

# **The Prostate and Its Problems**

## **Chapter 1 - Prostatitis**

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# The Prostate and Its Problems

## Chapter 1 - Prostatitis

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## Foreword

With the greying of the baby boomers prostate health is looming large and concern for cancer has become an increasingly frequent topic of conversation. Unfortunately, the topic has also become increasingly complex. During more than a quarter century as a practicing pathologist, I have repeatedly been asked if, how and when to screen for prostate cancer and how to proceed if positive. As Hans Larsen and William Ware have indicated in *The Prostate and Its Problems*, these issues of screening, diagnosis and treatment are hotly debated and make prostate cancer more controversial than any other cancer. Do I request a PSA blood test and run the risk of chasing a false positive or perhaps worse, worrying about not chasing it? If the biopsy is positive, what should I do? What are my chances of ending up impotent and/or incontinent as a result of surgery or radiation? And of course, what if I don't have any insurance? While there are no absolute answers, this comprehensive work provides the most recent relevant studies impacting these decisions. Indeed much of the material is directed toward maintaining a healthy prostate and minimizing the likelihood of ever having to embark on this treacherous and tortuous path.

For a small sampling of the controversy surrounding this cancer one need look no further than PSA. Over many years the screening triple play of transrectal ultrasound, digital rectal exam and PSA has been the cornerstone of medical dogma on prostate cancer. However, from the outset the value of PSA as a screening test for prostate cancer vs. BPH has been under constant assault and the test was even proclaimed dead in 2004 by eminent urologist Professor Thomas Stamey of Stanford University Medical School. This view was based on a large autopsy study that revealed 8% of males in their twenties had prostate cancer with incidence increasing each decade until 80% had it in their seventies. Yet according to the National Cancer Institute, death due to prostate cancer in those over 65 years is only 226 per 100,000. However, it's not just PSA anymore; refinements, such as per cent free PSA (the higher the better) and PSA density (how high is it relative to size of prostate) have been added. PSA velocity (how fast is it changing) is now very much in vogue and this book has a particularly elucidating discussion of this (Chapter 4).

Once you've been determined via screening to be at risk you must decide whether to undergo biopsy. Over the past few years I have seen the incidence of low-grade prostate cancer (Gleason score less than 7) decline and it is now seen very infrequently on biopsy specimens. Whether this is because pathologists tend to err on the side of caution for medicolegal reasons is hard to say, but in any case, it tends to push the decision regarding treatment (or not) firmly back into the laps of the patient and his physician. This means that if you decide on a biopsy you are likely to face the even more daunting dilemma of treatment or not. Given the conflicting data on efficacy of surgery vs. radiation vs. watchful waiting, whether or not to even embark on this slippery slope of screening and diagnosis has come into question. This book contains all the necessary data to make an informed decision at each juncture and, as it reiterates, to always have your biopsy slides reviewed by an independent pathologist before proceeding.

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Mainstream medical journal articles on both BPH and prostate cancer, many of which are financed by large pharmaceutical companies and touted as evidence-based, often fall well short of the mark on objectivity. For example, this book describes how the North American medical community has failed to embrace the well documented, evidence-based studies demonstrating the beneficial effect of saw palmetto on BPH symptoms. Saw palmetto has long been accepted by mainstream medicine in Europe as the first-line treatment for BPH; however, in North America the focus has been on surgery and finasteride despite this drug's already documented history of inducing sexual dysfunction.

*The Prostate and Its Problems* by Hans Larsen and William Ware tackles these thorny issues in a straightforward, easy to understand manner. The myriad questions are addressed via rigorous research translated into plain English. By sifting through all the medical literature they have presented a more balanced view, one that is both evidence-based and objective. Furthermore, unlike more traditional medical texts there is a strong emphasis on alternative, preventive strategies for avoiding inflammation, hyperplasia and cancer of the prostate. Neither author has received funding for this extraordinarily comprehensive work. Both are true scholars motivated purely by the sheer joy of learning and teaching others, and their total dedication to this goal is readily apparent in every page.

This book has appeal well beyond males. Life changing decisions on treatment for prostate cancer should be a joint decision. Oftentimes males are not prepared either emotionally or intellectually to undertake the requisite research to arrive at a well informed choice tailored to their specific situation. This then falls to their spouse. Furthermore, given that prostate and breast cancer are both hormone-dependent cancers and that men with a family history of breast cancer are more likely to get prostate cancer and women with a family history of prostate cancer are more likely to get breast cancer (Chapter 3), much of the presented preventive strategies may have equal gender appeal. Furthermore, antioxidant and anti-inflammatory strategies are of proven benefit for longevity, minimizing both cardiovascular disease and cancer in general.

If you are an informed consumer wishing to become more empowered in your healthcare decisions, then this book is for you. When made by others, many of these decisions are influenced by medicolegal and financial considerations of which you may not even be aware. Wouldn't it be better to know the most recent data and to digest them for yourself rather than to have the decision made for you? Ultimately, it's your life and your money. Hopefully, your PSA level will never become abnormal. However, if you want to become more prepared to deal with such an occurrence before the associated emotional cloud descends to color your thinking, then *The Prostate and Its Problems* by Hans Larsen and William Ware is highly recommended.

**Patrick Chambers, MD**  
**Kailua, Oahu, HI**  
**August 2006**

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**Patrick Chambers** received his baccalaureate degree from Princeton University in Mathematics in 1971 followed shortly thereafter by completion of medical studies at the University of California at Davis. He completed his specialty training in pathology at the Los Angeles County/University of Southern California Medical Center. After more than 25 years as a practicing pathologist and laboratory director at Torrance Memorial Medical Center he recently retired to Kailua, Hawaii, where plentiful sunlight and high vitamin D levels hopefully keep his prostate healthy and cancer free. In an annual review of 4000 American acute care hospitals Torrance Memorial was the only non-teaching hospital of any size to be named a Top 100 Hospital three years in a row (1993, 1994, 1995).





# Preface

**Hans R. Larsen and William R. Ware**

When we decided to join forces in the spring of 2005 to embark on the venture of writing this book, we had both for some time been following the peer-reviewed literature concerning prostate problems and in particular had done a fair amount of research into prostate cancer. One of us (WRW) had closely studied and followed developments in the diagnosis and conventional treatment of this disease, and the other (HRL) had researched alternative methods for prevention and treatment. We both had read numerous books on cancer and prostate cancer in particular and had, somewhat surprisingly, reached the conclusion that no one book covered the entire spectrum of problems. Some books written for the lay audience were excellent in explaining conventional treatment methods, others were quite comprehensive in their discussion of herbs and supplements that might prevent cancer, but none, it seemed to us, really provided the whole gamut of information necessary for a man who wants to take charge of his own health and, along with his physician, make reasoned decisions regarding diagnostic options and possible treatments of prostate problems. Prostatitis and benign prostate enlargement (BPH), although affecting millions of men, did not seem to be covered very well, perhaps because conventional treatment, certainly in the case of prostatitis, is often less than satisfactory.

So our mission was clear, to write a book that covered the three major prostate problems – prostatitis, BPH and cancer – from etiology to therapy, including both alternative and conventional measures of prevention and treatment. The intended audience includes laymen who want to be thoroughly informed and health-care professionals involved in primary care. We also agreed that all statements made in the book would be backed up with references to peer-reviewed medical journals. Another condition was that the material must include the most recent relevant published literature. Given the constraints of the cut-off date for publication, this was no small task, but you are now holding the result in your hands – over 400 pages of information documented with over 1200 references plus appendices providing additional useful information and resources.

If you have prostate problems now, the book provides a comprehensive discussion of your options and offers the opportunity to acquire the background knowledge necessary to understand the diagnosis, prognosis, and possible treatments along with the associated complications and side effects. This knowledge should enable a man to engage in a truly informed interaction with the physician or physicians involved in providing advice and treatment. Given that many of the decisions faced by a man with prostate problems are far from clear-cut, especially in the case of cancer, and that he is frequently given a choice among options, this knowledge turns out to be vital. On the other hand, if you are one of the lucky ones not yet experiencing problems, our book “The Prostate and Its Problems” may help you avoid them in the future.

This book is a thoroughly cooperative effort on the part of two authors, but it would not have been possible without the whole-hearted support of the wife of one of the authors, Judi Larsen, who was instrumental in seeing it come to fruition. Without her word processing skills, editing advice and encouragement, we could not have accomplished the task. Also acknowledged is the assistance of Hannah Koppenhoefer in connection with the artwork.

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**August 2006**

## INTRODUCTION

### The Prostate and Its Problems

Hans R. Larsen MSc ChE

The prostate is a gland located in the pelvic area directly beneath the bladder. It surrounds the urethra (the tube that conducts urine from the bladder to the penis). The prostate is both a gland and a muscle. As a gland it produces a milky, alkaline fluid that is mixed with sperm (produced in the testicles) to produce the fluid (semen) ejaculated during sexual intercourse and masturbation. The prostate gland also contains an enzyme, 5-alpha-reductase, which converts testosterone to dihydrotestosterone. As a muscle the prostate works to propel seminal fluid through the urethra and out of the penis during ejaculation. The muscle part of the prostate also acts as a “gate” for the flow of urine. There are two shut-off valves that control urination, one (internal sphincter) at the junction of the bladder and the upper part of the prostate, the other (external sphincter) at the base (apex) of the prostate. Both are required to prevent incontinence and dribbling. The upper shut-off valve also prevents seminal fluid from “shooting backwards” into the bladder during ejaculation (retrograde ejaculation).

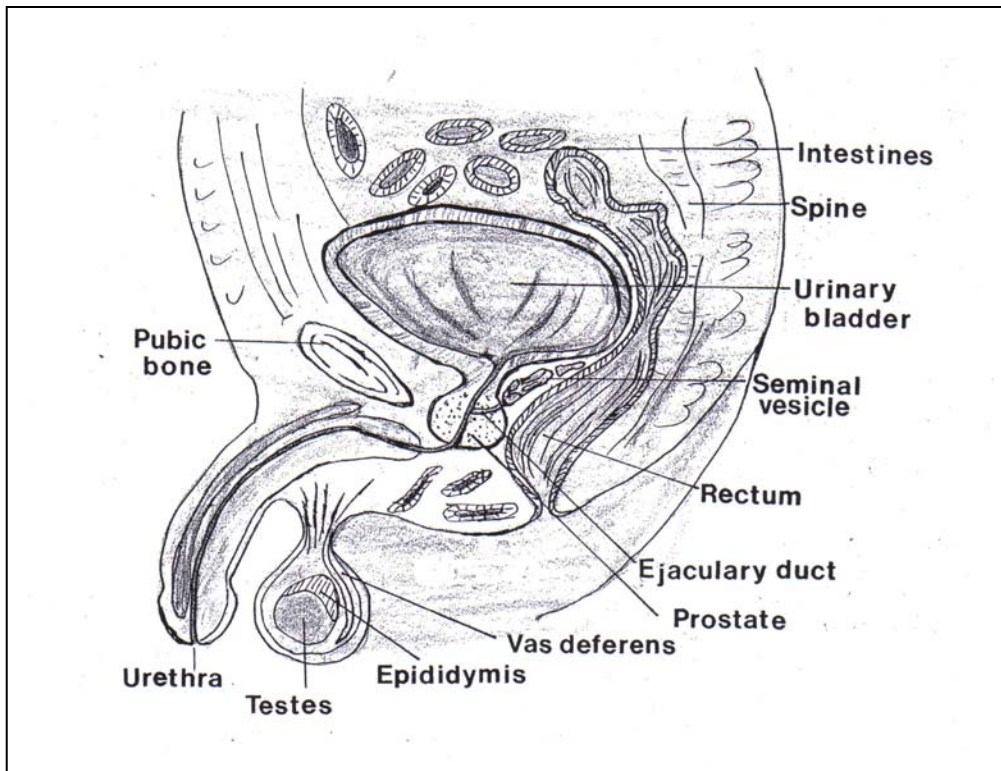
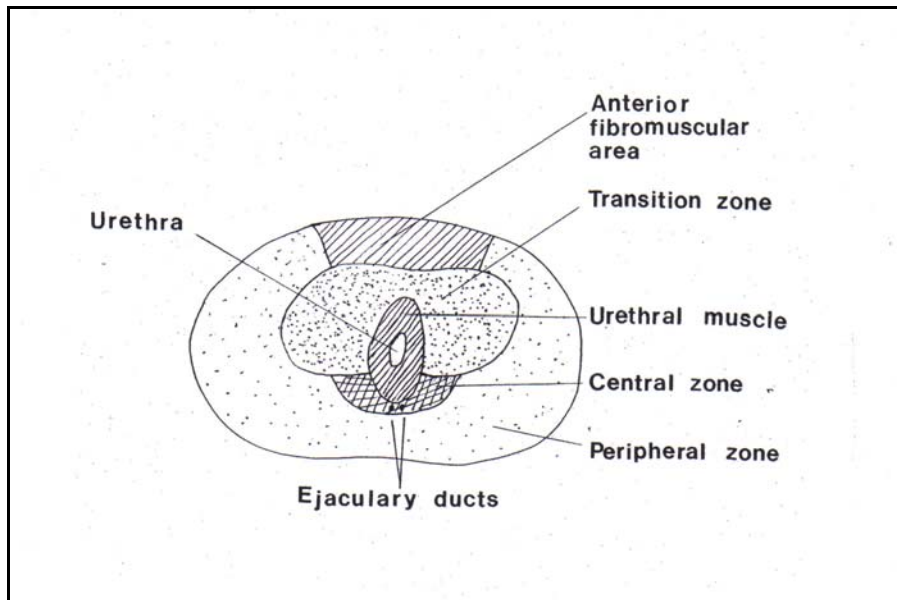


Figure 1-1. Male Pelvic Area

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The prostate, prior to puberty, is quite small, about the size of a marble. It undergoes a rapid growth spurt during puberty and reaches the size of a walnut in adolescence. In middle age the prostate usually begins enlarging again and can exceed the size of a golf ball. The average weight of a normal adult prostate is 20-40 grams.

The prostate is surrounded by a dense fibrous capsule and can be divided into three zones – the peripheral zone, the central zone, and the transition zone.



**Figure 1-2. Prostate Cross-sectional View**

The prostate contains three different types of cells:

- Stromal cells, which form the overall structure of the gland.
- Glandular cells, which produce a milky, alkaline fluid which, when mixed with sperm, become semen.
- Smooth muscle cells, which contract during sexual intercourse and squeeze the fluid produced by the glandular cells into the urethra. Here it mixes with semen and is then ejaculated through the penis.

As most men over the age of 50 years know only too well, the prostate is a prominent source of problems and discomfort, especially problems with urination and pain in the pelvic area. The three most common disease conditions associated with the prostate are prostatitis (inflamed prostate), prostate enlargement (benign prostatic hyperplasia or BPH), and the most feared of them all, prostate cancer. Both prostatitis and BPH usually manifest themselves through difficulties in urination (lower urinary tract symptoms or LUTS); thus it is important to understand how the urination (micturition) process works.

## THE MICTURITION PROCESS

In infants, the micturition process is involuntary, in other words, it happens when it happens. However, after maturation of the nervous system the process becomes voluntary, in other words, the individual can control when and where to urinate. This control can be lost again as a result of aging, neural injury, or severe BPH. Losing control of normal bladder function is, unfortunately, very common. It is estimated that about 17 million men and women in the USA alone suffer from bladder control problems.[1]

The lower urinary tract (bladder, sphincters and urethra) is innervated by the two branches of the autonomic nervous system (ANS), the parasympathetic (vagal) branch and the sympathetic (adrenergic) branch, and also receives input from pudendal nerves originating in the somatic nervous system. These different nerves work in unison (most of the time) to control the two phases of the micturition cycle, the filling (storage) phase, and the voiding (elimination) phase. During the filling phase filtered urine flows from the kidneys through the ureter into the bladder. The bladder walls (detrusor muscle) are kept in a relaxed state by the combined action of the sympathetic and parasympathetic branches of the ANS and thus allows for filling. At the same time, sympathetic nerve activity keeps the bladder sphincter (shut-off valve) and urethra tightly closed so that leakage is avoided.

When the bladder reaches its storage capacity (about 100-150 mL or 3.5-5 ounces) a message is sent to the control center in the brain indicating that it is time for the emptying phase to begin. People without urinary dysfunction can, to a large extent, control the timing of voiding, but eventually the process must proceed. The voiding phase involves activation of vagal nerves in the bladder and expulsion of the urine through the bladder neck, sphincters and urethra. The successful voiding process needs the cooperation of the pudendal nerves and the sympathetic branch of the ANS to relax the sphincters and urethra and thus make voiding possible. It is also believed that the increased parasympathetic activity in the voiding cycle causes the release of nitric oxide, which further relaxes the outlet musculature.[2]

It is clear that the urination process is by no means simple and that things can easily go wrong. There is now evidence that some of the urinary difficulties (frequency, urgency, intermittent stream, and nocturia) involved in both prostatitis and BPH are, at least in part, due to excessive sympathetic activity which keeps the external sphincter and urethra compressed when they should be relaxed.[2,3]

The main neurotransmitter released by the nerve endings of the sympathetic branch is norepinephrine. It is well established that alpha-adrenoreceptor blockers, which inhibit the muscle-tightening effects of norepinephrine, can be helpful in dealing with prostatitis and BPH (see Chapters 1 and 2).

Sympathetic nervous system over-activity restricting urinary flow could potentially lead to a thickening of the bladder wall (development of more muscle power) in an attempt to overcome the obstruction. Obstruction of the urethra by overgrowth (BPH) can also result in the development of a thickened and overly muscular bladder wall (detrusor).

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Thus, both prostatitis and BPH can affect bladder function and create a vicious feedback loop leading to a worsening of LUTS.

#### **UNDERLYING CAUSES OF PROSTATE PROBLEMS**

The three major prostate disorders, prostatitis, BPH and cancer, involve one or more of the following underlying problems:

- Uncontrolled cell growth (benign or malignant)
- Over-activity of the sympathetic nervous system (SNS)
- Bacterial infection
- Inflammation
- Neuromuscular spasm
- Severe emotional stress

Prostatitis may involve bacterial infection, inflammation, neuromuscular spasm, SNS over-activity and severe emotional stress. BPH involves SNS over-activity and benign, uncontrolled cell growth – or rather lack of controlled cell death (apoptosis). Prostate cancer involves malignant, uncontrolled cell growth and inhibited apoptosis and can, in the later stages, also involve LUTS due to pressure exerted on the urethra by the tumor.

#### **PROSTATITIS**

The name “prostatitis” is, unfortunately, somewhat misleading as neither the prostate nor an inflammation is necessarily involved. The causes, risk factors, prevention and treatment of this common disorder are discussed in detail in Volume 1 of *The Prostate and Its Problems*.

#### **BENIGN PROSTATIC HYPERPLASIA (BPH)**

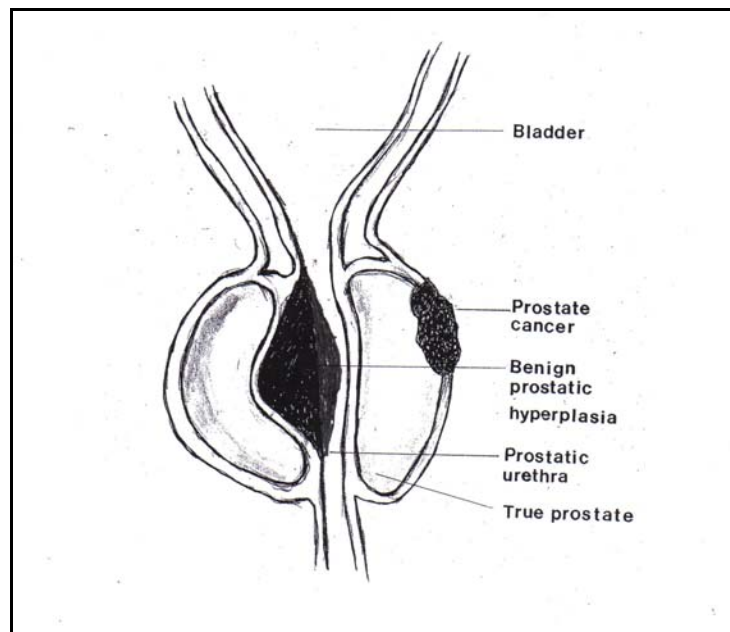
The name “benign prostatic hyperplasia” or “enlarged prostate” is also, to some extent, a misnomer. Many cases of BPH do not involve an abnormally large prostate and are treated successfully with alpha-receptor blockers indicating that their main cause is SNS over-activity rather than overgrowth causing narrowing and pressure on the urethra. Furthermore, there is evidence that it is not really uncontrolled growth of benign cells in the transition zone (the zone bordering the urethra) that is the problem, but rather a lack of controlled cell death. The causes, risk factors, prevention and treatment of BPH are discussed in detail in Volume 2 of *The Prostate and Its Problems*.

#### **PROSTATE CANCER**

Prostate cancer involves the growth of abnormal (malignant) cells generally in the peripheral zone, most often close to the outer surface of the prostate. Prostate tumors thus do not, at least in the initial stages, put pressure on the urethra and thus produce

no urinary symptoms. Because the tumors are on the outer part of the gland they can, however, often be felt during a digital rectal examination (DRE).

While neither prostatitis nor BPH are life-threatening in their own right, prostate cancer certainly is. Thus, three volumes of *The Prostate and Its Problems* are devoted to this disease. Volume 3 discusses causes, risk factors, diagnosis and prevention. Volume 4 covers conventional treatment of localized and advanced cancer, while Volume 5 provides information about alternative treatments, specialized cancer clinics and emerging trends in diagnosis, procedures and treatment for prostate problems.



**Figure 1-3. Location of BPH and Cancer**

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# Prostatitis

Hans R. Larsen MSc ChE

## INTRODUCTION

Prostatitis is a poorly understood disease highly resistant to effective treatment. It is the most common urologic diagnosis in men below the age of 50 years and rivals BPH and prostate cancer incidence in men above the age of 50 years. More than 2 million visits to physicians in the USA every year are related to prostatitis and it is estimated that 26% of all men will have been diagnosed with prostatitis by the time they reach the age of 85 years.[1,2] The prevalence (percentage of men with the disease at any given point in time) is estimated at 10-16% in the USA, 13-14% in Europe, and about 9% in Malaysia.[3] It is clear that prostatitis not only blights the lives of many men, but also poses a significant burden on the health care system.

Prostatitis (inflammation of the prostate) is actually a misnomer as the disease may not involve inflammation and may not even be related to the prostate at all. In 1999 the National Institutes of Health agreed on standard definitions and classifications for the five different types of prostatitis found in clinical practice.[4]

<b>NIH Classification System for Prostatitis</b>	
Category I	Acute bacterial prostatitis
Category II	Chronic bacterial prostatitis
Category IIIA	Chronic inflammatory, nonbacterial prostatitis (symptomatic)
Category IIIB	Chronic non-inflammatory, nonbacterial prostatitis (symptomatic)
Category IV	Asymptomatic inflammatory prostatitis

### **CATEGORY I – ACUTE BACTERIAL PROSTATITIS**

This form of prostatitis is quite rare probably accounting for only 2-5% of all cases. It is a serious condition that requires prompt treatment.[4]

## SYMPTOMS AND DIAGNOSIS

Acute bacterial prostatitis involves a bacterial infection of the prostate and its main symptoms are pain in the pelvic/perineal area and frequent and painful urination. Since it is an acute infection, it is also often accompanied by fever, chills and general malaise. The diagnostic workup for patients suspected of having the condition involves physical examination (with gentle digital rectal examination), microscopic evaluation of a



urine sample, a urine culture to determine the most appropriate antibiotic for treatment, and if systemic symptoms are present, cultures of blood samples. The patient's recent medical history is discussed with particular emphasis on the status of the immune system, recent urinary tract infections (UTIs), and recent medical tests such as cystoscopy, biopsies or use of catheters. The digital rectal examination (DRE) will usually reveal a tender prostate. The patient should also be assessed for urinary retention by palpating (feeling) the bladder or through an ultrasound scan.[4] The PSA (prostate specific antigen) is usually substantially elevated during the acute phase of category I prostatitis and it may take 2 to 3 months before it returns to normal even with optimum antibiotic treatment.[5] Clearly, a decision to have a prostate biopsy should not be based on a PSA value obtained within 3 months of the resolution of an acute prostatitis episode.

### **CAUSES AND RISK FACTORS**

Category I acute bacterial prostatitis is associated with a lower urinary tract infection in most cases (65-80%) involving *Escherichia coli* (*E. coli*), a common bacteria found in the gastrointestinal tract. *Staphylococcus aureus*, *Pseudomonas* and other bacteria may also be involved.[1] It is believed that the condition is caused by an infection working its way up through the urethra and/or by reflux of infected urine into prostatic ducts.[6] The infectious bacteria can be transmitted through sexual intercourse (especially unprotected anal intercourse), from contaminated water, from swimming in a dirty pool or a contaminated lake, or from an infection elsewhere in the body. Acute prostatitis is often associated with a bladder infection.

### **PREVENTION**

The most important preventive measure is to avoid the risk factors mentioned above and to maintain a generally good state of health, specifically a well-functioning immune system. It is also important to avoid bladder infections (cystitis) and if one does occur to eliminate it quickly. Cranberry juice or cranberry extract has been found quite effective in preventing and eliminating lower urinary tract infections.[7]

### **TREATMENT**

If symptoms of general sepsis (fever, chills, general malaise) are present then hospitalization is frequently necessary. Treatment consists of intravenous administration of antibiotics (fluoroquinolones), intravenous hydration, and urinary drainage if urinary retention is an issue. Once the systemic symptoms are resolved treatment with antibiotics is usually continued for 3-4 weeks on an outpatient basis. As it is possible that the UTI initiating the prostatitis may be caused by stones, diverticula or anatomic abnormalities, it is also recommended that additional tests (ultrasound, CT scans, MRI) be performed in order to determine if an underlying cause can be found and eliminated.[4]

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It is very important to supplement with live probiotics (*L. acidophilus*, *L. bifidus*, *L. casei*, etc.) during and for a couple of months after treatment with antibiotics, especially the broad-spectrum ones like fluoroquinolones. These antibiotics destroy the normal flora in the gut (large intestine) and their use can result in a nasty case of candidiasis, which can be very difficult to eradicate.[8]

### CATEGORY II – CHRONIC BACTERIAL PROSTATITIS

The chronic form of bacterial prostatitis is also quite rare accounting for only 2-5% of all prostatitis diagnoses. Although chronic bacterial prostatitis shares many of the symptoms of the acute form, it is only rarely that category I prostatitis transforms into category II.[4]

#### SYMPTOMS AND DIAGNOSIS

Chronic bacterial prostatitis is a chronic or persistent infection of the prostate without the systemic involvement found in the acute form. It usually manifests itself as intermittent cystitis-like urinary symptoms (frequent and painful urination) accompanied by low level discomfort or pain in the pelvic area. A history of previous urinary tract infections is common among category II patients and should alert the physician to the diagnosis.[4]

The recommended diagnostic workup includes physical examination, medical history, urinalysis as well as referral for tests to determine potential causes of the UTIs. Urology textbooks also recommend that the Meares-Stamey localization test be performed.

The **Meares-Stamey test** is the gold standard for the diagnosis of prostatitis. The test involves the collection and analysis of three urine samples (before, during, and after prostatic massage) and one sample of prostatic secretion obtained by massage of the prostate (EPS or expressed prostatic secretion). Analysis of the samples makes it possible to determine whether bacteria and/or inflammation are present in the urethra, bladder and/or prostate.[4] The test is rarely used in today's time-constrained environment. Instead, a course of antibiotics is prescribed. If this solves the problem, then the diagnosis was probably category II prostatitis – if not, then further testing is warranted.[9,10]

#### CAUSES, RISK FACTORS AND PREVENTION

As in the case of acute bacterial prostatitis, category II prostatitis is caused by a bacterial infection, most often with *E. coli*. The risk factors are also similar to those for category I with special emphasis on recurrent bladder infections. Thus, the main preventive action required is to avoid such infections.

## TREATMENT

The standard treatment for chronic bacterial prostatitis involves a 1-3 months course of prostate-penetrating antibiotics such as fluoroquinolones, trimethoprim-sulfamethoxazole (Septra), or trimethoprim (Protoprim). The cure rate is 60-80% with fluoroquinolones and about 30-50% with Septra and Protoprim. Overall, it is estimated that about one-third of category II patients have recurrences after a seemingly successful first treatment.[1] It is not clear why this is, but there is some speculation that stones (calculi) and other debris lodged in the ducts of the prostate may prevent the antibiotics from reaching and completely eliminating the infectious bacteria.[11]

**Massage of the prostate gland**, sort of an extended DRE, used to be a mainstay in the treatment of chronic prostatitis. It is possible that it may have had some beneficial effect by pushing debris and perhaps small stones out of the prostatic ducts, but it is rarely used nowadays.[10] However, there is some evidence that repetitive prostatic massage combined with antibiotic therapy may be beneficial in category II prostatitis. This approach was originally developed in the Philippines and has been evaluated by J.C. Nickel and colleagues at Queen's University in Canada. Their study involved 22 men who underwent tri-weekly prostatic massage combined with specific culture-directed antibiotic treatment for 6 to 12 weeks. The Canadian researchers conclude that 46% of the patients had a greater than 60% decrease (improvement) in symptom severity and suggest that a combination of prostatic massage and culture-specific antibiotics looks promising for the treatment of chronic bacterial prostatitis.[11]

It is possible that transurethral prostate resection (TURP) or injection of antibiotics directly into the prostate may result in a cure, but if not, lifelong medication with antibiotics in doses just high enough to prevent bladder infections may be the only option.[4]

Long-term treatment with **fluoroquinolones** such as ofloxacin (Floxin), ciprofloxacin (Cipro), and norfloxacin (Noroxin) is, however, not without problems. Professor Jay S. Cohen of the University of California has identified 45 cases where patients developed serious adverse effects after taking Cipro or other fluoroquinolones. The primary reactions involved the peripheral nervous system and were manifested as numbness, twitching, spasms, tingling or burning pain. About 78% of the cases also had central nervous system involvement with symptoms such as dizziness, agitation, hallucination, and impaired cognitive function. Over 90% of the adverse reactions showed up within 2 weeks with 33% occurring within 24 hours of beginning treatment. Symptoms were often long-term in nature with 58% of patients having them for a year or more. In 40% of the cases the prescribing physician did not recognize the symptoms as a reaction to fluoroquinolones or dismissed their significance. Dr. Cohen concludes that fluoroquinolones such as Cipro are far from benign and should be used with great care. He also points out that less dangerous antibiotics such as penicillin and doxycycline are often all this is required to cure an infection.[12]

The potential problems with long-term use of fluoroquinolones are also highlighted in a study reported by a team of Dutch and British researchers. They found a significantly increased risk of Achilles tendon rupture and Achilles tendonitis in men using fluoroquinolones. The risk increased with age, dosage and concomitant use of

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corticosteroids (prednisone).[13] There are now also signs that some bacteria are becoming resistant to fluoroquinolones; a problem, no doubt, partly caused by the liberal prescription of the drugs for the nonbacterial types of prostatitis.[10] Antibiotics and especially fluoroquinolones can also cause nasty candida infections, both in the colon and on the head of the penis. They should not be taken without concomitant supplementation with probiotics.

### CATEGORY III – NONBACTERIAL CHRONIC PROSTATITIS

Category III prostatitis, also known as **chronic pelvic pain syndrome** (CPPS), is by far the most common form and constitutes about 90-95% of all cases. It is characterized by the absence of detectable bacterial infection (Meares-Stamey test) and is further divided into two sub-categories – category IIIA where there is evidence of inflammation (presence of white blood cells in semen, post-DRE urine, and EPS), and category IIIB (also known as prostatodynia) where there is no evidence of inflammation.[14] Both categories share the characteristics of pain in the pelvic area (perineum, penis, scrotum, lower abdomen, back or groin), frequent, painful or difficult urination, and incomplete voiding of the bladder. Some patients also experience pain upon ejaculation, or erectile dysfunction.[4,15]

Although not life-threatening as such, CPPS can seriously affect quality of life. Several studies have shown that men with severe category III disease experience a quality of life comparable to that of patients with unstable angina, a recent heart attack, or Crohn's disease. Their mental outlook has been reported to be poorer than that of men with diabetes or congestive heart failure.[3] It is estimated that about 267,000 men between the ages of 25 and 84 years are diagnosed each year with category III prostatitis in the USA alone.[2]

Some treatment modalities are more applicable to category IIIA than to category IIIB. However, the two categories are usually combined in clinical studies and management recommendations. The following discussion adheres to this convention.

### SYMPTOMS AND DIAGNOSIS

The most characteristic symptom of category III prostatitis is pain and this symptom is often the main distinguishing factor between prostatitis and benign prostatic hyperplasia (BPH). The pain is felt in the pelvic area specifically in the perineal area, the tip of the penis, scrotum, lower abdomen, back or groin, and may or may not originate from the prostate itself. Urinary symptoms are similar to those experienced in BPH, lower urinary tract infections (UTIs), and category I and II prostatitis. These symptoms, also known as LUTS (lower urinary tract symptoms) include frequent, difficult or painful urination, incomplete voiding of the bladder, and urgency.[2,4]

The recommended diagnostic workup for suspected category III prostatitis includes a physical examination with DRE, medical history, urinalysis and urine culture (pre and

post DRE), and examination and tests to find possible causes of the UTI. The Meares-Stamey test is rarely used due to the time and effort involved in its execution. In interpreting the results of the diagnostic tests, it needs to be kept in mind that the symptoms of category III prostatitis can mimic those of lower urinary tract obstruction, bladder stones, ejaculatory duct obstruction, testicular cancer, and other chronic pain syndromes such as fibromyalgia.[4]

The initial evaluation in case of suspected category III prostatitis may also include the completion of the NIH-CPSI (National Institutes of Health Chronic Prostatitis Symptom Index) questionnaire. It includes questions designed to determine the source and severity of pain, the nature and degree of urinary difficulties, and the impact of the condition on the patient's quality of life (see Appendix D). The completed questionnaire is useful in directing treatment and measuring its benefit. [1,9,10]

There is, unfortunately, no agreement as yet as to what range of values (1-8, etc) would constitute mild, moderate, and severe prostatitis.[9,10]

Although the protocol to be followed in diagnosing men with suspected category III prostatitis is well described in urology textbooks and major review articles, it is probably rarely used in practice. It is time-consuming and expensive, so most GPs and urologists follow a more empirical approach by prescribing a 3-6 week course of antibiotics, perhaps accompanied by an anti-inflammatory and an alpha-blocker to relieve urinary symptoms. If this treatment resolves the problem then all is well - if not, then further evaluation and testing is clearly indicated. [4,9,10]

### **Prostatitis, PSA and LUTS**

Some physicians also order a PSA (prostate specific antigen) test as part of the routine examination. This may produce misleading results in the case of suspected category III prostatitis or chronic pelvic pain syndrome (CPPS). As mentioned earlier, PSA levels can increase dramatically during the acute phase of category I prostatitis. Values as high as 50-100 ng/mL are not uncommon and it can take up to 6 months after the infection is resolved before PSA levels return to normal. [9] It is believed that inflammation disrupts the barriers that normally keep PSA within the prostate thus allowing it to escape into the blood stream resulting in higher test results.[5] Yaman *et al.* at the University of Ankara have found that PSA levels increase with increasing aggressiveness of inflammation in the prostate.[16]

The situation in case of category III prostatitis is similar, at least as far as category IIIA (inflammatory) is concerned. Caleb Bozeman and colleagues at Louisiana State University performed PSA testing on 95 men diagnosed with category IIIA prostatitis and found that they had an average PSA level of 8.48 ng/mL. The men were scheduled for biopsies, but were first given a 4-week course of antibiotics (fluoroquinolones or doxycycline) and anti-inflammatories (ibuprofen or celecoxib). At the end of the 4 weeks, 44 of the men (46.3%) had experienced a significant reduction in PSA level (to an average of 2.48 ng/mL) and their biopsies were cancelled. The researchers conclude that treatment of chronic prostatitis in men with high PSA levels can substantially reduce the need for biopsies. They also noted that PSA levels in men diagnosed with cancer following the 4-week treatment period only experienced an insignificant drop in PSA from 8.32 to 7.92 ng/mL on average.[17]

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Other researchers have found average PSA values as high as 28.5 ng/mL among patients diagnosed with chronic, inflammatory prostatitis [18]. There is no indication that PSA levels are increased in non-inflammatory (category IIIB) prostatitis.

Porter *et al.* at the Virginia Mason Medical Center in Seattle determined severity of LUTS according to the American Urologic Association Symptom Score (AUAS – See Appendix E) in 569 patients who had undergone needle biopsy of the prostate guided by transrectal ultrasound (TRUS). They found a clear association between a low AUAS score (<8) and a positive biopsy result. They conclude that a low AUAS score (indicative of the absence of benign disease) is an important predictor of prostate cancer.[19] The conclusions from these studies are:

- Men with an elevated PSA level suspected of having prostatitis should undergo a 3-4 week course of antibiotics and anti-inflammatories before a decision regarding biopsy is made.
- Men with severe LUTS are less likely to have prostate cancer than are men with a low AUAS score.

### CAUSES OF CHRONIC PELVIC PAIN SYNDROME

Before one can even begin to hope to understand the causes of category III prostatitis (chronic non-bacterial prostatitis), it is necessary to erase the name from one's memory and instead focus on the alternative name of the condition – **chronic pelvic pain syndrome or CPPS**. This designation corresponds much closer to reality since the pain experienced in CPPS may not originate in the prostate at all, and the condition may or may not involve inflammation.

The frustration of not knowing the cause of CPPS is shared by patient and physician alike and is aptly described in statements like the following:

*“Despite its prevalence and its drain on health care resources, our understanding of the etiology, diagnosis and treatment of prostatitis has not advanced with that of other prostate diseases.”*[6]

*“The prostatitis syndromes are some of the most prevalent conditions in urology, but also the most poorly understood.”*[20]

*“Prostatitis is an ill-defined condition without clear-cut diagnostic criteria and treatment strategies.”*[21]

*“By contrast, the much more common nonbacterial prostatitis and prostatodynia syndromes remain an enigma, both in etiology, appropriate work-up and therapy.”*[15]

*“In contrast, chronic prostatitis/chronic pelvic pain syndrome (category III), which accounts for 90-95% of prostatitis cases, is of unknown etiology and is marked by a mixture of pain, urinary, and ejaculatory symptoms with no uniformly effective therapy.”[4]*

So in other words, we don't know what causes CPPS, we don't know how to diagnose it accurately, and we don't know how to treat it effectively.

Research into CPPS is ongoing and recent findings have shed some light on the condition. The most common symptoms of CPPS are:[2]

- Dysuria (difficult and painful urination) – 46.6%
- Perineal pain (pain in area between rectum and testicles) – 34.4%
- Frequent need to urinate – 39.2%
- Pain in the bladder/suprapubic area – 39.2%

CPPS does not necessarily involve inflammation and is perhaps more likely to be a bladder problem or a problem with the musculature of the pelvic floor (perineal bundle). Says urologist Stephen Jones MD of the Cleveland Clinic, “If the prostate is not tender on DRE then prostate inflammation is not the problem.” According to Dr. Jones many of his patients actually suffer from a muscle spasm in the perineal muscle bundle, a condition that certainly would fall under the umbrella term CPPS, but has nothing to do with the prostate.[10]

Dr. Regula Doggweiler Wiygul MD, a prostatitis expert at the University of Tennessee wonders if CPPS and interstitial/painful bladder syndrome are the same disease. Dr. Wiygul also believes that neurogenic inflammation, that is, inflammation caused by the release of certain neuropeptides from sympathetic nerve endings play a role in CPPS-related inflammation. She also suggests that myofascial pain syndrome (similar to that encountered in fibromyalgia) may be involved in CPPS-related pain, particularly in the pelvic floor (perineum) muscle bundle.[22]

Drs. Michel Pontari and Michael Ruggieri at Temple University School of Medicine have studied CPPS in detail and reached the following conclusions:[14]

- There is no correlation between the number of white blood cells (an indication of inflammation) in semen, EPS or post-DRE urine and degree of pain indicating that degree of inflammation and pain are not related. This is further supported by the fact that category IV prostatitis can involve extensive inflammation, but no pain.
- It is possible that high levels of pro-inflammatory cytokines (signalling molecules) may be involved, as may inhibitors of pro-inflammatory cytokines, especially IL-10. There is some evidence that high levels of pro-inflammatory cytokines and low levels of their inhibitors are associated with pelvic pain.

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- Only 33% of CPPS patients undergoing prostate biopsy are actually found to have signs of inflammation leading to the question, “Is the prostate even actually involved in the symptoms of CPPS?”
- Testosterone seems to dampen inflammation. This may be why 5-alpha reductase inhibitors such as finasteride sometimes help; presumably because they prevent the conversion of testosterone to dihydrotestosterone (DHT) thereby maintaining a higher level of testosterone.
- Mast cells (large cells located in connective tissue) when activated release, among other compounds, histamine and nerve growth factor (NGF) and NGF concentration correlates closely with pain severity.
- Psychological stress is a common feature in men with CPPS and can activate mast cells and thus indirectly increase pain. Psychological stress may also be involved in precipitating a spasm in the pelvic floor muscle bundle and thus result in pain.[10]
- Depression correlates with lower levels of IL-10, a potent inhibitor of pro-inflammatory cytokines; thus, depression could presumably indirectly result in an increase in pain level.
- It is likely that oxidative stress is involved in the process leading to pain, thus explaining why antioxidants like quercetin have been found helpful.

Drs. Pontari and Ruggieri conclude that, “The symptoms of CPPS appear to result from an interplay between psychological factors and dysfunction in the immune, neurological and endocrine systems.”[14]

Researchers at the University of Washington School of Medicine have found a clear correlation between stress and subsequent pain and disability among men with CPPS.[23] Another study carried out at Queen’s University in Canada confirmed a strong correlation between poor quality of life and a high level of pain in CPPS patients.[24] The results of this study prompted Richard E. Berger MD to comment, “This study suggests that better use of pain medications and antidepressive therapy may improve the quality of life in many men with pelvic pain. Perhaps our treatment would be better directed at palliating the symptoms of prostatitis rather than administering frequent ineffectual courses of antibiotics.”[25]

Some researchers believe that congestion of the prostate could be involved in prostatitis[3,21]; however, others dismiss this possibility. Prostate congestion involves a feeling of fullness or pressure in the area of the prostate. It results from the build-up of semen that has not been released through ejaculation. The prostate has a built-in feedback system, which adjusts semen production to the level of sexual activity. If this level is decreased due to abstinence for extended periods of time, then the prostate can become congested with accumulated semen.



There is evidence that stones (calculi) can form in the ducts of the prostate. Cleveland Clinic researchers estimate that about 20% of men with CPPS have calculi in their prostates.[26] Bedir *et al* at the Gulhane Military Academy in Ankara, Turkey report the case of a 50-year-old man with many calculi in his prostate as indicated on DRE and x-rays. The Turkish urologists removed more than 30 stones endoscopically and analyzed their composition. They all consisted of a mixture of calcium phosphate (apatite) and calcium carbonate. After removal of the stones the patient recovered fully from the urinary retention problem that had brought him to the hospital.[27] There is also evidence that reflux of urine into the intraprostatic ducts can result in stone formation and perhaps the formation of urate crystals.[1,6] Stones or urate crystals in the ducts of the prostate could clearly lead to inflammation and pain.

It is abundantly clear from the above that CPPS is a multifactorial disease and needs to be treated as such using elements from drug therapy, phytotherapy, physical therapy, Chinese medicine and, as a last resort, surgery.

## **RISK FACTORS AND PREVENTION**

In view of the significant pain and disability caused by CPPS, it is clearly important to know what, if any, factors might increase the risk of developing the disorder and what can be done to prevent it.

### **RISK FACTORS**

A team of researchers from Harvard Medical School, Brigham and Women's Hospital, Harvard School of Public Health, and Massachusetts General Hospital surveyed 31,681 male American health professionals and found that 5,053 (16%) had, at some point, been diagnosed with prostatitis (category not specified). A majority of these men (57.2%) also had a history of BPH indicating that the two disorders are often coexistent (or improperly diagnosed). There was a clear indication that the probability of receiving a diagnosis of prostatitis increased with age. However, the average age of men with prostatitis was generally about 10 years younger than the average age of men with BPH. Other factors found to affect the risk of prostatitis include:[21]

- Not working full or part time
- A history of BPH
- A history of sexually transmitted disease
- A history of lower urinary tract symptoms
- A vasectomy
- A family history of prostate cancer
- Moderate alcohol consumption (1-2 drinks a day)
- Severe stress at work or at home

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Most of the above factors only affected risk to a very limited degree. However, a prior history of BPH increased risk by 7.7 times and a history of severe voiding symptoms increased it by a factor of 2.8. No correlation was observed between bicycle riding and prostatitis risk; however, other researchers have noted such a correlation, as well as a correlation between prolonged sitting (nerve entrapment) and risk.[22,28]

Ja Hyeon Ku and colleagues at the Seoul National University College of Medicine in South Korea have presented a survey of known risk factors for prostatitis.[3]

- They found no significant differences in the prevalence of prostatitis among younger (less than 50 years of age) and older (more than 50 years of age) men and conclude that age, as such, is not a significant risk factor.
- The association with race and socioeconomic stage is unclear as is the possible effect of different kinds of physical activity.
- Having a sexually transmitted disease is associated with greater risk of prostatitis, but frequency of sexual intercourse is not.
- A history of BPH and urinary tract infections is associated with an increased risk of prostatitis, as is exposure to colonoscopy and severe stress at home and at work.
- Symptoms tend to be more severe during the winter months perhaps indicating that sunlight exposure or vitamin D deficiency could play a role.

A previous history of BPH and urinary tract infections are the strongest risk factors for prostatitis with stress, exposure to colonoscopy and sexually transmitted diseases being less significant factors.

### **PREVENTION**

With the great uncertainty still surrounding the causes of CPPS and the lack of clearly-defined risk factors, except for BPH and LUTS, it is difficult to propose an effective prevention protocol. However, the following measures may be appropriate:

- Avoid prostatic congestion by avoiding sexual practices that may lead to accumulation of semen or prevent ejaculation.
- Prevent the development of BPH using the measures outlined in Chapter 2.
- Protect against sexually transmitted diseases
- Ensure an adequate intake of dietary antioxidants (vitamin A, vitamin C, vitamin E, beta-carotene, alpha-lipoic acid, selenium, resveratrol or grape seed extract) to prevent oxidative stress, which has been implicated in the etiology of CPPS.

- Treat infections of any kind promptly.
- Be alert to the symptoms of lower urinary tract infections (UTIs) and treat them promptly. Cranberry juice or capsules containing concentrated cranberry juice extract (*CranActin* or *Cran-UTI*) are quite effective in washing away bacteria clinging to the walls of the bladder and urethra.[7]
- Supplement with natural anti-inflammatories on a regular basis. Quercetin, turmeric, or Boswellia are good choices.
- There is some indication that men with CPPS have low magnesium levels in prostatic fluids[29]; however, there is no evidence that magnesium supplementation is helpful.

### **TREATMENT OF CHRONIC PELVIC PAIN SYNDROME**

Even though the causes of CPPS are not well understood, there are pharmaceutical drugs, herbal therapies, physical treatments, minimally invasive procedures, and multimodal approaches that have proven somewhat effective in dealing with both the pain and urinary symptoms of CPPS. Some of these therapies are useful on their own, while others are used in various combinations reflecting the multi-factorial origins of CPPS.

#### **PHARMACEUTICAL THERAPY**

Although there is no evidence from clinical trials that antibiotics are effective in the treatment of CPPS which, by definition, is not caused by a bacterial infection, most GPs and urologists treating CPPS start out with a 3-6 week course of antibiotics.[1,6,9] The rationale for this is that laboratory tests may have missed the presence of bacteria, that some antibiotics may have independent anti-inflammatory properties, and that empirical evidence shows that a good proportion of CPPS patients improve if given antibiotics.[1,9] It is, of course, also possible that a large measure of the placebo effect plays a role here.[1] In any case, most physicians agree that treatment with antibiotics should not be continued if it has not proven effective at the end of 6 weeks.

Treatment with antibiotics is often combined with a dose of alpha-adrenergic receptor blocker such as tamsulosin (Flomax).[1,6,20] The rationale for this is that the alpha-blocker may improve urinary flow and thus help the antibiotics penetrate further into the prostate.[20] Some smaller trials have shown the combination to be effective, but a recent, large, randomized, double-blind trial found that neither fluoroquinolones (ciprofloxacin) nor tamsulosin nor their combination had a significant effect on pain or urinary difficulty scores (NIH-CPSI score, see Appendix D).[30] The clinical trial involved 196 men with CPPS who were treated in 10 different urology outpatient clinics. The

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men had suffered from CPPS for an average of 6.2 years and had a minimum NIH-CPSI score of 15. The study participants were randomized to receive a placebo, 500 mg of ciprofloxacin twice a day, 0.4 mg of tamsulosin once a day, or a combination of the two drugs. The treatment lasted for 6 weeks at which point the men were reassessed using the NIH-CPSI; they were also reassessed 9 and 12 months after beginning the treatment to evaluate long-term response. At baseline, the average total NIH-CPSI score for the men was 25 with pain score making up 12 of this, urinary score accounted for 5, and the remaining 8 related to quality-of-life. At the end of the 6-week trial period, the total score had decreased by 5 points (2 for pain, 1 for urinary difficulties, and 2 for quality-of-life). The group on ciprofloxacin scored slightly better after treatment, but the difference was not statistically significant. The percentage of men reporting marked to moderate improvement after the 6-week treatment was 22% in the placebo group, 22% in the ciprofloxacin group, 24% in the tamsulosin group, and 11% in the combination group. The researchers conclude that their data do not support the use of ciprofloxacin, tamsulosin or their combination in the treatment of men with long-standing CPPS and at least moderate symptoms according to the NIH-CPSI score.[30]

It is also common practice to prescribe NSAIDs or COX-2 inhibitors to men suffering pain from CPPS and, in many cases, they do indeed help ameliorate the pain.[1,6,9]

The use of finasteride (5-alpha-reductase inhibitor) to alleviate CPPS has also been evaluated. The rationale for this is that finasteride may improve urinary flow by shrinking the prostate and may also indirectly help reduce inflammation by maintaining higher testosterone levels. A recent clinical trial evaluated finasteride in 64 men diagnosed with CPPS. The men had all been on antibiotics previously for at least 3 weeks and 82% had also been treated with alpha-receptor blockers. The men were randomized to receive either 325 mg/day of saw palmetto or 5 mg/day of finasteride for the 1-year study period. At the end of the study, the average NIH-CPSI score had decreased from 23.9 to 18.1 in the finasteride group and from 24.7 to 24.6 in the saw palmetto group. Urinary symptoms did not improve in the finasteride group. The researchers conclude that finasteride may improve pain and quality-of-life scores in CPPS.[31]

Muscle relaxants such as baclofen and diazepam have also been suggested as means of ameliorating pain in CPPS, but there is no clinical evidence that they are effective.

There clearly is no one magic drug that will help reduce the symptoms of CPPS let alone eliminate them. However, some agents have shown promise and may help certain subgroups of men.

### **PHYTOTHERAPY**

Because of the limited success obtained with pharmaceutical drugs, many CPPS sufferers and even the medical profession itself have investigated the possible benefits of herbal therapy. The most investigated and promising agents for the treatment of CPPS are quercetin, Cernilton (bee pollen), saw palmetto, and small-flowered willow herb (*Epilobium parviflorum*).

**Quercetin** is a naturally occurring bioflavonoid found in green tea, onions, and red wine. It has documented anti-inflammatory, antioxidant, and nitric oxide-inhibiting properties. Several studies have shown it to be effective in the treatment of chronic prostatitis, particularly the non-bacterial form (CPPS). Daniel Shoskes and colleagues at the University of California Medical Center evaluated the effect of supplementation with 500 mg of quercetin twice daily in a group of 30 men diagnosed with CPPS (inflammatory or non-inflammatory). The men were randomized to receive a placebo or quercetin for one month and were then re-evaluated using the NIH-CPSI score. The score decreased from 20.2 to 18.8 (not significant) in the placebo group, but decreased a very significant 38% (from 21.0 to 13.1) in the quercetin group. Two-thirds (67%) of men taking quercetin had an improvement in symptoms of at least 25% as compared to only 20% of the placebo group experiencing a 25% improvement. In a follow-up experiment, 17 patients were treated with a proprietary formulation (*Prosta-Q*) containing quercetin as well as bromelain and papain to aid in quercetin absorption. In this group, 82% experienced at least a 25% improvement in symptom score. Quercetin was particularly effective in reducing pain and improving quality-of-life score. The researchers conclude that quercetin gives significant symptomatic relief in men with non-bacterial chronic prostatitis (CPPS).[32]

**Cernilton or cernitin** is bee pollen gathered from the rye flower. At least two clinical trials have found it to be effective in alleviating CPPS symptoms. In 1989 Buck *et al* reported that 13 out of 15 patients with CPPS experienced complete and lasting relief or a marked improvement after supplementing with cernilton.[33] The same group later reported that cernilton also was effective in alleviating symptoms of BPH.[34] A 1993 follow-up study by Rugendorff *et al* at the University of Gottingen confirmed Buck's findings. The clinical trial involved 90 patients with CPPS who were treated with one tablet of *Cernilton N* three times daily for 6 months. The group consisted of 72 men with no complicating factors and 18 men who did have complicating factors like urethral strictures, prostatic calculi (stones), or bladder neck sclerosis. Among the 72 men with no complicating factors, 78% had a favorable response, with 36% being completely cured and 42% improving significantly. In the group with complicating factors, only one patient showed a response. Cernilton was well-tolerated by 97% of the patients.[35]

**Saw palmetto** is being used successfully in the treatment of BPH [36] (see Chapter 2). However, there are no clinical trials indicating that it is effective in the treatment of CPPS. As a matter of fact, one trial comparing finasteride and saw palmetto in the treatment of CPPS found no beneficial effect of saw palmetto.[31,37] Unfortunately, the authors of the trial did not specify the brand of saw palmetto used. It is well known that the effectiveness of saw palmetto extracts is highly dependent on the solvent used in the extraction process. The German prescription product *Permixon* is extracted with hexane and is the most effective and the one most often used in successful clinical trials.

**Small-flowered willow herb (*Epilobium parviflorum*)** is a well known folk remedy for the treatment of prostate problems, including BPH and prostatitis.[38] In 2006 Steenkamp *et al* at the University of Pretoria in South Africa evaluated 5 herbal remedies that have reputed benefits in the treatment of BPH and prostatitis, included among them were small-flowered willow herb, *pygeum africanum*, *Serenoa serrulata* (a form of saw palmetto), *Agathosma betulina*, and *Hypoxis hemero callidea*, two plants native to South

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Africa. The researchers found that *Epilobium*, both as a tea and ethanol extract was highly effective in inhibiting the growth of *E. coli* in culture; the ethanol extract was substantially more effective than the water extract (tea). The ethanol extract of *Epilobium* was also very effective as both a COX-1 and COX-2 inhibitor in culture experiments and showed significant antioxidant activity. The South African researchers conclude, "Although these results support the traditional use of *Epilobium parviflorum* for treatment of BPH and prostatitis, further investigation is required for this promising plant." [39]

### PHYSICAL THERAPY

Dr. Stephen Jones of the Cleveland Clinic believes that much of the pain involved in CPPS stems from a spasm or a myofascial trigger point (a specific point on a muscle at which application of pressure will elicit pain) in the perineal muscle bundle supporting the pelvic floor. He suggests hot sitz baths and sitting on a donut-shaped cushion for relief. [10] Other physical therapies mainly aimed at pain relief include acupuncture, biofeedback, high-frequency electrostimulation, and electromagnetic stimulation.

#### Acupuncture

Acupuncture is effective in providing pain relief and is also capable of adjusting the balance between the sympathetic and parasympathetic branches of the autonomic nervous system (ANS). [40-42] Since CPPS involves pain and likely an ANS dysfunction as evidenced by voiding difficulties, it is not surprising that acupuncture has been found effective in the treatment of prostatitis. Canadian researchers evaluated the benefits of acupuncture in 12 men with CPPS. The men had all been treated unsuccessfully with antibiotics, alpha-blockers, anti-inflammatories, and phytotherapy. They were given twice-weekly treatments for 6 weeks and were then followed for an average of 33 weeks. The treatment employed 30 needles 8 of which were electrically stimulated. At the 33-week point, average total NIH-CPSI scores had dropped from 28.2 to 8.5, pain score from 14.1 to 4.8, urinary symptoms score from 5.2 to 1.3, and quality-of-life score improved from 8.8 to 2.3. Eighty-three per cent of the patients had a sustained greater than 50% decrease in NIH-SPSI score at their final visit (average of 33 weeks). The researchers conclude that acupuncture is a safe, effective and durable therapy for CPPS. [43]

Japanese researchers have found acupuncture highly effective in treating CPPS accompanied by intrapelvic venous congestion (accumulation of blood in the veins draining the pelvic area). [44] Chinese medical researchers treated 200 patients with CPPS with acupuncture and mild moxibustion (heating of the needles with smouldering cones of herbs) and observed remarkable improvement. They conclude that acupuncture improves blood circulation in the prostate, inhibits or kills pathogenic micro-organisms, strengthens and regulates immune function, and relieves obstruction in the prostatic ducts. [45]

#### Biofeedback

At least two studies have evaluated the use of biofeedback in the treatment of CPPS. Ye, *et al* at the Huazhong University of Science and Technology in China treated 62 men with CPPS with biofeedback with excellent results. All the men had previously been

treated unsuccessfully with antibiotics and alpha-blockers. The patients were treated with biofeedback 5 times a week for 2 weeks (20-minute sessions). At the end of the treatments 60 patients (97%) were significantly improved or cured with no apparent side effects. Pain was relieved after 2-3 treatments and other symptoms disappeared after 4-5 treatments.[46] Clemens, *et al* at Northwestern University Medical School in Chicago believe that a pelvic floor muscle spasm may be a crucial factor in many cases of CPPS. They enrolled 19 men with CPPS in a 12-week program of bi-weekly biofeedback sessions aimed at bladder training and at relieving the spasm and preventing its recurrence. The patients were assessed using the American Urological Association (AUA) score (see Appendix D) at the beginning and end of the treatment period. Overall, AUA score decreased from 15.0 to 7.5, pain score from 5.0 to 2.0, and the average urgency score decreased from 5.0 to 2.0. Median voiding interval increased from 0.88 hours to 3.0 hours. The Chicago researchers conclude that a formalized program of neuromuscular re-education of the pelvic floor muscles together with interval bladder training can significantly and permanently improve CPPS symptoms.[47]

### **High-Frequency Electrostimulation**

John Hubert and colleagues at the Zurich University Hospital in Switzerland have developed an electrostimulation device which markedly reduces symptoms of CPPS. The device consists of a frequency generator with two probes; one is inserted into the urethra and one is inserted into the rectum. The frequency-generator generates impulses with a frequency of 450-500 Hz and a voltage of 6 volts. The current flow can be set by the patient (between 1 and 10 mA) to a level where the patient feels a distinct, but tolerable tingling sensation in the pelvic floor (perineum). The device was tested on 14 men with non-inflammatory CPPS. They underwent twice-weekly, 30-minute sessions for 5 weeks. The overall, average NIH-CPSI score decreased from 29 prior to treatment to 14 after treatment, pain score decreased from 15 to 7, urinary complaint score from 2.5 to 1, and quality-of-life score improved from 9.5 to 5.5. The Swiss researchers conclude that the new device is effective in relieving symptoms of non-inflammatory CPPS (category IIIB). The device is technically simple and can be used by the patient at home.[48]

### **Low-Frequency Electromagnetic Stimulation**

Urologists at St. Mary's Hospital in London, England also believe that pelvic floor spasms and exaggerated neural sensitivity are the underlying factors in many cases of CPPS. They evaluated the use of electromagnetic therapy targeting the pelvic floor (perineum) as a means of reducing the spasm and accompanying pain. Twenty-one men with CPPS were randomized to receive placebo treatments or twice-weekly electromagnetic treatments for 4 weeks using a *Neotonus* electromagnetic chair. The active treatment sessions consisted of pelvic floor stimulation for 15 minutes at 10 Hz followed by a further 15 minutes at 50 Hz. During the placebo treatments the electromagnetic pulse generator was switched off. The men were evaluated at baseline, and at 3 months and 1 year after the end of treatment. The mean pain score decreased by 45% in the active treatment group, but remained unchanged in the placebo group after 1 year. Average urinary symptoms scores decreased by 32% in the active treatment group after 3 months, but reverted to baseline after 1 year. No significant change was observed in the placebo group. The British researchers conclude that pelvic floor electromagnetic therapy may be a promising new non-invasive option for CPPS.[49]

### **MINIMALLY INVASIVE THERAPIES**

These therapies are similar to those used in the treatment of BPH (see Chapter 2) and are considered last resorts for the treatment of CPPS. While some trials have shown positive results, there is no data indicating whether the benefits are long-term or only temporary.

**Hyperthermia (heat therapy)** can be delivered transrectally (via the rectum) or transurethrally (via the urethra). The heat source is usually microwave energy. It is believed that hyperthermia works by eliminating hidden bacterial infections and by destroying some sensory nerves and alpha-adrenoreceptors.[50] Transrectal hyperthermia has not gained wide acceptance among urologists as its efficacy is limited due to the difficulty in obtaining high enough temperatures in the prostate without damaging the rectum.[50]

**Transurethral thermotherapy or TUMT** (see Chapter 2) has been evaluated by Nickel and Sorenson in two small studies. They found the procedure useful for the treatment of category IIIA (inflammatory) CPPS, but not for the treatment of category IIIB (non-inflammatory) CPPS. The treatment was found to elevate prostate interstitial temperature to between 45° and 60° C and resulted in significant improvement (greater than 50%) in 70% of patients.[51,52] Choi, *et al* evaluated 78 patients with CPPS using TUMT. The study participants underwent a 1-hour session of TUMT using the *Prostatron* equipment. Complete symptom disappearance was obtained in 23% of the men and a partial response occurred in 43%.[53]

**Transurethral needle ablation or TUNA** (see Chapter 2) has been evaluated by Taiwanese, Korean and Finnish researchers. Results are mixed. While the Taiwanese and Korean groups found TUNA to be beneficial, the Finnish researchers found it no better than sham treatment.[54-56]

### **MULTIMODAL THERAPIES**

Because of the relatively poor response achieved with standard conventional monotherapies, some specialized urological centers have developed protocols which encompass a series of different treatments. Daniel Shoskes and colleagues at the Cleveland Clinic in Florida report good results with a multimodal approach involving antibiotics, prostatic massage, alpha-receptor blockers, quercetin, and neuromuscular agents. A clinical trial of this approach included 53 patients with chronic prostatitis; 13% of the cases were category II, 41% were category IIIA, and the remaining 46% were category IIIB. The average (mean) age of the patients was 45 years and they had been suffering from chronic prostatitis for an average (median) of 3.5 years. Antibiotics were used first for 2-4 weeks if they had never been used before, or had proven effective for a previous episode. Prostatic massage was performed once to twice weekly in patients who had felt benefit from the first massage administered to all participants in order to obtain expressed prostatic secretions (EPS) for diagnosis. Patients who had significant urinary problems were also given tamsulosin. If the above treatment was not effective then quercetin (*Prosta-Q*) was administered and, as a last measure, neuromuscular



agents such as amitriptyline and gabapentin were tried. The results of the trial were as follows:[57]

- Sixteen patients were initially treated with antibiotics because of good previous response or positive cultures. Ten of the patients also received prostatic massage and two received tamsulosin. A beneficial response was noted in 9 patients, 6 of whom had received both antibiotics and prostatic massage; however, 5 of the 9 patients experienced recurrence of their symptoms once the treatment stopped.
- Thirty patients were treated with quercetin and 6 patients were treated with quercetin and tamsulosin combined. Twenty-five (83%) of those treated with quercetin were deemed cured and required no further treatment. Three of the 6 patients (50%) on the quercetin/tamsulosin combination were also deemed cured.
- Of the 17 patients not helped by the above protocols, 10 were given tamsulosin which proved effective in 7 patients.
- Eight patients received amitriptyline alone or in combination with gabapentin and this was effective in 3 patients.

The study participants were followed for an average of 417 days at which time their NIH-CPSI score was measured and compared to their baseline score. Pain score decreased from an average of 10.4 to 5.9, urinary symptom score from 4.2 to 2.0, quality-of-life score from 8.2 to 4.7, and overall score from 22.7 to 13.2. An overall global subjective assessment concluded that 80% of the patients had improved. The researchers conclude that a step-wise approach using antibiotics, anti-inflammatories (quercetin), and neuromuscular agents can be successful in the majority of patients with long-standing chronic prostatitis.[57]

## **CHELATION**

It is estimated that about 20% of CPPS patients have stones (calculi) in their prostates. These may contribute to inflammation and pain on their own, or prevent effective treatment by clogging up the prostatic ducts. The stones consist mainly of apatite (calcium phosphate) and are thought to be formed by reflux of nanobacteria in urine into the prostatic ducts. Nanobacteria (newly-discovered, small microorganisms with the ability to form calcium phosphate crystals at neutral pH) are also believed to be responsible for calcification of arteries.

Daniel Shoskes and his team at the Florida Cleveland Clinic recently evaluated a multimodal chelation therapy for dissolving prostatic calculi. Fifteen men who had failed all previous therapies and had evidence of prostatic calculi on transrectal ultrasound (TRUS) participated in the trial. The average age of the men was 45 years and the patients had suffered from category III prostatitis (CPPS) for an average of 6.3 years. Seven of the men had category IIIA (inflammatory) disease, while the remaining 8 had non-inflammatory CPPS.

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The treatment, which was administered at bedtime for a 3-month period, included a rectal suppository containing 1500 mg of the chelating agent ethylenediaminetetraacetic acid (EDTA), 500 mg tetracycline taken orally, and a proprietary formulation called *Nanobac*. *Nanobac* contains vitamin C, selenium, EDTA, coenzyme Q10, bromelain, grapeseed extract, hawthorn berry, quercetin, l-arginine, l-lysine, l-ornithine, trypsin, papain, and vitamins B3, B6 and B9.[26] This treatment, also known as *ComET*, has been found useful in decalcification of arteries.

At the end of the treatment, the overall NIH-CPSI score had decreased from 25.6 to 13.7, pain score from 11.3 to 4.9, urinary difficulty score from 4.7 to 3.1, and quality-of-life problems score from 9.7 to 5.7. Overall, 8 patients experienced a greater than 50% improvement, 4 an improvement between 25 and 49%, and 3 patients had less than 25% improvement. Two of these 3 patients had no signs of nanobacteria in their blood or urine.

Ten patients underwent TRUS after the treatment. In 1 patient all stones had disappeared, in 5 they had decreased in number and/or size, and in 4 patients they were unchanged. The researchers conclude that the *ComET* treatment may provide significant relief in men who have failed other treatments and have signs of calculi on TRUS. They recommend larger, placebo-controlled trials to evaluate the treatment further.[26]

## CONCLUSION

Category III prostatitis or chronic pelvic pain syndrome (CPPS) is a condition of multifactorial origin. There is increasing recognition that an inflamed prostate may not be the main feature of CPPS with some researchers believing that a muscle spasm or myofascial trigger point in the pelvic floor (perineum) is a major source of the pain accompanying CPPS. Precisely because of its multifactorial origin, treatment options are many and varied from antibiotics to herbal anti-inflammatories, acupuncture, and electrical or electromagnetic stimulation. It is unrealistic to expect the average GP or urologist to be aware of all these options, so it is largely up to the patient to propose to his physician that they be explored.

One very promising option that should be considered is supplementation with quercetin (500 mg twice a day). At least two studies have shown that this safe and effective natural bioflavonoid can markedly reduce symptoms in two-thirds or more of patients diagnosed with CPPS.[32,57] Quercetin is available in most health food stores and an even more effective proprietary formulation of the supplement (*Prosta-Q*) is available from Farr Laboratories, Santa Clarita, CA ([www.farrlabs.com](http://www.farrlabs.com))

**CATEGORY IV – ASYMPTOMATIC INFLAMMATORY PROSTATITIS**

Category IV prostatitis is completely asymptomatic and its presence only noted in biopsy samples or prostatic tissue removed during treatment of BPH or cancer. Its prevalence is unknown and no treatment is necessary as long as it remains symptomless.

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# Appendix A

## Glossary Of Terms

(See also Glossary of Abbreviations – Appendix B)

**ABDOMEN:** The part of the body above the pelvic bone but below the ribs. Contains the intestines and organs such as liver, kidneys and stomach.

**ABLATION:** Refers to removal or destruction of tissue or blocking the effects of the binding of chemicals to cell receptors.

**ACTIVE SURVEILLANCE:** Monitoring a condition such as prostate cancer with the intent to intervene if and when appropriate treatment intended to cure is indicated.

**ACUTE URINARY RETENTION:** Complete inability to urinate due to obstruction or constriction.

**ADENOCARCINOMA:** Cancer that develops from a malignant abnormality in the epithelial cells in a glandular organ. Almost all prostate cancers are of this type.

**ADJUVANT:** Auxiliary. Treatment given in addition or auxiliary to the primary one.

**AGONIST:** A drug or substance capable of combining with receptors to influence biochemical activity.

**ALPHA-BLOCKER:** Prescription drugs that block alpha-receptors in the prostate and bladder. The net result is smooth muscle relaxation which improves voiding. Used to treat BPH

and prostatitis. Historically used to treat hypertension, but recently alpha-blockers which are prostate-specific have come into common usage.

**ANABOLIC:** Promoting or relating to anabolism.

**ANABOLISM:** The building up of complex molecules from simpler ones, e.g. proteins from amino acids. The opposite of catabolism.

**ANASTOMOSIS:** The site where the urethra is connected to the bladder neck after the prostate has been removed.

**ANDROGEN DEPRIVATION THERAPY:** Treatment that prevents the body from making or using androgens. Includes castration as well as drug therapy.

**ANDROGEN:** A hormone that promotes the development of male sexual characteristics and stimulates the activity of male sex organs.

**ANTHROPOMETRIC:** Relating to anthropometry.

**ANTHROPOMETRY:** The branch of anthropology concerned with comparative measurements related to the human body.

**ANTIANDROGEN:** A drug that blocks the effect of testosterone at the cellular level.

**APEX:** The lower end of the prostate where the urethra exits.

**APOPTOSIS:** Programmed cell death. This is a natural process where cells self-destruct and are replaced by new cells. Cancer cells have defects in this process which allow uncontrolled proliferation.

**AUA SCORE:** American Urological Association score. A measure of adverse urinary symptoms based on answers to a number of questions related to urination.

**AUTONOMIC:** Relating to the autonomic nervous system.

**AUTONOMIC NERVOUS SYSTEM:** The part of the nervous system that represents the motor innervation of smooth muscle, cardiac muscle and gland cells.

**BASELINE:** In a study, the characteristics of the participants are termed *baseline* if established at the start of the study.

**BENIGN:** Non-cancerous. Applied to growths and tumors.

**BENIGN PROSTATIC HYPERPLASIA:** The enlargement (hypertrophy) of the prostate.

**BILATERAL:** Occurring on both sides. Bilateral tumor growth would involve both lobes of the prostate.

**BIOCHEMICAL FAILURE:** The failure of definitive treatment to eradicate prostate cancer as indicated by PSA levels rather than by clinically evident symptoms.

**BIOMARKER:** A tissue, cellular or serum indicator of biological activity

that can be used to monitor the state of health or disease. Generally a chemical compound.

**BIOPSY:** Removal and microscopic examination of tissue to establish the presence or absence of disease.

**BISPHOSPHONATES:** A class of drugs that stop bone loss (resorption).

**BLADDER NECK:** The portion of the bladder that attaches to the prostate.

**BODY MASS INDEX:** A numerical measure of being underweight, normal weight, overweight obese.  $BMI = \text{weight (kg)} \div \text{height (m)}^2$  (or  $703 \times \text{weight in pounds} \div \text{height in inches}^2$ ).

**BONE SCAN:** A radioactive isotope based procedure used to detect prostate cancer activity in bones. Abnormal concentrations of the isotope detected in the scan indicate potential cancer sites.

**BRACHYTHERAPY:** The use of implanted radioactive seeds or pellets as a radiation source for therapy.

**BUMP:** In the context of prostate cancer, a rise and fall of the serum level of PSA after therapy.

**CAPSULE:** The outer layer or “skin” of the prostate.

**CARCINOGENESIS:** The process whereby cancer is initiated.

**CASTRATE:** To remove the testicles surgically.

**CATHETER:** A thin flexible tube. In the context of urology, it is used to drain the bladder.

**CAVERNOUS NERVES:** The erectile nerves that run along each side of the prostate and control erections.

**CENTRAL ZONE:** See transition zone.

**CLINICAL STAGE:** Clinical staging of prostate cancer involves estimating how advanced the cancer is based only on clinical information available prior to treatment, as distinct from information gained after surgery through pathological examination of tissues removed.

**COLLIMATOR:** A device or system of baffles designed to shape a beam of radiation.

**COMORBIDITY:** Coexisting health problems.

**COMPUTERIZED TOMOGRAPHY:** An x-ray imaging technique employing computer software that facilitates the presentation of the images as slices through selected sections of the body. The so-called CT scan.

**CONFORMAL:** Conforming to the shape of an object, such as a conformal radiation beam with a field shape matching that of the prostate with controlled margins.

**CONFOUNDING:** A situation where the effects of two or more processes are not separated or the distortion of the apparent effects of a factor related to risk brought about by an association with other factors that can influence the outcome. For example, the effect of heavy drinking on the incidence of lung cancer must be corrected for confounding associated with the high prevalence of smoking among heavy drinkers.

**CRYOSURGERY:** Freezing of an organ to kill tissue including tumor tissue.

**CRYOTHERAPY:** See Cryosurgery.

**CYROABLATION:** See Cryosurgery.

**CYSTITIS:** Inflammation of the bladder.

**CYSTOSCOPY:** A procedure where the interior of the bladder is examined visually with an instrument called a cystoscopy inserted through the urethra.

**DETRUSOR:** Smooth muscle in the wall of the bladder that contracts the bladder and expels the urine.

**DIFFERENTIATION:** Relates to the morphology of cells with normal cells being well differentiated whereas primitive and aggressive cancer cells are much less differentiated.

**DOWNSTAGING:** In the context of prostate cancer, a decrease in the stage and thus the predicted seriousness of the cancer that can occur when pathological samples are compared with biopsy tissue.

**EMBOLISM:** A blood clot. For example pulmonary embolism involves a blood clot moving generally from the leg to the lung.

**ENZYME:** A protein produced by cells which influences the rate of biochemical reactions without undergoing a change itself, i.e. a biological catalyst.

**EPITHELIAL:** Relating to or consisting of the epithelium.

**EPITHELIUM:** Cells covering all surfaces.

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**ESTROGEN:** Predominantly female hormone produced mainly in the ovaries. It is also present in males.

**ETIOLOGY:** The science and study of the causes of disease or the science of causes and causality.

**EXTRACAPSULAR EXTENSION:** The situation where cancer has spread beyond the prostatic capsule.

**EXTERNAL URINARY SPHINCTER:** The valve at the exit end of the prostate which controls the flow of urine. The simultaneous opening of this sphincter and the closing of the internal urinary sphincter allows for ejaculation through the urethra.

**GENE:** A hereditary unit. A sequence of chromosomal DNA involved in the cellular production of a biochemically functional product.

**GENOME:** The complete DNA sequence containing the entire genetic information of an individual or population.

**GLEASON SCORE:** A system for classifying cells seen in prostate tissue samples according to the extent of cell differentiation. Used both with biopsy specimens and in scoring tumor tissue in prostates removed at radical prostatectomy or tissue recovered during transurethral resection.

**GRAY SCALE:** An energy scale used for high-energy radiation. Abbreviated GY.

**GYNECOMASTIA:** Excessive development of male breasts. A frequent side effect associated with hormone treatment for prostate cancer.

**HALF-LIFE:** The time for some quantity to decline to half its value. Used to

quantify the rate of decay of radioactive (unstable) isotopes and the rate of disappearance of substances such as drugs in the circulation system. A constant half-life, which is characteristic of radioactive isotopes, implies exponential decay.

**HEMATOSPERMIA:** Blood in the seminal fluid.

**HEMATURIA:** Blood in the urine.

**HESITANCY:** Delay or difficulty in starting the urinary stream.

**HIGH-GRADE PIN (PROSTATIC INTRAEPITHELIAL NEOPLASIA):** Clusters of cells in the prostate thought to be premalignant, the presence of which increases the probability of future prostate cancer. High-grade PIN cells also occur along with established prostate cancer.

**HORMONE:** A chemical produced in one organ that regulates the functions of another, i.e. a signaling chemical.

**HORMONE REFRACTORY:** Prostate cancer that does not respond to androgen deprivation (hormone therapy).

**HORMONE SENSITIVE:** In the case of prostate cancer, the cancer cell growth is dependent on testosterone.

**HORMONE THERAPY:** Manipulation of the testosterone levels in the circulation and the blocking of testosterone binding sites in the prostate in order to prevent its action associated with cell proliferation.

**HYPERLIPIDEMIA:** Elevated serum cholesterol and/or triglycerides.



**INCONTINENCE:** Inability to retain urine or control its flow.

**INDOLENT CANCER:** A tiny cancer that is thought to pose no immediate threat.

**INNERVATE:** To supply a body part, tissue or organ with nerves or nervous stimulation.

**INTENSITY MODULATED RADIATION THERAPY (IMRT):** A modification of 3D-conformal radiation therapy. The intensity of the beam is variable throughout the irradiated area as dictated by the treatment plan and controlled by the operator.

**INTERMITTENCY:** A urination dysfunction where the attempt to completely empty the bladder is described as accomplished in spurts.

**INTERNAL URINARY SPHINCTER:** Muscular valve structure in the bladder neck that retains urine until it is voluntarily released.

**ISOTOPE:** Isotopes of a given element have the same atomic number (nuclear charge and thus chemistry) but different atomic masses. Most elements have both stable and unstable isotopes, the latter being radioactive.

**LAPROSCOPIC SURGERY:** Surgical technique employing small incisions through which a laproscope and other instruments are inserted.

**LOBE:** A subdivision of an organ or body part bounded by fissures or other structural boundaries.

**LOCALIZED:** Restricted to a defined region, as for example a tumor localized inside the prostate.

**LYMPH NODES:** Small glands located throughout the body that are associated with the immune system and are involved in protection from infection and the spread of disease.

**MALIGNANT:** Cancerous, having the invasive and metastatic characteristics of cancer.

**MARGIN:** In the context of the prostate, margin generally refers to “surgical margin” which is the outer edge of the tissue removed at surgery. If cancer cells are found at the margin, the implication is that some were on the other side of the margin and that not all the cancer cells were removed.

**MAXIMUM ANDROGEN BLOCKAGE:** The combined use of both androgen agonists and antiandrogen drugs to minimize both the levels and the activity of androgens in the prostate.

**MEATUS:** Opening

**MEDICAL CASTRATION:** Drug use accomplishing the same effect on testosterone production as achieved with surgical castration.

**METASTASIS:** A secondary tumor formed elsewhere and originating from a primary tumor. Plural-metastases. Also, a term denoting the process of spreading of cancer from the primary site.

**METASTATIC:** Adjective referring to metastasis.

**MORBIDITY:** A diseased state or the frequency of appearance of complications following surgical or other treatment.

**MORTALITY:** Death rate or fatal outcome.

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**MYOFASCIAL PAIN:** Chronic pain in muscle tissues.

**NADIR:** The lowest value a marker reaches after treatment.

**NEOADJUVANT:** A therapy that precedes the definitive therapy.

**NEOPLASM:** An abnormal tissue exhibiting more rapid growth through proliferation which continues to grow after the stimuli that initiate new growth are no longer present.

**NEUROVASCULAR BUNDLE:** Cordlike structures attached to the surface of the prostate and containing microscopic nerves that are involved in the erection process. Included in these bundles are both arteries and veins. Preserved in the so-called nerve sparing radical prostatectomy.

**NOCTURIA:** Frequent need to urinate during the night.

**NOMOGRAM:** A graphic representation of a set of variables associated with an outcome such that weighting factors can be graphically determined and then summed to get the probability of the outcome. Can be automated for on-line use where the parameters are specified and the program calculates the probability of a given outcome.

**NON-INVASIVE:** Not involving the insertion of an instrument into the body or the use of an incision.

**NUCLEAR MEDICINE:** The use of radioactive isotopes for diagnosis and treatment.

**OBSTRUCTIVE SYMPTOMS:** Symptoms of difficulties associated with obstruction of urine flow such as intermittency, hesitancy etc.

**ODDS RATIO:** Odds ratio. The probability that a particular event (e.g. a disease) will occur divided by the probability that the event will not occur.

**ONCOLITIC:** Pertaining to, causing or characterized by oncolysis, a process which involves the destruction of a neoplasm.

**ORCHIECTOMY:** Surgical castration

**ORGAN CONFINED DISEASE:** Physical manifestation of the disease confined to the organ in question, e.g. localized prostate cancer.

**OVERSTAGING:** Determining the stage of a disease which later turns out to be overly pessimistic.

**P-VALUE:** The probability that a difference observed in a study is in fact due to chance and no difference really exists. The usual cut-off for statistical significance is a p value of  $> 0.05$ , i.e. a chance of 1 in 20 that an observed difference has occurred by chance.

**PALLIATION:** Alleviation of symptoms, e.g. pain, without curing the disease.

**PALPABLE:** In the context of prostate cancer, a lump, lesion or nodule that can be felt during the digital rectal examination.

**PALPATE:** Process of feeling for palpable features.

**PARASYMPATHETIC:** Pertaining to a division of the autonomic nervous system into opposing sympathetic and parasympathetic functions.

**PERINEUM:** Region between the scrotum and the anus.

**PERIPHERAL ZONE:** The part of the prostate immediately inside the capsule. The peripheral zone surrounds the transitional zone.

**PHYTOCHEMICAL:** A chemical substance having its origin in natural sources such as plants.

**PHOTODYNAMIC THERAPY:** A mode of treatment where light is used to activate a chemical to become toxic or produce a cytotoxic product. Forms of the chemical are used which preferentially accumulate in tumors after which light directed to the tumor (frequently with a laser and a flexible light pipe) is used to activate the cytotoxic process.

**PHYTOTHERAPY:** Therapeutic use of phytochemicals.

**POLYMORPHISM:** Occurrence together in a population of two or more alternative genotypes, each at a prevalence greater than that which could be maintained by recurrent mutation.

**POSITIVE SURGICAL MARGINS:** See margins.

**POSITRON EMISSION TOMOGRAPHY:** A radioactive isotope is taken up by tissue (e.g. tumor tissue) and highlighted in a scan that detects the two gamma rays emitted when the positron from the initial decay of the isotope is annihilated (so-called *positron annihilation radiation*). Great sensitivity and high signal-to-noise is provided by the fact that the two gamma rays are emitted simultaneously and at 180 degrees from each other and have identical energies. Radiation detection systems can be designed to detect only these gamma rays (a PET scan). The positron is really antimatter

and it interacts after emission from the nucleus with a nearby electron followed by conversion of mass completely into energy, yielding two gamma rays of 0.51 MEV energy.

**POST-VOID RESIDUAL VOLUME:** The amount of urine remaining in the bladder at the end of urination. Can be imaged by ultrasound.

**PROCTITIS:** Inflammation of the mucus membrane of the rectum. An adverse effect that sometimes is associated with damage from radiation therapy.

**PROSTATECTOMY:** The surgical removal of the prostate and seminal vesicles.

**PROSTATITIS:** Infection or inflammation of the prostate.

**PROTOCOL:** A well-defined set of methods or rules by which a procedure or study is executed.

**RADIATION CYSTITIS:** Inflammation of the bladder caused by radiation.

**RADIATION PROCTITIS:** See Proctitis.

**RADIATION THERAPY:** The use of radiation to kill cancer cells and other tissue.

**RADIATION URETHRITIS:** Radiation induced inflammation of the urethra.

**RADICAL:** Relating to or directed at eliminating the root cause of a disease. Also, in chemistry, a molecule with an unpaired electron which makes it highly reactive (also termed a free radical).

**RADIOACTIVE:** Applies to unstable isotopes which decay with the emission of radiation.

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**RELATIVE RISK:** The likelihood of the occurrence of a particular event among persons exposed to a given risk divided by the corresponding likelihood among persons unexposed to the same risk.

**RESIDUAL VOLUME:** In the context of BPH, the amount of urine remaining in the bladder after urination.

**RESORPTION:** Loss of bone through breakdown with the resultant reduction in bone mass.

**RETROGRADE EJACULATION:** Ejaculation into the bladder. Can be partial or complete.

**SALVAGE THERAPY:** A procedure carried out after the failure of a definitive therapy in the hope of accomplishing what the failed therapy attempted to do. The term is used with both radiation therapy and radical prostatectomy.

**SATURATION BIOPSY:** Prostate biopsy involving generally twenty or more cores, performed to reduce the probability of missing cancer when fewer cores are taken. The procedure rarely uses more than 40 cores.

**SCREENING:** Testing asymptomatic individuals in the hope of early detection of a health problem. Prime examples are the use of mammography for breast cancer and serum PSA for prostate cancer.

**SEMINAL VESICLE:** Structures located above and behind the prostate that secrete and store seminal fluid.

**SENSITIVITY:** In epidemiology, a statistical parameter. The probability that a diagnostic test will correctly identify the presence of a disease.

**SENSITIZER:** In photochemistry, a chemical which absorbs light and then because it is in an activated or excited state, initiates a physical or chemical process

**SEXTANT:** As applied to the biopsy, a technique that employs six needles, i.e. collects six cores.

**SPECIFICITY:** In epidemiology, a statistical parameter. The probability that a test will correctly identify the absence of a disease.

**SPHINCTER:** A muscle that encircles a duct, tube or orifice and can act as a valve or control flow.

**STRICTURE:** A narrowing, for example of the urethra, which can be caused by scar tissue.

**SYMPATHETIC:** See parasympathetic.

**TESTOSTERONE:** Male sex hormone, produced mainly by the testicles with small amounts produced by the adrenal glands.

**THERMAL THERAPY:** Use of heat to kill tissue, including tumor tissue.

**TRANSITION ZONE:** The part of the prostate immediately surrounding the urethra. BPH occurs in the transition zone, although cancer can also arise there, it is more commonly found in the peripheral zone.

**TRANSRECTAL ULTRASOUND:** The use of an ultrasound probe inserted into the rectum for the purpose of imaging the prostate and adjacent structures, and guiding the placement of biopsy needles and the infusion of local anesthetic.

**TRANSRECTAL:** Generally applied to describe a procedure carried out through the rectum, such as a biopsy.

**TRANSURETHRAL:** A procedure carried out by inserting instruments or probes into the urethra for the purpose of diagnosis or surgery associated with the prostate or bladder.

**TRANSURETHRAL MICROWAVE THERAPY (TUMT):** A treatment for BPH that involves heating prostate tissue with a microwave antenna inserted in the urethra.

**ULTRASOUND:** High-frequency (inaudible) sound waves. Note that sound waves require a medium for propagation whereas electromagnetic waves such as x-rays and gamma rays and light do not.

**UNDERSTAGING:** See Overstaging.

**URETER:** Tube that carries urine from the kidneys to the bladder.

**URETHRA:** Tube from the bladder, which passes through the prostate, and carries urine from the bladder to the outside.

**URETHRAL:** Of or pertaining to the urethra.

**URGE INCONTINENCE:** A strong, sudden urge to urinate which may or may not be controllable.

**URINARY RETENTION:** Generally refers to the complete inability to urinate. Also termed an acute urinary retention episode.

**VASECTOMY:** A male birth-control procedure involving the surgical cutting of the vas deferens (the secretory duct of the testicle) in order to prevent sperm from the testicles reaching the prostate.

**WATCHFUL WAITING:** In general, leaving a patient untreated and observing the progression, if any, of a disease, and offering only palliation. Can also involve observation and testing with the intent to intervene with treatment when with the intent to cure is indicated. This latter usage is being replaced by the term *active surveillance* or the equivalent.

## Appendix B

### Glossary Of Abbreviations

(See also the Glossary of Terms – Appendix A)

< : Less than  
> : Greater than  
≤ : Equal to or less than  
≥ : Equal to or greater than  
≈ : Approximately equal to

**3D-CRT:** Three-dimensional conformal radiation therapy. A modern version of EBRT where the radiation field precisely matches the shape of the organ or tumor.

**5ARI:** 5-alpha-reductase inhibitor. An inhibitor of the enzyme that converts testosterone to dihydrotestosterone.

**%fPSA:** Percent free PSA. The serum free PSA divided by the total PSA, expressed as a percentage.

**ADT:** Androgen deprivation therapy. Therapy that prevents androgens from activating androgen receptors, either by blocking or by reducing androgen concentrations.

**ANS:** Autonomic nervous system.

**AS:** Active surveillance.

**ASTRO:** American Society for Therapeutic Radiology and Oncology.

**AUA:** American Urological Association.

**AUR:** Acute urinary retention.

**BCR:** Biochemical recurrence. See Biochemical failure in Appendix A.

**BF:** Biochemical failure. Recurrence of cancer after treatment detected by an elevated or increasing PSA.

**BMD:** Bone mineral density. Measured by x-ray techniques to establish bone health and the extent of resorption.

**BMI:** Body mass index.

**BPH:** Benign prostatic hyperplasia (hypertrophy).

**CAT:** Computerized axial tomography. This imaging technique allows combining of images from multiple x-rays through computer control to produce cross-sectional or three-dimensional pictures of internal organs.

**CI:** A statistical confidence limit. For example the 95% CI provides a range in which 95% of additional measurements would be expected to fall.

**COX:** Cyclooxygenase, an enzyme involved in the conversion of long-chain fatty acids in the cell walls of white blood cells into pro- and anti-inflammatory substances. Targets for non-steroidal anti-inflammatory drugs such as ibuprofen and Celebrex. There are two forms, COX-1 and COX-2.

**CP:** Chronic prostatitis.

**CPPS:** Chronic pelvic pain syndrome.

**DES:** Diethylstilbestrol. A synthetic estrogen no longer used in North America.

**DHEA:** Dehydroepiandrosterone. An adrenal androgen precursor produced by the adrenal cortex. It is converted to testosterone in the prostate.

**DHT:** Dihydrotestosterone, an androgen derived from testosterone through a chemical reaction involving the enzyme 5-alpha-reductase.

**DRE:** Digital rectal exam where the physician palpates the prostate through the rectal wall using a finger. Abnormalities which can be felt suggest the possibility of cancer.

**EAU:** European Association of Urology.

**EBRT:** External beam radiation therapy. Irradiation from outside the body, generally with a collimated or focused beam.

**EPS:** Expressed prostatic secretion. A fluid sample obtained by repeated massage of the prostate.

**fPSA:** Free PSA, as distinguished from complexed PSA.

**GS:** Gleason score.

**Gy:** Abbreviation of the unit of radiation called "Gray" used with the Gray Scale.

**HDR:** High density radiation. A term generally used with brachytherapy to denote high doses for short periods.

**HIFU:** High-intensity focused ultrasound. Can refer to a treatment procedure that uses heat produced by high-frequency ultrasound to kill prostate cells including tumor cells.

**IMRT:** Intensity modulated radiation therapy. A form of 3D-CRT where the intensity within the field of radiation can be varied to suit a predetermined irradiation protocol.

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**IPPS:** International prostate symptom score. Equivalent to the AUA symptom score.

**LE:** Life expectancy.

**LH:** Luteinizing hormone. Production of testosterone in the testicles is stimulated by this pituitary hormone.

**LHRH:** Luteinizing hormone-releasing hormone (GnRH or gonadotrophin releasing hormone). Hypothalamus generated hormone that interacts with the LHRH receptor in the pituitary gland to release LH which then stimulates testosterone production in the testicles.

**LRP:** Laparoscopic radical prostatectomy.

**LUTS:** Lower urinary tract symptoms. Symptoms associated with difficulties of urination.

**MEV:** Million electron volts. An energy unit commonly used to characterize high-energy radiation.

**mL:** abbreviation for milliliter, 1/1000 of a liter.

**ng:** abbreviation for nanogram, one billionth of a gram.

**NCCN:** National Comprehensive Cancer Network.

**NSAID:** Non-steroidal anti-inflammatory. A class of over-the-counter and prescription drugs that treat inflammation. Most act on one or both of the forms of the enzyme cyclooxygenase (COX) to decrease the production of inflammatory substances derived from long-chain fatty acids in the cell walls of white blood cells.

**OR:** Odds ratio. See Appendix A

**p:** So-called p-value. See Appendix A

**PSAD:** PSA density. Serum PSA value divided by the prostate volume in cc.

**PC:** Prostate cancer.

**PDT:** Photodynamic therapy.

**PET:** Positron emission tomography.

**PIN:** Prostatic intraepithelial neoplasia. Abnormal cells believed to be precursors to prostate cancer.

**PNS:** Parasympathetic nervous system.



**PSATZD:** PSA transition zone density. Serum PSA level divided by the volume of the prostate transition zone.

**PSAV:** PSA velocity. The rate of change of PSA level with time, generally measured in months or years.

**RP:** Radical prostatectomy. A surgical procedure to remove the entire prostate gland and seminal vesicles.

**RR:** Relative risk. See Appendix A

**RT:** Radiation therapy. The use of radiation to kill malignant cells.

**SD:** Standard deviation. A statistical index of the degree of deviation from a mean or median. For example, the square root of the average of the squared deviations from a mean.

**SNS:** Sympathetic nervous system.

**TNM:** Tumor, Nodes, Metastasis. A popular system for staging prostate cancer which takes into account the extent and location of the tumor (T) and the presence and extent of lymph node invasion (N) and metastasis (M). E.g. T1c—detected by elevated PSA with a normal DRE.

**tPSA:** Total serum PSA—the PSA normally measured.

**TRUS:** Transrectal ultrasound.

**TUIP:** Transurethral incision of the prostate. Used to treat BPH.

**TUMT:** Transurethral Microwave Thermotherapy. Used to treat BPH.

**TURP:** Transurethral resection of the prostate. The so-called roto-rooter operation. A surgical procedure where tissue obstructing the urethra is removed. Used to treat BPH.

**TUVP:** Transurethral electrovaporization. Used to treat BPH.

**TWOC:** Trial without catheter. A test of an individual's ability to urinate successfully when the catheter is removed after relieving an acute urinary retention episode.

**TZ:** Transition zone.

**UTI:** Urinary tract infection.

## Appendix C

### Grading Prostatitis Symptoms

#### National Institutes of Health Chronic Prostatitis Symptom Index (1)

##### Pain or Discomfort

1. In the last week, have you experienced any pain or discomfort in the:

	<u>Yes</u>	<u>No</u>
a. area between rectum and testicles (perineum)?	1	2
b. testicles?	1	2
c. tip of the penis (not related to urination)?	1	2
d. below your waist, in your pubic or bladder area?	1	2

2. In the past week, have you experienced:

	<u>Yes</u>	<u>No</u>
a. pain or burning during urination?	1	2
b. pain or discomfort during or after sexual climax (ejaculation)?	1	2

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 experienced it over the last week?

0\*   1   2   3   4   5   6   7   8   9   10\*\*

\* No pain

\*\* Extreme pain

##### 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 2 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 = \_\_\_\_\_

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- CANHELP, INC. – Personalized information about the latest alternative and conventional cancer treatments is available (for a fee) from this site.  
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- *The Moss Reports* – Dr. Ralph Moss' site is an excellent starting point for people looking for advice concerning alternative cancer treatments.  
<http://www.cancerdecisions.com/>
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