EVALUATION OF ACUPUNCTURE THERAPY FOR CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME

by

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To my wonderful parents, Lee Peng Loon and Lim Siew Nai,

my lovely sister, Tracy

and adorable brother, Jason

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TABLE OF CONTENT

LIST OF TABLES

LIST OF TABLES

LIST OF TABLES

LIST OF TABLES

LIST OF FIGURES

LIST OF FIGURES

LIST OF PLATES

LIST OF ABBREVIATION

ACN	Acetonitrile
ANOVA	Analysis of variance
BPH	Benign prostatic hypertrophy
BPI	Brief Pain Inventory
CAM	Complimentary and alternative medicine
CI	Confidence interval
CP/CPPS	Chronic prostatitis/chronic pelvic pain syndrome
CPCRN	Chronic Prostatitis Collaborative Research Network
CSF	Cerebrospinal fluid
DRE	Digital rectal examination
EDTA	Ethylenediaminetetraacetic acid
EPS	Expressed prostatic secretion
GRA	Global response assessment
HADS	Hospital anxiety and depression scale
HCL	Hydrochloric acid
HR-QOL	Health related-quality of life
ICC	Intraclass correlation coefficient
ICPCN	International Chronic Prostatitis Collaborative Network
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IIEF-5	International index of erectile function – 5
IPSS	International Prostate Symptom score
leu-enkephalin	Leucine-enkephalin

LIST OF ABBREVIATION

LUTS	Lower urinary tract symptoms
MCS	Mental Health
MOS SF-12	Medical Outcome Questionnaire Short Form -12
MSHQ	Male sexual health questionnaire
NIDDK	National Institute of Diabetes, Digestive and Diseases of Kidney
NIH	National Institute of Health
NIH-CPC	National Institutes of Health Chronic Prostatitis Cohort
NIH-CPSI	National Institute of Health – Chronic Prostatitis Symptom Index
PCPs	Primary care physicians
PCS	Physical functioning
PGE_2	Prostaglandin E_2
PSA	Prostate specific antigen
QOL	Quality of life
ROS	Reactive oxygen species
RR	Relative risk
SD	Standard deviation
SEM	Standard error of mean
SPSS	Statistical package for social sciences
TCM	Traditional Chinese Medicine
TFA	Trifluoroacetic acid
TRUS	Transrectal ultrasound
TUMT	Transurethral microwave therapy

LIST OF ABBREVIATION

USM-CPC	University of Science Malaysia-Penang Chronic Prostatitis Cohort
UWSS	University of Washington Symptom Score
VAS	Visual analogue scale
VB_1	First voided urine specimen
VB_2	Second voided/ midstream urine specimen
VB_3	Third voided urine specimen/ post prostatic massage urine
WBC	White blood cell

LIST OF APPENDICES

PENILAIAN RAWATAN AKUPUNKTUR UNTUK PROSTATITIS KRONIK/ SINDROM SAKIT PELVIS KRONIK

ABSTRAK

Penyakit prostatitis kronik/ sindrom sakit pelvis kronik merupakan sejenis sindrom yang mengecewakan, mengelirukan dan kerap ditemui. Sebanyak 2 juta orang dirawat untuk penyakit ini di Amerika Syarikat dan di Malaysia, penyakit ini dihidapi oleh 8.7% kaum lelaki. Hanya sejak 1995 penyakit ini mendapat perhatian perkhidmatan kesihatan di serata dunia.

Walaupun sebab-sebab penyakit ini tidak diketahui, banyak rawatan seperti antibiotik, penghalang alfa serta ubat penahan sakit telah digunakan dengan kejayaan yang terhad. Ini mendorong para penyelidik untuk menyelidik penyakit ini dengan lebih terperinci. Kajian terbaru ini mencadangkan bahawa akupunktur adalah amat berguna terutamanya untuk kes-kes yang kronik.

Untuk mengesahkan keberkesanan rawatan, borang soal-selidik "Brief Pain Inventory" dan "Hospital Anxiety Depression Scale" digunakan dan borang tersebut disahkan benar. Dalam kajian yang seterusnya, rawatan serta diagnosis penyakit prostatitis oleh doktor telah disoal-selidiki. Didapati bahawa pesakit prostatitis biasanya tidak mendapat rawatan optimum untuk penyakit mereka, mengukuhkan keperluan kajian ini.

Simptom-simptom serta maklumat peribadi pesakit yang menghidapi penyakit prostatitis kronik dikaji untuk memahami penyakit ini serta kesan-kesan terhadap taraf kesihatan dengan lebih mendalam. Lelaki yang menghidapi penyakit ini didapati mempunyai masalah sakit, kencing, fungsi seks serta mental. Selain itu, didapati bahawa simptom mereka adalah sama seperti pesakit di Amerika.

Akhirnya, subset pesakit yang menghidapi penyakit dijemput untuk menyertai kajian secara rambang, dengan plasebo menggunakan akupunktur untuk merawat penyakit prostatitis kronik. Pesakit dirawat 2 kali seminggu untuk 10 minggu dengan akupunktur ataupun plasebo. Akupunktur di dapati berkesan untuk 32 (73%) daripada 44 pesakit manakala plasebo di dapati berkesan untuk 21 (47%) daripada 45 pesakit ($p=0.01$).

Ketika rawatan, pesakit juga menilai tahap sakit serta penerimaan rawatan mereka terhadap akupunktur, untuk mengetahui jikalau hasil kajian dapat digunakan bagi penduduk negara ini. Akupunktur mudah diterima oleh kebanyakkan pesakit yang menyertai kajian ini. Dalam pada itu juga, sampel darah diambil untuk mendapatkan satu penerangan secara saintifik bagi akupunktur. Tahap β-endorphin, leucine-enkephalin serta kortisol didapati sama untuk kedua-dua kumpulan pesakit tetapi terdapat perubahan dalam tahap sel darah putih, mencadangkan fungsi imun dalam penyakit ini.

EVALUATION OF ACUPUNCTURE THERAPY FOR CHRONIC PROSTATITIS/ CHRONIC PELVIC PAIN SYNDROME

ABSTRACT

Chronic prostatitis/ chronic pelvic pain syndrome is a frustrating, confusing and prevalent syndrome. It accounts for nearly 2 million visits to the physicians annually in US, and in Malaysia, is known to affect the lives of approximately 8.7% of the male population. As recent as 1995, only did this syndrome gain the attention of healthcare providers worldwide.

While the causes of chronic prostatitis/ chronic pelvic pain syndrome remain unknown, many therapies have been used with limited success, the most common being antibiotics, alpha-blockers and anti-inflammatories. This prompted many to search for more effective therapies and recent studies suggest that acupuncture may be helpful especially in chronic cases.

Prior to conducting the study, the validity of 2 questionnaires used to evaluate the efficacy of treatment outcomes were examined in the local population. The Brief Pain Inventory and Hospital Anxiety Depression Scale were demonstrated to have good reliability and validity as an outcome measure. In the next part, the diagnosis and treatment of prostatitis-like symptoms by primary care physicians were examined. It was found that many patients with prostatitis like symptoms were receiving less than optimal treatment for their condition, further strengthening the need for this study.

To achieve a better understanding of this condition and the health status impact on men, the baseline demographics and clinical characteristics of men with chronic prostatitis were evaluated. It was concluded that men experienced disability in the various domains of pain, urinary, sexual function and mental health. The demographics of these participants were similar to those in the United States.

Finally, a subset of participants were invited to participate into a randomised, double-blind, sham controlled study involving acupuncture or its corresponding placebo for the treatment of chronic prostatitis. These participants were treated twice weekly for a total of 10 weeks with acupuncture or sham. Thirty-two (73%) of 44 participants responded in the acupuncture group compared to 21 (47%) of 45 participants who responded in the sham group ($p=0{\cdot}01$).

To determine the applicability of these results in the general population, participants also rated the tolerability and acceptability of acupuncture treatment. Acupuncture was found to be tolerable by majority of participants. Blood samples were also taken to elucidate a scientific explanation for the response of participants. The levels of neurotransmitter β-endorphin, leucine-enkephalin and cortisol were mostly similar between groups but changes in the white cell levels were observed suggesting the role of immune function in the pathogenesis of this disease.

CHAPTER 1 PROSTATITIS

1.1 INTRODUCTION

Prostatitis is a major healthcare problem for men. It is one of the most common urological disorders in young men aged 20 and above, accounting for almost 2 million physicians visits a year in the United States (McNaughton Collins *et al.,* 1998). Recent epidemiological studies have shown that prostatitis afflicts 2-10% of the population worldwide, with a prevalence of 8.7% in Malaysia (Krieger *et al.,* 2003, Cheah *et al.,* 2003a). This disease is characterised mostly by chronic pelvic pain accompanied by variable disturbances in voiding and sexual life.

During the last ten years, a new and more appropriate clinical classification of prostatitis was proposed by the National Institutes of Health (NIH) (Krieger *et al.*, 1999). This was followed by the NIH-Chronic Prostatitis Symptom Index (NIH-CPSI) for measuring the severity of symptoms in prostatitis patients in May 1999 (Litwin *et al.*, 1999). More recently, a second initiative have also been established by the National Diabetes and Diseases of Kidney (NIDDK) of the NIH to search for a treatment for prostatitis and also to elucidate its aetiology.

1.2 BASIC ANATOMY, HISTOLOGY AND PHYSIOLOGY RELATED TO THE PROSTATE GLAND

The prostate gland consists of 2 parts, the fibro-muscular glandular part and the stroma. It has the shape of a pyramid and lies on the pelvic musculofascial floor, being surrounded by a thin layer of connective tissue (Dixon *et al.*, 1999). The gland has a base and an apex, anterior and posterior surfaces and two infero-lateral surfaces. The base is connected to the bladder neck and the apex is surrounded inferiorly by the external sphincter, all forming together the proximal urethra, the main continence mechanism in the male (Figure 1.1). The prostate is separated posteriorly from the rectum by the anterior layer of Dennonvillier's fascia and is fixed anteriorly to the pubic bone with the puboprostatic ligaments, being held in the dorsal vein plexus between these structures. A thin layer of connective tissue forms the "true" capsule in the periphery of the prostate, outside of which the pelvic fascia forms the "false" capsule (Dixon *et al.*, 1999).

The main arterial supply to the prostate gland is from the prostatic branches of the inferior vesical artery, and it is also supplied by small branches from the middle rectal and pudendal vessels. The veins are situated mainly between the "true" and "false" capsules. The lymphatic vessels from the prostate gland drain into internal iliac lymph nodes (Dixon *et al.*, 1999).

The prostatic urethra is about 3cm long and two ejaculatory ducts (one or two orifices) open in the colliculus seminalis (or verumontanum) near the

external sphincter. Histologically, the prostate gland can be divided into three parts.

- The peripheral zone which forms about 70% of glandular prostate
- The central zone forms about 25% of the glandular prostate
- The transitional zone (about 5%) consists of two small lobes

The human prostate gland receives dual autonomic innervations from both parasympathetic (cholinergic) and sympathetic (noradrenergic) nerves in the prostatic nerve plexus. The pelvic plexus receives its parasympathetic input from the sacral segments of the spinal cord (S2-4) and sympathetic fibres from the hypogastric presacral nerves (T10-L2). Both cholinergic and noradrenergic fibres innervate the prostate stroma, and cholinergic nerves innervate the smooth muscle of the capsule and the space around the blood vessels and are responsible for the secretory function of the epithelial part. The symphathetic nerve control the prostatic musculature, and their excitation closes the bladder neck during ejaculation of the seminal fluid into the urethra (Dixon *et al.*, 1999).

The ejaculate from the human prostate is a slightly acidic (pH 6.5), serous fluid in which several major secretory products can be identified, notably acid phosphatase, citrate, zinc, soluble fraction proteins, carbohydrates, electrolytes, polyamines, hormones, lipids and growth factors. (Weidner *et al.*, 1991, Zaichick *et al.*, 1996)

Up to 57 major protein groups, of which 27 is non-serum proteins have been identified. Major prostate-specific proteins are prostatic acid phosphatase (PAP), prostate specific antigen (PSA) and prostate binding protein (PBP), which are expressed at pubertal and adult ages. Proteolysis is the major function of prostate secretion, being rich in exopeptidase and endopeptidase. The most extensively studied protease is PSA, also known as seminin, seminal protease or chymotrypsin-like protease (Neal *et al.*, 1992, Dixon *et al.*, 1999)

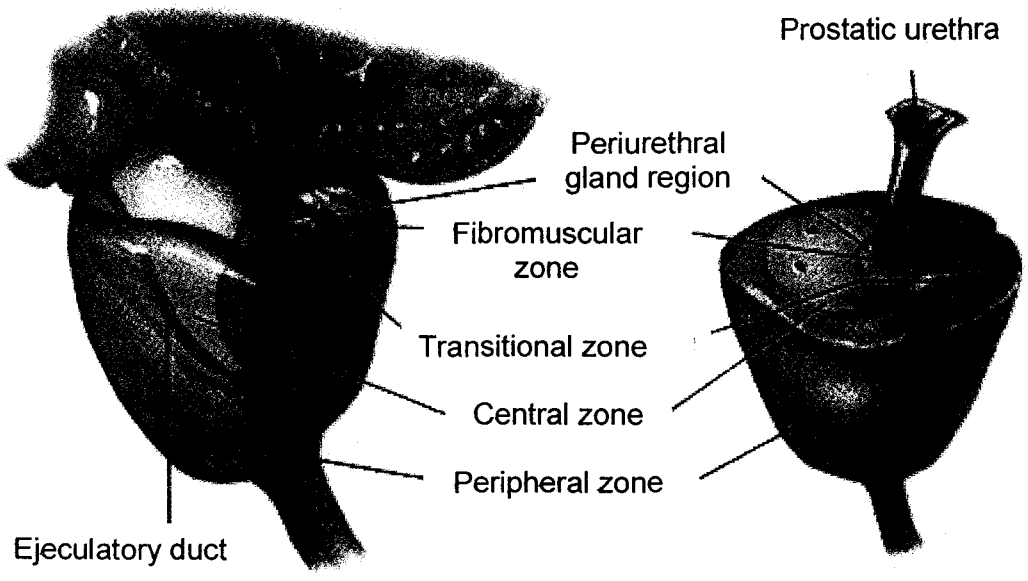

Figure 1.1: The prostate gland consists of 3 different zones, a central zone, a peripheral zone and a transitional zone. The peripheral zone is usually the site for development of prostate cancer while transitional zone is the site for development of benign prostatic hypertrophy. However, the same analogy cannot be distinguished for prostatitis. (Adapted from Kirby and McConnell, 2002)

1.3 EARLY CLASSIFICATION OF PROSTATITIS

The pathology of prostate diseases was initially described only as acute prostatitis, a complication of either acute septic invasion of the prostate by bacteria or chronic inflammation of the prostate. In the 1920s, von Lackum classified prostatitis into active, latent and bacterial types, the aetiology of the disease being determined only by microbiological culture (von Lackum, 1927).

Later, prostatitis was divided into two main groups according to their bacterial aetiology: a primary group- after gonorrhoeal infection (three types: simple, true and atopic prostatitis), and a secondary group – without proven gonococcus termed the focal type of prostatitis, based on the focal infection theory that attracted much attention among researchers. In 1938, Grant proposed that the classification be divided into 3 types: acute, occluded chronic and recalcitrant prostatitis, where the latter denoted persistent infection after the failure of treatment.

It was not until the publication by Meares and Stamey (1968) concerning suggestion for diagnosing prostatitis by the "four-glass test" that led to the proposal of a traditional classification of prostatitis by Drach et al in 1978. Inflammation of the prostate gland was defined on the basis of finding leukocytes in the prostatic fluid. Based in this description, the traditional classification is illustrated in Table 1.1.

Table 1.1: The traditional classification of prostatitis first proposed by Drach *et al* in 1978.

Category	Classification	Description
I	Acute bacterial prostatitis	Acute infection of prostate
II	Chronic bacterial prostatitis	Significant infection (>10^3 cfu) of bacteria recovered in EPS
III	Chronic non-bacterial prostatitis	Absence of bacteria but significant number of leukocytes (>10 per hpf) in EPS
IV	Prostatodynia	No signs of bacteria or inflammation in prostate

Acute bacterial prostatitis: Recommendations are to avoid massage of the prostate gland, and the diagnosis is based on culture and detection of a swollen, tender prostate in rectal examination. Signs of general illness (fever, chills and malaise) with history of urinary tract infection are present.

Chronic bacterial prostatitis: Diagnosis is confirmed when pathogenic bacteria are recovered from the prostatic fluid in significant numbers ($>10^3$), a urine culture is negative and may be positive, and there are no signs of systemic infection

Chronic non-bacterial prostatitis: No bacterium is found in the prostatic fluid but a significant number of leukocytes (>10 per hpf) are seen. Drach *et al* (1978) pointed the possibility of cryptic/hidden infections through *Trichomonas*, fungi, *Chlamydia* or *Mycoplasma.*

Prostatodynia: Consistent pain in the prostate (pelvic pain). Diagnosis is preferred when there are no bacteria or signs of inflammation (leukocytes) in the prostatic fluid.

1.4 THE NEW NATIONAL INSTITUTES OF HEALTH (NIH) CLASSIFICATION OF PROSTATITIS

In December 1995, the NIH Workshop on Chronic Prostatitis and the NIH-supported International Chronic Prostatitis Collaborative Research Network (ICPCN) in Washington proposed a new classification for diagnosing and characterizing prostatitis. The new definition recognizes that pain is the leading symptom of chronic prostatitis, together with a wide range of voiding, psychological and sexual disturbances. This classification, presented in Table 1.2, was later accepted by urologist and validated by a number of university clinics and published for clinical use in 1999 (Krieger *et al.*, 1999).

The new classification system is based on results of microscopic and bacterial culture of the expressed prostate secretion (EPS), semen culture, post-massage urine and biopsy of prostate gland. As shown in Table 1.2, clinical categories I and II are as in the previous classification of Drach *et al* (1978). The main differences are in clinical category III, which is divided into subcategories A and B, chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) with or without signs of inflammation (leukocytes > or < 10 per hpf). Additionally, category IV was included, defined as patients with histologically proven chronic prostatitis without clinical symptoms of pain and/or diseases at all.

Table 1.2: The new NIH consensus classification of prostatitis. It was developed based on microscopic and bacterial culture and recognises that in some cases, prostatitis may occur in asymptomatic patients

Category	Designation	Infection status
I	Acute bacterial prostatitis	Acute infection of the prostate
II	Chronic bacterial prostatitis	Recurrent infection of the prostate
III	Chronic prostatitis/ Chronic pelvic pain syndrome	Discomfort or pain in the pelvic region. Variable voiding and sexual symptoms with no demonstrable infection
IIIa	Inflammatory	Leukocytes in semen, expressed prostatic secretions (EPS), or voided bladder urine-3 (VB-3).
IIIb	Non-inflammatory	No leukocytes in semen, EPS and VB-3
IV	Asymptomatic inflammatory prostatitis	No subjective symptoms detected but leukocytes are found in prostate secretions or in prostate tissue during an evaluation for other disorders.

Unfortunately, this classification still has some limitations, largely due to our inadequate understanding of the relevance of white blood cells, lack of standardisation of leukocyte investigation techniques and the lack of comparable cut-off points for elevated number of leukocytes in the EPS and/or semen (Krieger *et al.*, 2000a, Krieger *et al.*, 2000b). Most problems are related to the lack of understanding of the relevance and importance of fastidious/cryptic microorganism. All said, this new classification system is a clear improvement over the old one, brings more effectiveness and clarity into clinical practice and research protocols.

1.5 PRACTICAL CLINICAL PRACTICE PATTERNS IN PROSTATITIS

The first investigation into practical patterns related to prostatitis was published by de la Rosette *et al* (1992), containing information on prostatitis among patients seen by primary care physicians and urologist. This study pointed out three main discrepancies: that physician see older patients than urologist, that physicians see only a tenth of the number of patients that urologist do, and that physicians mainly think that the aetiology of prostatitis is infectious, whereas urologist consider non-infectious causes most important. At least half of the physician and urologist think that it is very important to take note of the psychic component of chronic prostatitis. Half of the urologists perform EPS and semen culture for diagnostic purposes and treatment consists of one or more courses of antibiotics, analgesics and some supportive advice.

Many other authors (Moon, 1997, Nickel *et al.*, 1998) also reported similar results with regard to the opinions of physicians and urologist. These surveys show quite remarkable consistency from country to country, but the differences in the number of patients seen by doctors mainly represent the differences between health care services rather than diagnosis.

These surveys (de la Rosette *et al.*, 1992, Moon, 1997, Nickel *et al.*, 1998) also show that the use of antibiotics without any reason or any evidence of bacteria in the prostatic fluid and/or urine is the norm rather than the exception. It represents largely accepted behaviour and is supported by results of Berger *et al* (1997) concerning "cryptic infection" of the prostate gland.

The textbooks of urology presume that acute and chronic bacterial prostatitis are easily defined, diagnosed and treated (Meares, 1993). Fortunately, even when no prostatic fluid culture is performed, the use of one or more courses of antibiotics will generally elicit a therapeutic response. Category III patients are a problem to diagnose and treat, as inflammation may or may not be present (Krieger *et al.*, 2000b). Additionally, when about 90% of bacterial cultures are negative this causes a normalising tendency, or clinical behaviour designed to avoid proper laboratory diagnostic in clinical practice, leading to an erroneous basis for reaching treatment decisions.

1.6 AETIOLOGY AND PATHOGENESIS OF PROSATITIS

Even as we advance into the 21st century, the specific cause of most cases of non-acute prostatitis is unknown. Likewise, important aspects concerning the route of possible infection and pathogenesis remains uncertain in clear instances of bacterial prostatitis (Krieger, 1984, Krieger and Riley, 2002)

Currently, four aetiological reasons for the induction of prostate inflammation are generally accepted, and the recovery or chronicity of the process depends on balances or imbalances between predisposing factors and/or host defence mechanisms (Figure 1.2).

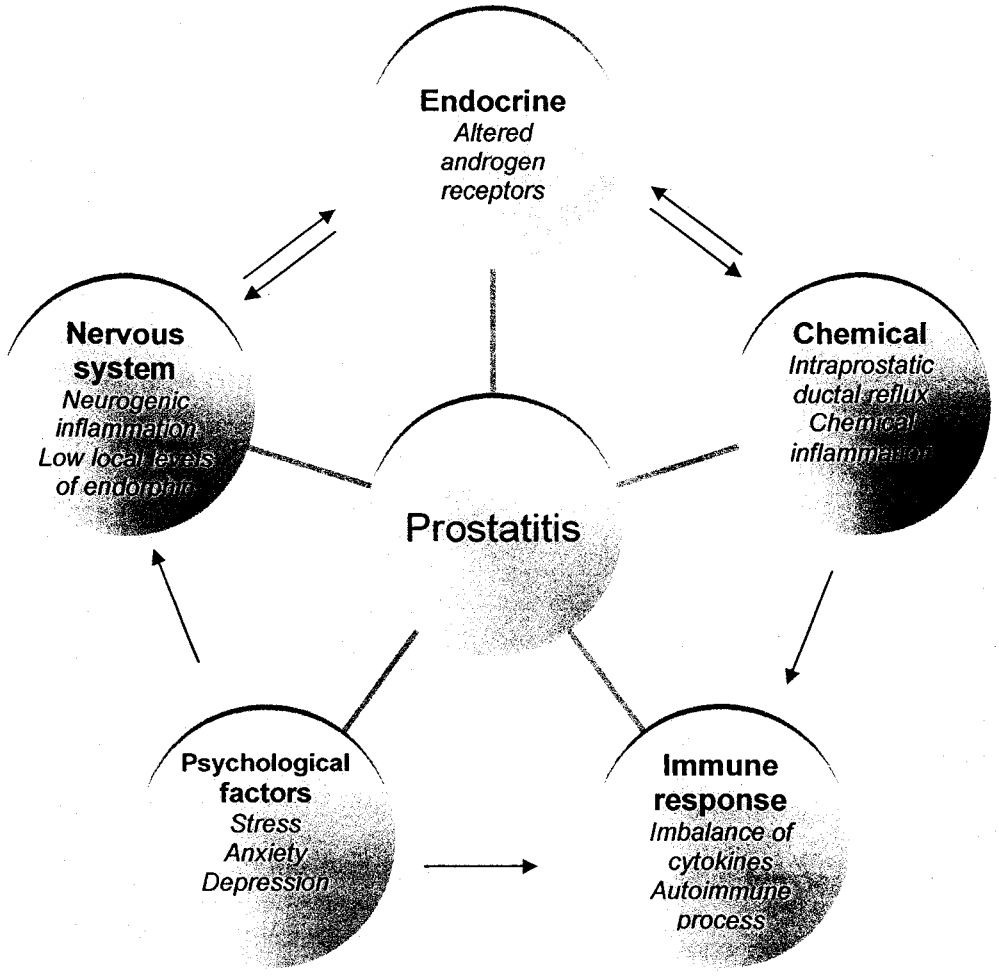

Figure 1.2 Possible interplay of immunological, endocrine, chemical, neurological and psychological factors which may play a role in the development of CP/CPPS (Adapted from Pontari and Ruggieri, 2004)

1.6.1 Microbiological aspects of prostatitis

It is essential to be able to demonstrate bacteria reliably in the EPS, semen or both in order to reach the correct treatment decision and to ensure a good outcome. Laboratory findings have shown that in practice almost all standard localisation cultures are negative and that success in culturing bacteria from the EPS is complicated by the presence of inhibitory substances known to exist in prostate secretion and by a history of multiple previous course of antibiotics (Nickel and McLean, 1998).

Clear confirmation of the pathogenicity of bacteria in prostate tissue and/or ducts has been obtained with a group of gram-negative uropathogens including *E. coli, Klebsiella* spp., *Serratia* and *Pseudomonas* spp. (Meares and Stamey, 1968, Domingue and Hellstrom, 1998). Possible temporary pathogens in prostate tissue and/or ducts under certain conditions can be : coagulase-negative *Staphylococcus* species, *Chlamydia, Ureaplasma, Candida* and *Trichomonas* (Potts *et al.*, 2000, Nickel, 2000). Acknowledged not to be pathogens so far are: *Diptheroidds, Lactobacilli* and *Corynebacteria* spp. (Domingue and Hellstrom, 1998, Nickel, 2000)

A number of prostatitis studies provide some support for a new concept, the use of immunochemistry, electron microscopy, and ultrasensitive molecular PCR methods for detecting bacteria or their remnants in prostate tissue, implying that at least the majority of patients with prostatitis, and perhaps all of

them, have a microbiological cause for their symptoms (Domingue and Hellstrom, 1998, Terai *et al.*, 2000, Krieger *et al.*, 2000c).

Last but not least, it must also be mention that cryptic non-culturable organisms such as altered 'biofilm forming colonies', viruses and cell wall-deficient bacteria, the importance of which for the immune system of the host is not finally clear (Arakawa *et al.*, 1993, Domingue and Hellstrom, 1998)

1.6.2 Immunological aspects of prostatitis

The secretory immune response is an essential factor in helping the mucosal barrier to resist bacterial invasion into the glandular-epithelial system of the prostate gland. The prostate secretes local antibodies in response to infection or the remnants of bacterial protein, in which this local response is often different from systemic ones reflected in the serum findings. The amounts of immunoglobulin G and A (IgG and IgA) have been found to be much lower in normal human prostatic fluid than in patients with prostatitis. It thus appears that measurements of antigen-specific IgA and IgG levels in the prostatic fluid can be helpful in the diagnosis of prostatitis and in determining the possible response to long-term courses of antibiotics in patients with a confirmed aetiology (Shortliffe *et al.*, 1981, Fowler and Mariano, 1984, Kumon, 1992)

The most common aetiological factor having a strong immunological effect on the secretion of antigen-specific IgA into the prostatic fluid, independent of the systemic immune response, is *E. coli* and very occasionally certain *Enterococcus* species, while the role of staphylococci being more questionable (Fowler and Mariano, 1984).

On the other hand, Nickel and Costerton (1993) showed cultures from prostate tissue that coagulase-negative staphylococci formed focal microcolonies that adhered to the walls of the prostatic ducts and were protected with glycocalyxlime and deduced that it was not the bacteria themselves that led to tissue damage but the immune-mediated inflammation.

Typical over-reaction of the host response and delayed hypersensitivity reactions are represented by inflammatory infiltrates from T-lymphocytes ($CD4^+$ T helper/ inducer cells and $CD8^+$ T cytotoxic/suppressor cells), which are distributed variously between the epithelial and stromal components. This can be due to intraprostatic spermatozoa intrusion, which is known to have a powerful autoimmunization capacity and activity in some cases (McClinton *et al.*, 1990). It has been shown in autopsy material that sperm may penetrate into the somatic cells and that this can produce tissue changes similar to those induced by a variety of carcinogens in experiments performed with human tissue. This phenomenon was confirmed by (Alexander *et al.*, 1997) who showed that the CD4/ T cell proliferative response to seminal plasma was significant in cases of CP/CPPS as compared with normal men. Ponniah *et al* (2000) showed that some men with symptoms of chronic prostatitis have evidence of a proliferative CD4/ T cell response to PSA, one antigen candidate for possible autoimmune prostatitis while others have confirmed that T-lymphocytes have a role in the excretion of inflammatory mediators such as complements C3, C4, and IL6 in the serum and ejaculate (John *et al.*, 2001). They also found an increase in IgA in the ejaculate. The concentrations of these markers decreased with the relief of prostatitis symptoms.

1.6.3 Chemical and functional disorder aspects of prostatitis

Persson and Ronquist (1996) studied the chemical composition of EPS and urine, showing that the origin of the chemical reaction and the basis for tissue inflammation was reflux into the prostatic ducts. Analogical findings were described by Ramirez *et al* (1980) showing that prostatic calculi are partly composed of the remains of ingredients coming from the urine reflux.

If prostatic ducts are obstructed by calculi, there may be a mechanical reaction on the epithelia through rising intraductal fluid pressure or direct irritation from calculi and age can also be a co-relating factor (Ramirez *et al.*, 1980).

Most patients with prostatitis have been shown to have an abnormal flowmetry parameters and distinct flow patterns (Ghobish, 2002). Thus, measurements of urine flow rate should be an integral part of the evaluation of prostatitis patients, as recommended by the current guidelines issued by the ICPCN in 1999 (Nickel, 2002). Synchronous video-pressure flow studies using a triple-lumen catheter with synchronous electromyography of the external urethral sphincter have demonstrated increased maximal urethral closure pressure in the proximal prostatic and membranous urethral segments as compared to controls (Barbalias *et al.*, 1998) and also decreased maximum and average flow rates. These findings were originally confirmed in patients with prostatodynia, but identical observation were made in patients with an inflammatory prostate (Barbalias, 1990) causing the author to abandon the term

prostatodynia in favour of "painful urethral syndrome". It was concluded that the findings could be attributed to a symphathetically mediated spasm.

Increased pressure in the prostatic urethra causes reflux into the prostatic ducts and ejaculatory ducts accompanied by prostate tissue irritation. Thus, it would be appropriate to perform video-urodynamic assessment to rule out possible neurological reasons for voiding disturbances and/or to validate any findings of organic causes of lower urinary tract symptoms (LUTS) and recurrent symptoms of CP/CPPS, thus also exploring the indication for alpha-blocker treatment (Kaplan *et al.*, 1997, Barbalias *et al.*, 1998)

An irony is that until now, it is unclear which came first: anatomical structural changes or functional disorder. It may be that reflux comes first, leading to chronic inflammation, upon which local reaction and tissue pressure leading to voiding disturbances with more reflux of urine, sterile or infection (Persson and Ronquist, 1996, Barbalias, 2002).

1.6.4 Myalgia aspects of prostatitis

Some patients with CP/CPPS may also appear to suffer mainly from tension myalgia of the pelvic floor and symptoms thought to arise from habitual contraction or spasm of the pelvic floor muscles (Barbalias, 2002). Patients report pain and discomfort associated with sitting, running or other physical activity that lead to spasms in the perineal muscles. It is possible that a rectal examination may demonstrate a spastic anal sphincter and paraprostatic tenderness, but not a tender prostate at all (Lillius and Valtonen, 1972, Segura *et al.*, 1979, Potts, 2003)

Alternatively, CP/CPPS is thought to be caused by the compression neuropathy of the pudendal nerve. The bony remodeling as a result of the activity of pelvic floor muscles lead to juxtaposition of the sacrospinal and sacrotuberal ligaments, which compress the pudendal nerve in the narrowed interligamentous space. (Antolak *et al.*, 2002)

1.6.5 Psychological aspects of prostatitis

Psychological factors are considered to play an important role in the aetiology of CP/CPPS even as early as the late 1960s and the 1970s. Urological patients with prostatitis generally tend to exhibit psychiatric problems, and there is a widely held belief among urologist that these patients are "neurotic". On this regard, CP/CPPS patients are often characterised as having problems with their male sexual identity. Symptoms such as anxiety, depression, fear, sexual disturbances and feeling of insecurity in human relationship especially psychological stress are common findings. Similarly, psychosomatic factors were found to be impaired (de la Rosette *et al.*, 1993, Egan and Krieger, 1994).

Thus, psychological evaluation, relationship counseling and even medical treatment for depression may play an important role in the overall approach to chronic prostatitis patients. This is in some cases obligatory in order to achieve any improvement in the symptoms or to avoid worsening of the mental distress (Egan and Krieger, 1994, Berghuis *et al.*, 1996).

1.7 DIAGNOSTIC PROCEDURE OF PROSTATITIS

To correctively evaluate a patient with prostatitis is an extremely complicated task, because the disease is defined only in terms of subjective symptoms with no objective, measurable parameters to divide the patients into diagnostic categories for clearly defined modes of treatment. Pain and discomfort is the most severe and common symptom, usually occurring in the region of the lower abdomen or more specifically at the suprapubic, perineal, scrotal, inguinal and penile areas (Figure 1.3). They can be accompanied by voiding complaints of varying severity and related symptoms. Temporary sexual dysfunction and mental distress may also be present in these patients.

The baseline information should be obtained by taking a complete medical history of all the facts related to urinary tract infections and any previous history of possible sexually transmitted diseases and relating this to the number of sexual contacts. A previous history of urological procedures can provide some explanations on which to base a clinical conclusion, and similar importance can be given to co-morbidity factors reflecting on the host defense mechanism and haematuria which may require cystoscopy and urinary tract imaging.

Clinical examination should focus on a careful assessment of the patients' inguinal regions and scrotum for hernias and varicocele, penis for plaques suggestive of Peryronie's disease or epididymoorchiditis, which can cause pain in the penis, a careful inspection of the perineum for evidence of