

# Prostatitis: lessons from the 20th century

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## Introduction

The end of the 19th century was an exciting time in prostatitis research; the diagnostic entity of prostatitis had been recently recognized and its clinical characteristics well described. This occurred at about the same time as the dawn of modern microbiological research, which opened exciting possibilities to discover the causes of this enigmatic disease. Progress in pathogenesis, diagnosis and treatment continued into the 1960s, when stagnation and lethargy characterized progress in the field for almost three decades.

BPH and prostate cancer became the prostate diseases of the day, as a multitude of rapidly occurring events and discoveries, including medical therapy, PSA, minimally invasive surgical therapies, symptom scoring and industrial involvement, propagated an exciting flurry of research and clinical endeavour. Unfortunately, the third prostate disease, prostatitis, was left far behind. However, as the present century closes and new challenges are presented in prostate-related disease in the 21st century, exciting and promising developments suggest that prostatitis will once again become an important field in urology. As the next century begins, progress in this disease will depend on lessons learned from the 20th century.

## Epidemiological considerations

Up to the last few years, there was no appreciation of the incidence and prevalence of prostatitis. One of the pioneers of prostatitis research in the latter half of the 20th century, Stamey, estimated that half of men suffer prostatitis at some time in their life [1]. A recent international study [2] suggests that this estimate may be correct; 35% of patients had symptoms of prostatitis over the last year and for 8% that represented at least a minor problem. Epidemiological studies recently published show that the prevalence is 5–8% [3,4]. Prostatitis is the most common reason for a man under 50 years old to consult a urologist, accounting for 8% of all urology visits in the USA [5]. The average urologist sees 150–250 patients with prostatitis in a year [6,7],  $\approx 50$  of whom are

new patients [8]. The impact on a patient's quality of life is significant, with similarities to those patients suffering from a recent myocardial infarction, unstable angina or active Crohn's disease [9].

## Searching for a cause: a century of frustration

In the late 1800s it was believed that the chronic prostatitis syndrome then seen was related to either repetitive perineal trauma (e.g. from buggy or horseback riding) or from abnormal (masturbation) or excessive sexual activity [10]. As understanding of inflammatory diseases changed in the early 1900s, with the new awareness of bacterial aetiology and infectious diseases, researchers, urologists and microbiologists looked to the bacterium as the cause of this disease. The gonococcal organism was the predominant cause of infectious prostatitis for the first quarter of the 20th century [11]. Large and extremely elaborate microbiological analyses of the lower urinary tract in the 1920s and 1930s [12,13] appeared to confirm the hypothesis that Gram-negative and -positive bacteria were intimately involved in the pathogenesis of prostatic inflammation. The presence of bacteria in the lower urinary tract and leukocytosis in expressed prostatic secretion remained the accepted cause and consequences of such infection for almost five decades [14]. It was not until the 1950s that it was acknowledged that there may be a nonbacterial cause for prostatic symptoms and inflammation [15]. The dogma of 'leukocytes and bacteria' and their relevance in the initiation, persistence and treatment in those cases where they were both identified was even challenged [16]. In the late 1960s, Meares and Stamey [17], building on the important work by Nickel [12] and Von Lackum [13] in the 1920s and 1930s, proposed their 'four-glass' segmented lower urinary tract localization test. Although never properly validated, this test became urological dogma and subsequently the 'gold standard' for identifying bacterial pathogenesis in the prostate. The vast majority of patients with prostatitis, in whom no uropathogenic bacteria can be identified, were felt to have a combination of high-pressure dysfunctional and turbulent voiding associated with intraprostatic ductal reflux [18]. Chemical [19] or immunological factors [20] then propagated a chronic inflammatory

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reaction in the prostate. No one has yet been able to propose an evidence-based, satisfactory mechanism for the development of 'so-called' prostatodynia (i.e. no bacteria or leukocytes identified in prostate-specific specimens), but it is generally felt to be a neuromuscular disorder of the pelvic floor/perineal complex [21].

Researchers must now build on a century of investigation to determine the exact aetiopathogenic mechanisms involved. The lessons from the past century are outlined in Table 1. There will probably not be one mechanism but the various categories of disease will be found to have many causes.

### Classification systems from the 20th century

By the turn of the century, physicians and urologists recognized the clinical difference between the categories of acute and chronic prostatic inflammation [10]. Urologists became adept at distinguishing the clinical characteristics between these classes of prostatitis. Early in the century, prostatitis was classified as active, latent or bacterial [13]. As understanding of the microbiological causes of this disease progressed, urologists classified the disease either as primary (secondary to gonorrhoeal infection) or secondary (other infection) [22]. By the 1930s, a third group of prostatitis was described as recalcitrant [23]. This is the well recognized form of prostatitis that did not resolve with appropriate therapy. By the middle of the 20th century, some proposed a classification of 'silent prostatitis' as no symptoms were referable to the urinary tract or the prostate, yet the prostate was inflamed and/or infected [14]. In 1978 the traditional classification of prostatitis, based on the Meares–Stamey four-glass localization test, was proposed [24]. This classification includes the well known

categories of acute or chronic bacterial prostatitis, nonbacterial prostatitis and prostatodynia. The urological community, continually frustrated by the categorization and lack of rational treatment of this patient population, immediately grasped the concept of this classification system and embraced it wholeheartedly. For the next two decades most patients with prostatitis were diagnosed as having one or other of these categories of prostatitis and treatment was directed toward what was thought to be the underlying cause. However, as the years passed, urologists and their patients became frustrated, not only with the classification system but with the diagnostic algorithm used to reach such a diagnosis [25]. Particularly frustrating was the concept of prostatodynia. As the 20th century ended, many researchers felt that in many cases the symptoms were not related to the prostate at all. These limitations in the traditional classification system led to the National Institutes of Health (NIH)/National Institute of Diabetes/Digestive/Kidney Diseases Consensus Meeting on Prostatitis, which was held in Bethesda, Maryland in December 1995 [26]. This meeting resulted in the development of a specific NIH classification system for research purposes [27]. The 1998 International Prostatitis Collaborative Network (IPCN) reviewed this classification after 3 years of clinical and research use, and confirmed its utility in dealing with this disease [28]. The classification system is shown in Table 2. Categories I and II are similar to the traditional classification of acute and chronic bacterial prostatitis, respectively. The new categories of chronic pelvic pain syndrome, inflammatory and non-inflammatory (category III) and asymptomatic inflammatory prostatitis (category IV) addressed the major problems and omissions of the traditional and historic classification system.

**Table 1** A hundred years of proposed causes for prostatitis. Unfortunately, the cause in most cases diagnosed as chronic prostatitis/chronic pelvic pain syndrome remains unknown

- Repetitive perineal trauma (horseback or buggy riding at turn of century, to bicycle riding now)
- Abnormal or excessive sexual practices, excessive lifestyle (too much rich food and alcoholic beverages)
- Gonococcal infection (major cause of prostate infection at turn of century, rare now)
- Bacteria other than gonococcal in the first half of the century:
- Any Gram-negative or -positive bacteria isolated in prostate-specific specimens
- Latter half of the century: acknowledged Gram-negative uropathogens (i.e. *Escherichia coli*, *Klebsiella* spp, *Pseudomonas* spp, etc.)
- Late in the century: Gram-positive uropathogens, e.g. *Enterococcus* spp, and other organisms such as *Chlamydia* and mycoplasma
- Recently, coagulase negative *Staphylococcus*, anaerobes, diphtheroids, *Corynebacterium* spp, cryptic uncultureable organism, 'biofilm bacteria', viruses, cell wall-deficient organisms, etc.
- Late century suggestions
- Immunological (i.e. autoimmune)
- Chemical – urine and its metabolites (i.e. uric acid)
- Neurogenic aetiologies

**Table 2** National Institutes of Health Classification of prostatitis [26,27]

Category	Name	Description
I	Acute bacterial prostatitis	Acute infection of the prostate gland
II	Chronic bacterial prostatitis	Recurrent urinary tract infection/chronic infection of the prostate
III	Chronic abacterial prostatitis/chronic pelvic pain syndrome	Discomfort or pain in the pelvic region/variable voiding and sexual symptoms/no demonstrable infection
IIIA	Inflammatory chronic pelvic pain syndrome	Excessive number of white cells in semen/EPS/VB3
IIIB	Non-inflammatory chronic pelvic pain syndrome	Insignificant number white cells in semen/EPS/VB3
IV	Asymptomatic inflammatory prostatitis (AIP)	Evidence of inflammation in biopsy/semen/EPS/VB3 no symptoms

### 100 years of diagnostic dilemmas

The diagnosis and classification of prostatitis for the entire 20th century depended on microscopic and culture evaluation of prostate-specific specimens (expressed prostatic fluid, ejaculate, urine samples obtained after prostatic massage, and/or prostate biopsy). Elaborate studies with thousands of patients in the 1920s and 1930s described the importance of careful microscopic examination and culture of expressed prostatic secretions [12,13]. In 1968, Meares and Stamey [17] reintroduced this type of lower urinary tract evaluation, but added an initial voided urine sample (VB1) to exclude urethral contamination of subsequent prostate-specific specimens. Although this detailed and well known technique has been described as the 'gold standard' and has become urological dogma, it has become obvious that urologists are not performing this test in patients who present with chronic prostatitis [8]. The reasons and explanations given are many, but the underlying rationale is that urologists and physicians did not feel that this time-consuming and expensive procedure played any role in the subsequent development of therapeutic strategies [25]. Several modifications to the original and difficult to perform Meares–Stamey test have been proposed, including the 'pre- and post-massage test' (PPMT) [29]. The PPMT can be used as a prostatitis screen, using microscopy and culture of urine before and after prostatic massage. For those few patients in whom uropathogenic bacteria are localized to the specimen after massage, a more extensive four-glass test can be performed if the urologist chooses (i.e. feels the need to exclude subclinical urethritis). Certainly a PPMT screen is better than carrying out no localization studies. The interpretation of the PPMT is described in Table 3. The challenge for the 21st century will be to develop a diagnostic test which will promote a validated classification and lead to rational treatment strategies.

Once a patient with chronic prostatitis is diagnosed and classified, how does the clinician or researcher follow his progress? Lessons learned from that other benign

prostate disease, BPH, a clinical condition which is also characterized by symptoms, provides the answer. Several attempts to develop validated symptom scores [30–33] met with various degrees of acceptance by the urological community. The NIH Chronic Prostatitis Clinical Research Network recently published a properly validated prostatitis-specific symptom index [34] which examines the main domains of prostatitis; pain, voiding and quality of life/impact. This NIH Chronic Prostatitis Symptom Index (CPSI) (Fig. 1) is a nine-question questionnaire that is simple, easy and quick to administer, and will be useful in research studies and clinical practice. The NIH International Prostatitis Collaborative Network suggested that this index be used as at least one of the outcome measures in future prostatitis research trials [28]. It also appears that the NIH-CPSI will be extremely useful in documenting and following symptoms of patients with chronic prostatitis in daily clinical practice.

### Perils and pitfalls of a century of treatment approaches

For most of the 20th century, the mainstay of therapy for chronic prostatitis was repetitive prostatic massage [35]. No one was sure how it worked, although many

**Table 3** Interpretation of the PPMT (pre- and postmassage test)

Specimen		Pre-M	Post-M
CAT II	WBC	±*	+
	Culture	±*	+
CAT IIIA	WBC	–	+
	Culture	–	–
CAT IIIB	WBC	–	–
	Culture	–	–

CAT, National Institutes of Health Classification Category (see classification table); WBC, white blood cells; Pre-M, urine specimen before prostate massage; Post-M, initial urine specimen after prostate massage.

**NIH-Chronic Prostatitis Symptom Index**

**(NIH-CPSI)**

**Pain or Discomfort**

1. In the last week, have you experienced any pain or discomfort in the following areas?

- |  |                            |                            |
|--|----------------------------|----------------------------|
|  | Yes                        | No                         |
| a. Area between rectum and testicles (perineum)    | <input type="checkbox"/> 1 | <input type="checkbox"/> 0 |
| b. Testicles                                       | <input type="checkbox"/> 1 | <input type="checkbox"/> 0 |
| c. Tip of the penis (not related to urination)     | <input type="checkbox"/> 1 | <input type="checkbox"/> 0 |
| d. Below your waist, in your pubic or bladder area | <input type="checkbox"/> 1 | <input type="checkbox"/> 0 |

2. In the last week, have you experienced:

- |  |                            |                            |
|--|----------------------------|----------------------------|
|  | Yes                        | No                         |
| a. Pain or burning during urination?                               | <input type="checkbox"/> 1 | <input type="checkbox"/> 0 |
| b. Pain or discomfort during or after sexual climax (ejaculation)? | <input type="checkbox"/> 1 | <input type="checkbox"/> 0 |

3. How often have you had pain or discomfort in any of these areas over the last week?

- 0 Never
- 1 Rarely
- 2 Sometimes
- 3 Often
- 4 Usually
- 5 Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?

- |                                   |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |
|-----------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| <input type="checkbox"/>          | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 0                                 | 1                        | 2                        | 3                        | 4                        | 5                        | 6                        | 7                        | 8                        | 9                        | 10                       |
| NO PAIN AS BAD AS YOU CAN IMAGINE |                          |                          |                          |                          |                          |                          |                          |                          |                          |                          |

**Urination**

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?

- 0 Not at all
- 1 Less than 1 time in 5
- 2 Less than half the time
- 3 About half the time
- 4 More than half the time
- 5 Almost always

6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?

- 0 Not at all
- 1 Less than 1 time in 5
- 2 Less than half the time
- 3 About half the time
- 4 More than half the time
- 5 Almost always

**Impact of Symptoms**

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

- 0 None
- 1 Only a little
- 2 Some
- 3 A lot

8. How much did you think about your symptoms, over the last week?

- 0 None
- 1 Only a little
- 2 Some
- 3 A lot

**Quality of Life**

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

- 0 Delighted
- 1 Pleased
- 2 Mostly satisfied
- 3 Mixed (about equally satisfied and dissatisfied)
- 4 Mostly dissatisfied
- 5 Unhappy
- 6 Terrible

**Scoring the NIH-Chronic Prostatitis Symptom Index Domains**

**Pain:** Total of items 1a, 1b, 1c,1d, 2a, 2b, 3, and 4 = \_\_\_\_

**Urinary Symptoms:** Total of items 5 and 6 = \_\_\_\_

**Quality of Life Impact:** Total of items 7, 8, and 9 = \_\_\_\_

Fig. 1. The National Institutes of Health Chronic Prostatitis Symptom Index is a validated symptom evaluation tool that explores the three important domains of pain, voiding symptoms and quality of life/impact. It should be useful in clinical research and in clinical practice. (Reprinted with permission from [34]).

hypothesized that this massage treatment cleared prostatic ducts blocked with bacteria and debris, or improved local blood supply to the area. While it appeared to benefit many patients, not all patients improved and prostatic massage continued to have its advocates and its adversaries throughout the latter half of the century.

Urologists generally did not favour this particular practice and in 1968, when Meares and Stamey gave them a reason, they abandoned it for a more modern approach of selective antibiotic therapy. However, antimicrobial agents had been used since they were first introduced in the 1930s and 1940s, and it was

conceded at the time and as the century progressed (even with more powerful drugs) that antimicrobial agents were of no benefit to most patients with prostatitis [36]. Indeed, even those patients with a definite uropathogenic presence in the prostate did not always respond to what seemed to be appropriate antibiotic therapy with drugs that seem to penetrate the prostate (e.g. trimethoprim and the quinolones). It is surprising, as antimicrobial agents are the first-line treatment used by almost all urologists and physicians for chronic prostatitis syndromes [6–8], that there are no well-designed randomized placebo-controlled trials published that show the efficacy and safety of antibiotics in this disease [37].

In the last 30 years, many studies were published evaluating a multitude of various treatment manoeuvres other than antibiotics for chronic prostatitis [36,38,39]. Many appeared to be successful, but on closer examination the studies were small, uncontrolled and brief research studies with undefined populations and unvalidated outcome measures. Except for sporadic small and inconclusive studies evaluating miscellaneous medications (e.g.  $\alpha$ -blockers, allopurinol, finasteride) and heat therapy (transurethral microwave thermotherapy), there is no large well-designed placebo-controlled study that provides significant evidence of the efficacy and safety of any device or treatment in the management of chronic prostatitis syndromes. In 1998, the IPCN developed a list of priorities that should be evaluated in properly designed trials in any future research endeavour [28]. These various and miscellaneous treatments, in order of priority, are outlined in Table 4. Recommendations for research studies in chronic prostatitis/chronic pelvic pain syndrome have been developed and published [28]. These guidelines suggest the use of a standardized definition and classification system [27] and the previously described validated symptom score [34] as an outcome measure.

Clinicians seeking guidance for rational treatment strategies from prostatitis research over the last century must use whatever evidence is available. The present author has distilled the available evidence in several reviews [38–40] and suggests the following treatments (and they are only suggestions, not guidelines).

Patients with *Category I* prostatitis (acute infection of the prostate gland) are effectively treated with antibiotics with or without intubated drainage of the bladder.

Patients with *Category II* prostatitis (chronic bacterial infection of the prostate gland and recurrent infection of the lower urinary tract) should be treated with a long course of effective antibiotic therapy (trimethoprim or quinolone antibiotics). For patients who are asymptomatic between acute flare-ups, 6 weeks is suggested; for patients who are chronically symptomatic, 12 weeks of

**Table 4** A listing of the potential therapies that have at least some evidence or theoretical basis for the treatment of chronic prostatitis/chronic pelvic pain syndrome. The list is in order of priorities established by the International Prostatitis Collaborative Network [28]

<i>Treatment category</i>	<i>Examples</i>
Antibiotics	Quinolones, trimethoprim
$\alpha$ -blockers	Terazosin, doxazosin, tamsulosin
Prostatic massage	Repetitive, trigger point release
Anti-inflammatories	NSAIDs, hydroxyzine,
Pain control measures	Gabapentin, tizanidine, amitriptyline
Biofeedback	Perineal (EMG or pressure probes)
Phytotherapy	Quercetin, saw palmetto, pollen extract
$\alpha$ -reductase inhibitors	finasteride
Muscle relaxants	Diazepam, baclofen
Devices	TUMT, TUNA, laser
Physical therapy	Massage therapy, air rings/'donuts'
Psychotherapy	Explore related psychopathologies
Alternate therapy	meditation, coping skills, acupuncture, etc.
Heparinoids	pentosan polysulphate
Other medications	Capsaicin, allopurinol
Surgery	TURBN, TURP, Radical prostatectomy

TUMT, transurethral microwave thermotherapy; TUNA, transurethral needle ablation; TURBN, transurethral resection of bladder neck.

antibiotics are suggested. Prophylactic or suppressive antibiotics with prostatic massage may be required in refractory, relapsing or recurrent disease. Surgery (except as definitive therapy for a lower urinary tract problem, e.g. bladder neck stenosis or urethral stricture) should be considered as only a last resort.

Patients with *Category IIIA*, chronic pelvic pain syndrome should have at least one course of a wide-spectrum antibiotic (quinolone or trimethoprim/ tetracycline, concurrently or sequentially) as the diagnostic accuracy of the lower urinary tract localization test is uncertain. It may also be possible that an uncultured or unculturable organisms (e.g. *Chlamydia* or mycoplasma) might be implicated. When these antibiotics fail, no further antibiotic therapy is warranted. Prostatic massage (with or without the antibiotics) appears to help perhaps a third of patients. For those patients obstructed (either clinically or confirmed with urodynamics)  $\alpha$ -blockade appears to be of benefit. Anti-inflammatories (for inflammatory type pain), finasteride (for patients with large, 'boggy' prostates), pentosan polysulphate (for patients with suprapubic pain and primarily irritative voiding symptoms) or phytotherapy (quercetin, pollen extract or saw palmetto) may benefit a few patients. As a last resort, transurethral thermotherapy may be considered.

Patients with *Category IIIB* chronic pelvic pain syndrome are extremely difficult to cure. Amelioration of symptoms should be the primary goal of therapy. Analgesics,  $\alpha$ -blockers, muscle relaxants and tricyclic antidepressants should be used either sequentially or concurrently (recommended). Biofeedback, pelvic floor massage therapy and other supportive and conservative therapies (diet and lifestyle modification) appears to be helpful in some patients.

By definition, *Category IV* prostatitis is asymptomatic and requires no therapy unless the patient is being evaluated for infertility, prostate cancer (elevated PSA level) or is about to undergo some form of lower urinary tract or endoscopic procedure.

### The challenges ahead

The 20th century has not provided truly effective management strategies for chronic prostatitis. However, the lessons learned from the last 100 years have clarified the challenges now faced. From knowledge of the last 100 years of prostatitis research, there must be an effort not to repeat the mistakes of the past, but rather use them to build a foundation for progress in the future. The challenge is being met; new researchers are establishing their credentials in the field of chronic prostatitis. Epidemiological data, standardized definitions and classifications, and validated symptom indices provide the potential for significant progress over the next decades. This progress will be fuelled by government and industry interest. However, it is obvious from this review that while the causes, epidemiology and diagnostic dilemmas are investigated, large properly designed, randomized placebo- or sham-controlled treatment trials should be pursued.

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