1995 [11], the NIH re-classified the various prostatitis and pelvic pain syndromes (Table II). It is evident that the majority of patients, who present with chronic pelvic pain, or severe discomfort lasting longer than 3 months, are in the NIH category III prostatitis sub-group.

Prevalence of chronic prostatitis/chronic pelvic pain syndrome

Clearly, chronic prostatitis, a disabling clinical disease, must be dealt with by the Urological Community. It is surprisingly prevalent in men between the ages of 30-50, worldwide, with no apparent ethnic, nor racial predisposition. Prevailing evidence indicates that the NIH category III, chronic pelvic pain syndrome, affects 10-14% of men of all ethnic origins [12-14] at some period in their life. A population-based Finnish study [12] confirmed this relatively high, 14% overall lifetime prevalence of prostatitis. Moreover, of these Finnish patients, 27% reported symptoms at least once each year and 16% complained of persistent prostatitis. Much of the epidemiology is, however, derived from North American studies. For example, of the young men in the Wisconsin National Guard, approximately 5% reported [15] a history of prostatitis. From a population-based study that analysed practice patterns of primary health care physicians and urologists in Canada [13], the prevalence of chronic prostatitis was of the order of 9.7%. In 1991, of approximately 13 million men who presented at Urological Clinics in the USA, it was reported [16] that 5.3% had suffered from inflammatory disease of the prostate gland.

A review of the Olmstead County Study of Urinary Symptoms in relation to Men's Health [17], an evaluation of results acquired between 1992-1996, revealed that about 11% of the men were diagnosed with prostatitis by the County's physicians.

Which pathogens are implicated in prostatitis?

Weidner continually emphasises [10] that chronic bacterial prostatitis is a serious, potentially disabling condition and also confirms that unequivocal evidence of bacterial infection is found in only 10% of patients. Moreover, controversy remains [18] on the specific bacteria, which can be readily recognised as pathogens implicated in infectious prostatitis (Table III). To date, only certain bacteria, Escherichia coli and other Gram-negative bacteria, which have been localised in

Table III. Recognised pathogens implicated in the aetiology of infectious prostatitis

Aetiologically recognised pathogens	Pathogens remaining controversial
Escherichia coli	Chlamydia trachomatis
Klebsiella spp.	Mycoplasma hominis and genitalium
Proteus mirabilis	Anaerobic bacteria
Pseudomonas aeruginos	Corynebacterium species
Other Gram-negative bacteria	Yeasts
Enterococcus faecalis	The protozoan trichomonas vaginalis
Staphylococcus aureus	Herpes simplex virus type 1 & 2
	Coagulase negative stapylococci

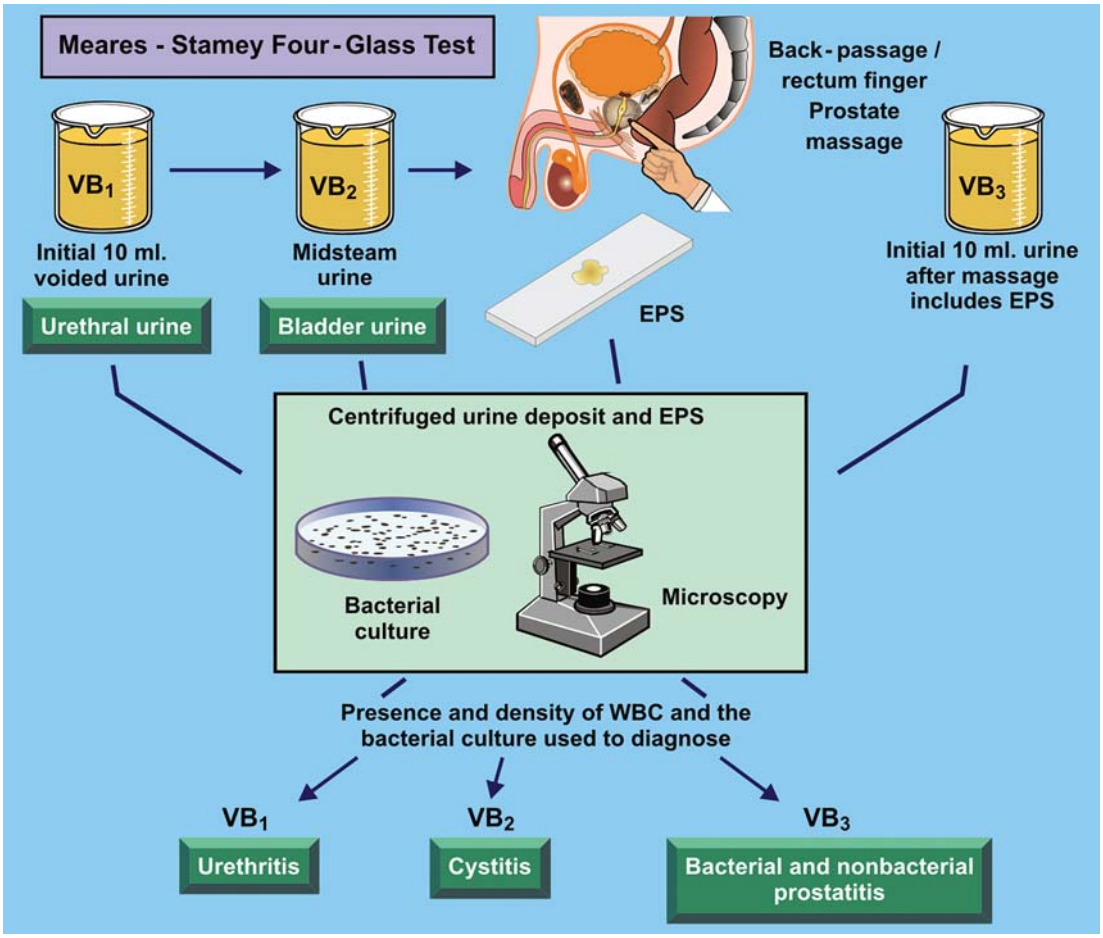

Figure 4. Diagrammatic representation of the Meares-Stamey Four Glass Test [21]

expressed prostate secretions, and those that cause recurrent urinary tract infections, are considered in relation to prostatitis. A proven infection, or a significant degree of colonisation, can also be associated with a high number of bacteria in the ejaculate, a condition referred to as bacteriospermia. Studies on its prevalence, underline its relevance in relation to chronic bacterial prostatitis, since the same pathogens detected in the standard four-glass-test, were cultured in up to 90% of the ejaculate samples [19, 20]. In contrast, in studies of men with CP/CPSS, the ejaculate cultures do not present reliable results [19].

In current clinical practise, the prostatitis histogram of the 'Meares and Stamey four-glass test' [21], would generally be considered the gold standard [10, 22] and most appropriate available determining factor, in establishing the criteria for the diagnosis of chronic bacterial prostatitis (Figure 4).

Relevant European data on chronic bacterial prostatitis

A detailed report of Weidner [23] describes 656 patients and 137 age-matched controls, presenting at a specialised outpatient department of the University of Giessen. They identified a frequency of chronic bacterial prostatitis of 7%, the precise classification dependent on an increase in leucocyte numbers in either expressed prostate fluid, or in urine after prostate massage, sometimes both, as well as a microbiological classification of the sequential bacterial quantitative culture of the urethral and bladder urine and prostate secretions [23]. The data from this comprehensive Giessen Prostatitis Cohort Study, is illustrated (Figure 5).

All patients, who had complained of at least three specific symptoms during the previous 12-month period, were investigated in depth [22, 23]. Important, are the healthy controls, men without symptoms, who showed no evidence of bacterial infection, emphasising the value of the specialised 'Prostatitis Clinic' and a well-trained staff, experienced in managing such patients and thereby controlling cross-infection.

During 2000, Weidner initiated a further prospective study of symptomatic patients with chronic pelvic pain syndrome [24], using the same protocol to identify uropathogens. Symptoms were precisely defined, following the NIH criteria [25, 26], with all patients considered to be symptomatic, according to

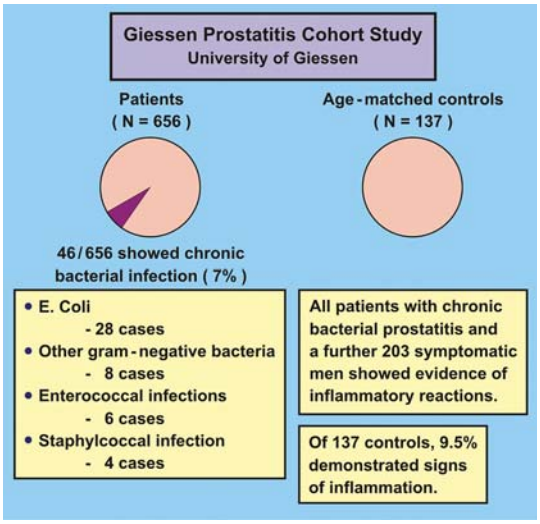

Figure 5. Data from the Giessen Prostatitis Cohort Study

the Chronic Prostatitis Symptom Index. Of all patients who entered the study, 168 (mean age 49, range 18-79) were clinically assessed by 2002. Of these, 144 patients were diagnosed as suffering from prostatitis, category II and III. Moreover, the data confirmed that only 7 patients with chronic prostatitis (4.7%), showed evidence of infection with the well-recognised pathogens, thereby allowing their classification to NIH, category II, essentially that of chronic bacterial prostatitis. The responsible pathogens were identified as Escherichia coli (3x), enterococci (3x), and Klebsiella pneumoniae (1x).

Such studies firmly support the view that the larger proportion of men who present with chronic prostatitis, with pelvic pain, lower urinary tract symptoms, impaired quality of life and possibly, sexual dysfunction, have no evidence of bacterial infection, as identified by the procedures currently used in clinical practice.

Nonetheless, antibiotics are widely used for the management of the disease, a treatment that undoubtedly provides symptomatic relief. Consequently, the importance of searching for other uropathogens that are associated with this disease is evident. Many of such patients do have inflammatory disease and some respond to antimicrobial therapy, although undisputed predictors of symptomatic outcome, associated with infection and inflammation, do not as yet, exist [27].

Can other pathogens be considered?

Evidence relating to the involvement of other pathogens (Table III) in the aetiology of prostatitis, has been comprehensively evaluated [28] although their role has yet to be unequivocally proven. Although most relate to those implicated in urinary tract infection, they are not normally isolated on standard media for culturing urine and it must again be emphasised, that few patients who present with chronic prostatitis, provide evidence of any infection with the well-recognised pathogens.

Various fungi and parasites have been thought to play a role [29] and the possibility that Chlamydia trachomatis has a pathogenic influence, was recently assessed [30]. Discussion inevitably centres on problems created by the current imprecise definition of urethral and prostatic inflammation. The symptoms of persistent non-gonococcal urethritis, essentially urinary frequency, dysuria and penile pain, are also those of chronic prostatitis. Perineal and testicular pain, together with pain and discomfort in the regions of the pubis and bladder and in association with ejaculation, are however, symptoms primarily of chronic prostatitis [31].

Controversy therefore continues on other uropathogens [31]. Genital mycoplasma (Mycoplasma-hominis and genitalium), and Ureaplasma urealyticum, can localise in the prostate and classically, anaerobic bacteria have long been implicated with prostatitis, but more recently [32], with regard to therapy-resistant chronic bacterial prostatitis. It is noteworthy, possibly important, that the Coryneforms, difficult-to-culture, would not be routinely identified in expressed prostate secretion, by analytical procedures currently in place.

Nevertheless, with molecular biology to the forefront, use of rRNA-based techniques to analyse bacteria has now provided evidence of Corynebacterium in expressed prostate fluid [33]. Such procedures now provide unequivocal evidence of bacterial DNAs within prostate tissue and in fluids taken from patients with prostate inflammation [34]. Over the coming years, this will offer an efficacious approach to bacterial infection within the prostate gland.

Unfortunately, the value of the four-glass test for bacterial colonisation [21] would appear compromised by the report from the NIH Chronic Prostatitis Cohort Study [35], that disease severity does not apparently relate to the bacterial counts. Clearly, this makes it difficult to determine whether patients should or should not be classified as NIH category II or III prostatitis. A more precise understanding of the pathology implicated in the inflammatory response must be established. Nickel [36], for example, has suggested that certain bacteria may be undetectable, because they are localised as aggregated 'biofilms' attached to the walls of prostate ducts. Alternately, they may be undetectable because they are 'hidden' in obstructed ducts.

Of importance, however, is that enhanced bacterial growth can be identified [37] in biopsies of prostates with a recognised inflammatory reaction, providing

evidence of bacterial colonisation, probably infection, within the prostate itself, events that can induce inflammation. A biopsy can offer necessary pathology to increase our understanding of prostate disease and a means of establishing an infectious source. Biopsy is an intrusive approach, however, some would say unethical and as yet, probably should remain within the domain of the clinical researcher.

A molecular approach to the aetiology of prostatitis

Despite impressive research directed to establishing the molecular basis for prostate disease, little has contributed to a better understanding of the aetiology of prostatitis, although a molecular approach to identifying uropathogens is a rational start [31], particularly the analysis of urethral and prostate samples.

For example, Krieger [31, 34] used specific PCR assays for the identification of particular pathogens. Some broad-spectrum PCRs were also used to recognise bacterial DNAs, such as the common tetracycline-resistant encoding genes and the bacterial ribosomal-encoding genes (16S rDNA). Data were obtained on 135 patients with chronic nonbacterial prostatitis [31], with particular care taken to exclude patients with bacteriuria, bacterial prostatitis and urethritis. To limit contamination, a double needle procedure was used to obtain a prostate biopsy. The studies identified C. trachomatis, M. genitalium and Trichomonas vaginalis in prostate tissue. Using the specific PCR assays, none were found positive for a general mycoplasma probe, the U. urealyticum probe, herpes virus probes, nor for the cytomegalo-virus probe. DNA encoding tetracycline-resistant genes, was found in 25% of patients, however, providing a possible reason why antibiotic therapy offers only transitory, if any relief for most patients. Moreover, 77% of patients presented evidence of 16S rDNAs, with a strong correlation to the expressed prostate secretion, inflammation and white cell count [38, 39].

Analysis that identifies uncommon, as well as common pathogens in the prostate with chronic prostatitis, is important. Nonetheless, as emphasised by Krieger [31], this by no means confirms a prominent role in causing chronic prostatitis, or CPPS. It would not be unreasonable, however, to assume, that their localisation within the prostate, probably does support a role during a particular phase in what may be a multi-step process in the pathogenesis of prostatitis.

The history and treatment outcome of prostatitis

The history of symptoms suffered by 179 patients from the NIH Chronic Prostatitis Cohort, men who were treated according to various modalities suggested by their individual physicians, was monitored for a 12-month period. The results of the assessments [34] are summarised in Figure 6.

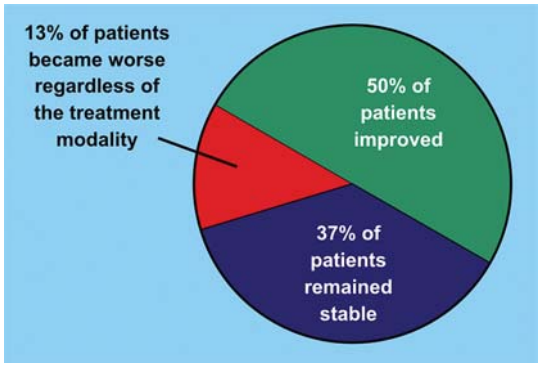

Figure 6. The history of patients from the NIH Chronic Prostatitis Cohort, treated with various modalities suggested by individual clinicians

A brief review of the diagnostic and treatment modalities currently in use is of value. Patients with prostatitis primarily present with discomfort, a disabling, severe pelvic pain, various lower urinary tract symptoms and often, sexual dysfunction, symptoms that impinge on quality of life issues. Very simply, prostatitis is a disease in which bacterial infection, inflammation and voiding problems, often co-exist and the treatment modalities and clinical management programme reflect this situation. A brief synopsis of the urological work-up of such patients, is shown in Table IV.

Treatment with antimicrobials

Acute bacterial prostatitis

Patients with acute bacterial prostatitis, a serious bacterial infection of the prostate and lower urinary tract, can readily be managed. They present with intense pelvic pain, fever, chills and vomiting, together with irritative and obstructive urinary symptoms. These include frequency, urgency and obstructive voiding, with dribbling and hesitancy. Patients can be very ill and hospitalisation is often necessary. The basic clinical assessment requires a history and a focused physical examination, together with a midstream urine analysis to establish bacteruria. The bacterial spectrum, generally characteristic of fecal flora, is probably the result of ascending urethral colonisation. The condition develops spontaneously, although associated factors such as acute epididymitis and penetrative anorectal intercourse may exercise an influence. Antimicrobial therapy is necessary and the parenteral administration of high-dose bactericidal antimicrobials such as broad-spectrum penicillin derivative, a third generation cephalosporin, or a fluoroquinolone, will generally be used until the fever and symptoms of the infection are controlled [28]. Oral treatment would then follow. For a less severe case,

Table IV. Evaluation of patients with CP/CPPS

Evaluation of the patient with chronic prostatitis/pelvic pain
Basic evaluation
• History • Physical examination, including digital rectal examination (DRE) • Urinalysis and urine culture, collecting midstream urine
Further evaluation
• Symptom inventory or index (NIH-CPSI) • Lower urinary tract localisation test – microscopic and culture • Urine flow rate • Residual urine determination
Evaluation in selected patients
Clinical
• International Prostate Symptom Score (IPSS) Questionnaire
Laboratory
• Urine cytology • Urethral evaluation – VB1 or urethral swab for culture • Semen analysis and culture • Prostate specific antigen (PSA) determination
Interventional studies
• Urodynamic evaluation • Pressure flow studies • Video urodynamics (including flow – EMG) • Cystoscopy
Imaging
• Transrectal ultrasonography (TRUS) • Abdominal/pelvic ultrasonography • CT-scan

oral fluoroquinolone for up to 4 weeks, provides an acceptable therapy [40].

Chronic bacterial prostatitis

Chronic bacterial prostatitis is suspected when the symptoms of acute bacterial prostatitis, although usually less severe, are present for at least 3 months. Classically, the condition has often been related to patients with a recurrent urinary tract infection. Naber [28] indicates that the appropriate diagnostic procedure to identify chronic bacterial prostatitis, demands quantitative segmental bacteriological localisation cultures and microscopy of expressed prostate secretion, as described by Meares and Stamey [21]. Culture of the ejaculate alone, is insufficient [19, 41].

The administration of an oral fluoroquinolone for 4-6 weeks after diagnosis (Figure 6), would be considered appropriate antimicrobial therapy for chronic bacterial prostatitis [42, 43]. Considerable experience has been gained with ciprofloxacin [28] and more recently with levofloxacin [44], which showed equivalent clinical and microbiological outcome using a dose of 500 mg, once daily, as compared to ciprofloxacin, 500 mg twice daily, for 28 days. Investigative studies are summarised in Table V. The injection of antimicrobials directly into the prostate is not recommended [52, 53]. The therapy is effective for E.coli and related family members, but less so, for chronic bacterial prostatitis associated with P.aeruginosa and enterococci [42]. Many patients respond well to antimicrobial therapy, however and remain asymptomatic for some time, until eventual relapse and recurrence occurs.

Inflammatory chronic pelvic pain syndrome

It is generally accepted that the management of chronic nonbacterial prostatitis, with associated inflammation (NIH category IIIA), but with no pathogens identified, still requires initial antimicrobial therapy. This is primarily on the basis that particular pathogens may well be present, but are undetectable by current, routine assays. Moreover, reports of successful treatment [54, 55] support the concept that first-line antimicrobial therapy is appropriate. Treatment with an oral fluoroquinolone for 2 weeks, after diagnosis, is therefore recommended and for up to a 6 week period, if symptomatic relief of pain is reported after the initial 2-week period [40].

Despite this, controversy still exists [40] with regard to the potential value of antimicrobial therapy

Table V. Fluoroquinolones in the treatment of chronic bacterial prostatitis with a follow-up of at least six months

Quinolone	Ref.	Dosage mg/day	Therapy duration (days)	Patients evaluated	Bacteriological eradication (%)	Follow-up duration (months)
Ciprofloxacin	[45]	1000	14	15	60	12
Ofloxacin	[46]	400	14	21	67	12
Norfloxacin	[47]	800	28	14	64	6
Norfloxacin	[48]	4-800	174	42	60	8
Ciprofloxacin	[49]	1000	28	16	63	21-36
Ciprofloxacin	[50]	1000	28	34	76	6
Ciprofloxacin Lomefloxacin	[51]	1000 400	28 28	78 75	72 63	6 6

for patients with both inflammatory and non-inflammatory CPPS, designated NIH category IIIA and IIIB [27]. Other considerations that impinge on the use of antimicrobials, deserve comment.

Some issues regarding treatment with antimicrobials

Effective antimicrobial therapy requires the pathogens at the site of infection to be exposed to a sufficiently high drug concentration to inhibit bacterial growth, or even eradicate the pathogens from that site. Because of their favourable pharmacokinetic and pharmacodynamic properties, the fluoroquinolones are, today, considered the drugs of choice for the antimicrobial treatment of bacterial prostatitis and vesiculitis.

Drug penetration is supposedly a passive transport mechanism dependent on diffusion and concentration [56, 57], determined by lipid solubility, degree of ionisation (biological membranes do not allow the passage of charged substances), the degree of protein binding and the size and shape of the molecule. Small water-soluble molecules can cross biological membranes as part of the free water diffusion. The presence of a pH gradient across a biological membrane introduces the phenomenon of ion trapping. In a stable system, the uncharged fraction of a lipid-soluble drug equilibrates on both sides of the membrane, whereas the charged fraction is greater on one side or the other, depending on the pH. The highest drug concentration, the sum of the charged and uncharged fractions, is on the side with the higher degree of ionisation. A weak base, like trimethoprim with a pK_a of 7.4, will therefore concentrate in an acidic prostate fluid, as found in dogs [58], but not in an alkaline milieu such as the seminal fluid.

The fluoroquinolones in clinical use are neither simple acids nor bases, but have characteristics of both, being amphoteric, or zwitter-ionic drugs [59, 60]. Amphoteric drugs have two ionising groups, one positively and one negatively charged, and thus two pK_a values. At a particular pH value, one which is between the two pK_a values and different for each amphoteric drug, the amount of charged drug is minimal (isoelectric point). At higher or lower pH values, more of the drug is charged. Since the highest drug concentration occurs on the side with higher degree of ionisation, drugs with an isoelectric point close to the pH of plasma, should therefore concentrate in fluids with a pH above and below plasma pH.

In contrast to dogs, in which most animal studies were performed and which have an acidic prostate fluid with a pH of about 6.5 [61], the pH of normal human prostate secretion is slightly alkaline, with a pH of approximately 7.3 [62]. Moreover, the pH in men with a prostate infection is markedly higher (mean value, 8.34). Further studies [63-65] have confirmed that the pH of the prostate fluid in patients with chronic bacterial prostatitis is alkaline, rather than acidic and thereby differs from both canine and normal healthy human males. Since the pH gradient is crucial to the ion-trapping phenomenon, studies in dogs cannot be extrapolated to humans. Furthermore, despite effective ion-trapping, it remains questionable as to whether the trapped, charged fraction of a drug would have any significant antibacterial effect, since it may not penetrate the bacterial wall.

In human studies, the comparatively high drug concentration in urine, makes contamination a major problem, especially since the prostate fluid is usually obtained in small amounts only by prostate massage. Even minimal contamination can therefore influence the analysis and consequently, only investigations in which urinary contamination is ruled out by the study design, are suitable for the determination of drug levels in the prostate fluid.

Such investigations have been undertaken in volunteers and patients [59, 60]. They demonstrated that the various fluoroquinolones, which are zwitter ions, differ not only in plasma concentrations, but also in their capacity to penetrate, not only body fluids such as prostate and seminal fluids, but also differing tissues. Comparative pharmacokinetic data determined simultaneously in the same subjects for example, showed not only the expected higher plasma concentrations of levofloxacin, relative to ciprofloxacin (Table VI), but also significantly higher levels in the prostate fluid, whereas those in the seminal fluid and the ejaculate were similar [66].

In general, the drug concentration in prostate fluid was well below the corresponding level in plasma. If too low in plasma, the drug concentration in prostate fluid might not exceed the necessary minimal inhibitory level to restrain the causative pathogen for a sufficient period of time. In contrast, the drug levels in both seminal fluid and prostate tissue, generally attained,or exceeded, the corresponding plasma concentrations.

Table VI. Concentrations in body fluids, three hours after single oral administration of 250 mg levofloxacin and 250 mg ciprofloxacin in 15 volunteers [66]

	Levofloxacin mg/L (n)	Ciprofloxacin mg/L (n)
Plasma(C_{max})	3.10 (15)*	1.37 (15)*
Prostatic fluid	0.89 (8)*	0.16 (7)*
Seminal fluid	3.25 (8)	2.59 (8)
Ejaculate	3.21 (8)	2.63 (5)

n – number of subjects in whom corresponding concentrations could be measured
**p<0.05*

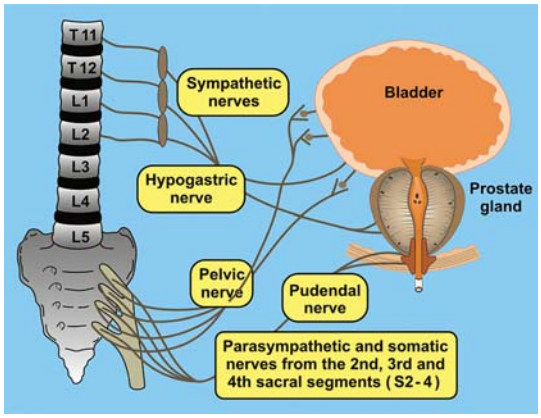

Figure 7. Innervation of the lower urinary tract. The sympathetic (hypogastric) and somatic (pudendal) nerves sustain prostate and urethral tone during bladder filling. The parasympathetic pelvic nerves promote detrusor contraction and micturition

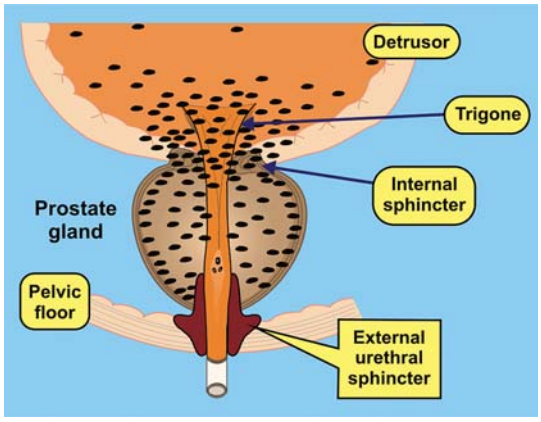

Figure 8. The α1-adrenoceptors have been identified and characterised in the body of the bladder, in the bladder neck and in the prostate gland. Their relative density and distribution is illustrated [71]

The fluoroquinolone concentration in prostate tissue, which represents intracellular levels, as well as those of residual blood, interstitial fluid and glandular secretion, is generally higher than that in plasma, demonstrating good tissue penetration [67]. Penetration rates of 1.88 for ciprofloxacin [68] and 2.96 for levofloxacin [69], were calculated. A new fluoroquinolone, prulifloxacin (registred in Italy, Japan and other European countries) with a wide mechanism of action, including a strong activity on Pseudomonas aeruginosa and characterised by practical daily mono-administration, represents today an interesting therapeutical agent for bacterial prostatitis.

In fact, a Japanese study, even though carried on a limited number of cases, showed a PK/PD favourable profile in prostatic human tissue. Four and six hours after drug administration the study showed a prostatic tissue/plasma ratio equal to 4.07 and 3.47, respectively [70].

Table VII. Possible causes of LUTS associated with BPH

• Prostatic stroma
• Detrusor, trigone, urethra
• Ganglia
• Spinal and/or supraspinal structures
• Changes in the smooth muscle of the LUT (hypertrophy, denen/ation)
• Defective central processing of afferent information
• Defects in efferent neurotransmission

Data from Andersson, 2000 [66]

Use of alpha-blockers to treat prostatitis

Most patients, who present with severe chronic pelvic pain, will also complain of irritative voiding symptoms and will present urodynamic evidence of pelvic floor dysfunction [71]. It is not unreasonable, therefore, that the use of α-adrenergic receptor blockers is efficacious for the management of these lower urinary tract symptoms. Muscular tone is modulated by the autonomic nervous system (Figure 7), dependent on noradrenaline release from the adrenergic nerves. The α1-adrenoceptor blockade relieves the tone of contractile smooth muscle of urethral and stromal elements of the prostate. It is noteworthy that α1-adrenoceptors are abundant [72], not just in the prostate, but in the neck of the bladder (Figure 8). Moreover, although the irritative storage symptoms are generally attributed to bladder dysfunction resulting from obstruction, the timely reminder from the late Tage Hald [73] that such symptoms are not exclusive to males, suggests they are not the simple consequence of 'dynamic prostate obstruction'. The action of α1-antagonists on receptors external to the prostate, in the bladder or within the nervous system, will undoubtedly be implicated in the relief of irritative storage symptoms [74], particularly since pelvic organs share innervation and reflex integration pathways. Andersson [75] has listed possible causes of lower urinary tract symptoms associated with BPH and possible sites of action of α-blockers (Table VII).

Barbalias [71] considers that for patients with either bacterial or nonbacterial chronic prostatitis, with lower urinary tract symptoms, administration of an α-blocker should be first-line therapy, restraining the vasodilatory action of noradrenaline and decreasing muscle tone. Clinical improvement is reported [76], particularly with regard to a lesser rate of disease recurrence. He believes [71] that specific urodynamic characteristics, an increased maximum urethral closure pressure and decreased peak and urinary flow rates, suggest a primary 'dynamic' dysfunction is implicated in prostatitis, an abnormality relating to the pelvic sympathetic nervous system, since patients with a very high intra-urethral pressure, attributed to enhanced adrenergic stimulation, respond more

favourably to therapy. This enhanced innervation and urethral hypertonia, would be seen to promote the reflux of urethral contents into the ducts of the peripheral zone of the prostate (Figure 9).

Moreover, Barbalidas considers adrenoceptor blockade should be prolonged, since after an early response, the symptoms and adverse urodynamic characteristics recur unless treatment is continued for a 6-8 month symptom-free period, with dosage titrated to achieve an effective clinical response.

It is understandable that controversy surrounds this empirical therapeutic approach, since neither flow rate, nor prostate size, can predict a patient's response. The hypothesis [71, 76], however, that dysfunctional autonomic innervation leads to sympathetically-mediated urethral hypertonia, relative detrusor inhibition and the irritative and painful voiding symptoms of prostatitis, is supported by these particular symptoms responding to adrenoceptor blockade. It appears that in patients with chronic bacterial prostatitis, or inflammatory CPPS, first-line treatment with both an antimicrobial and an alpha-blocker, provides effective therapy, but what is the role of anti-inflammatory agents?

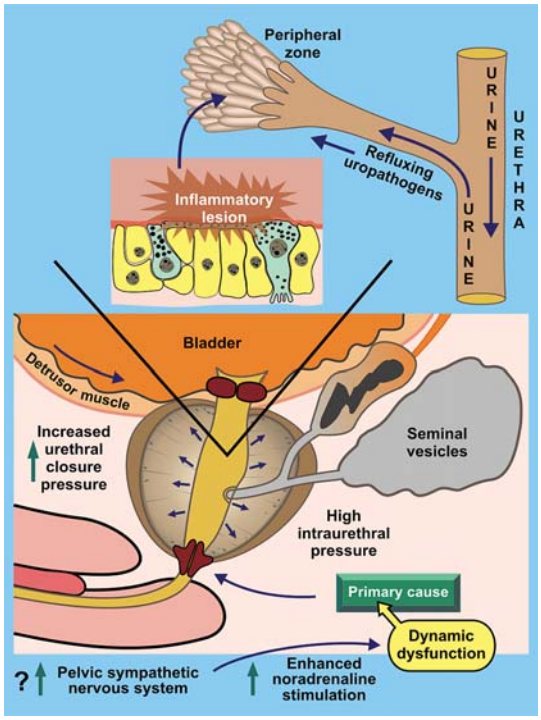

Figure 9. Diagrammatic representation of the reflex of urethral contents into the prostate ducts

Treatment with anti-inflammatory agents

Another confounding issue in managing chronic nonbacterial prostatitis, or CPPS, is that anti-inflammatory therapy is commonly prescribed [77]. In accordance with the classification of prostatitis [11], identification of white blood cells in the semen would be accepted as an acceptable marker of inflammation, although it appears that anti-inflammatory therapy is often prescribed, regardless of the presence of inflammation [77], simply seen as 'useful for symptom relief' [78].

No controlled clinical trials have been undertaken to support this management approach and since urologists rarely if ever, use the 4-glass test, nor other routine [79], but time consuming tests, the categorisation of patients with or without inflammation, category IIIA or IIIB, can only be arbitrary. Furthermore, the proportion of patients with inflammatory disease could possibly be grossly underestimated. Nonetheless, non-steroidal anti-inflammatory agents are often administered and there seems little doubt that they are clinically valuable in pain management and in restraining the inflammatory process.

A viewpoint on the management of prostatitis

Clearly, with much to learn about prostatitis and its diverse symptoms, diagnosis and treatment present a challenge. Previous clinical studies have been short term, with small numbers of patients and few have been randomised and placebo-controlled. Patient inclusion criteria have not always been precise, often were not comparable and the outcome criteria have not always been clearly defined. More clinical research is indeed necessary. Whereas antimicrobials, alpha-blockers and anti-inflammatory agents, singly, but generally in combination, offer effective treatment for chronic prostatitis / CPPS, uncertainty is reflected in the range of other agents (Table VIII) that have also been used, although most studies were either uncontrolled, or patient numbers were too small to reach any meaningful conclusions.

This range and diversity of agents underline the limited understanding of the condition, emphasise a need for an appropriate treatment schedule and reveal the physiological complexity of the disease. Interest centres on what should be the acceptable clinical treatment practice and a recent consensus conference [80] provided certain practical guidelines and the following recommendations:

The purpose of the initial diagnostic evaluation of the patient presenting with pelvic pain must be to rule out the possibility of another underlying disease, or disorder that caused the symptoms. Table IV illustrates an appropriate patient work-up:

- Diagnostic tests pertinent to a basic evaluation
- Further assessment is recommended to define and direct therapy, although this is not necessarily mandatory for all patients;
- Evaluation in selected patients, to investigate suspicions raised by the basic assessment. This

Table VIII. The wide, diverse range of agents used for the treatment of CP/CPPS

Agents used for the treatment of chronic prostatitis/pelvic pain syndrome
Antimicrobials, such as fluoroquinolones
Intraprostatic gentamicin-xylocain
Alpha-blockers
Antimicrobials in combination with an alphablocker
Muscle relaxants, such as Valium or Baclofen
Anticholinergic drugs
Non-steroid antirheumatic agents
Analgesics, including centrally effective drugs
Amitryptilin
Na-tartrate
Allopurinol
Low dosage oestrogen
Finasteride
Prostatilen
Phytotherapy, such as z.B. Cernilton, Prostabrit
Wobenzym
Botulinum – toxin
Phonophoresis with Methyluracil
TCM suppositories
Mepartricin

would include urine cytology to rule out bladder cancer, a flow rate determination to exclude bladder outlet obstruction, or a urethral swab culture to screen for chlamydia or gonorrhea, in men with a history of suspected sexual contact.

Lower urinary tract localisation tests, the traditional 4-glass, or the 2-glass tests are recommended to screen for the smaller proportion of patients with chronic, but treatable infections. A positive culture is a laboratory finding that requires interpretation in the context of a patient's history and symptoms. It is not by itself, diagnostic of chronic bacterial prostatitis, since asymptomatic controls can also have pathogens localised to prostate secretions, or the semen. A positive culture in a patient with pelvic pain does, however, provide a reasonable scientific rationale for treatment with antimicrobials. Before treating a patient infected with an uncommon pathogen, it is advisable to repeat the localisation tests and to limit false positives and negatives, they should be performed immediately, and in coordination with the laboratory, without transportation of samples to an outside laboratory. Such studies will also identify patients with prostate inflammation

Moreover, as with other chronic pain syndromes, patients with chronic prostatitis/CPPS are at increased risk for depression and other mood disorders and it may be appropriate to evaluate the patient for psychiatric co-morbidity. It is known that if untreated, such patients develop enhanced pain awareness and, generally, a reduced response to therapy. Finally, a methodical evaluation of the lower back and the pelvic floor musculature has been recommended, in order to screen for contributing musculo-skeletal factors that may be more responsive to physical therapies.

The role of the general practitioner

In the context of the guidelines for patient evaluation, consideration must be given to the precise role of the general practitioner, who may wish to do more in the initial screening of patients presenting with prostatitis, possibly offering early-phase treatment. This centres on the urologist and practitioner relationship, the important, shared-care concept. The purpose is not merely to relieve the burden on the specialist, but to improve the level of care general practitioners may prefer to offer their patients. An effective communication has developed over the past decade, in the management of BPH and sexual dysfunction.

The general practitioner should first determine whether there is acute urinary tract infection, BPH, or prostate cancer, associated with the severe pelvic pain syndrome. Unfortunately, it appears [79] that in North America, 80% of urologists do not even use the 4-glass test, some do not undertake urine analysis, nor culture and often treat a patient without a DRE. This may reflect a lack of faith in the established analytical procedures, possibly a lack of time, or even some degree of inconvenience, but whatever, there seems a real need for general practitioners to assume a greater responsibility for their patients presenting with prostatitis.

The prerequisite appears to involve a medical history and a physical examination, followed by urine analysis and culture. With no suspicion of an underlying disorder when CPPS has been diagnosed, the clinician could empirically initiate a basic treatment option, use of an alpha-blocker for example, based on inherent clinical experience. If there is no improvement within a few weeks, an experienced urologist should be consulted for further evaluation, as outlined earlier. During this examination, cytology to exclude bladder cancer, a DRE, possibly a PSA assay, a 4-glass test and appropriate urodynamic evaluation, could be undertaken if necessary. Treatment even then, would be somewhat empirical, based purely on clinical experience.

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