

**EPIDEMIOLOGICAL AND
DIAGNOSTICAL ASPECTS OF
PROSTATITIS**

**AARE
MEHIK**

Department of Surgery,
University of Oulu

OULU 2001



AARE MEHIK

**EPIDEMIOLOGICAL AND
DIAGNOSTICAL ASPECTS OF
PROSTATITIS**

Academic Dissertation to be presented with the assent of the Faculty of Medicine, University of Oulu, for public discussion in the Auditorium 1 of the Department of Surgery, on November 2nd, 2001, at 12 noon.

OULUN YLIOPISTO, OULU 2001

Copyright © 2001
University of Oulu, 2001

Manuscript received 15 September 2001
Manuscript accepted 20 September 2001

Communicated by
Professor Timo Lehtonen
Docent Kimmo Taari

ISBN 951-42-6506-8 (URL: <http://herkules.oulu.fi/isbn9514265068/>)

ALSO AVAILABLE IN PRINTED FORMAT
ISBN 951-42-6505-X
ISSN 0355-3221 (URL: <http://herkules.oulu.fi/issn03553221/>)

OULU UNIVERSITY PRESS
OULU 2001

Mehik, Aare, Epidemiological and diagnostical aspects of prostatitis

Department of Surgery, University of Oulu, P.O.Box 5000, FIN-90014 University of Oulu, Finland
2001

Oulu, Finland

(Manuscript received 15 September 2001)

Abstract

The principal aim of a population-based cross-sectional survey was to generate information on the lifetime occurrence of prostatitis in Finnish men and their exposure to the disease, and also on the influence of prostatitis-related fears and disturbances on their sexual life. A second aim was to develop and clinically validate a new diagnostic tool for differential diagnosis between the forms of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), especially between patients belonging to categories IIIA and IIIB in the new NIH (National Institutes of Health) clinical classification.

Altogether 1832 men out of 2500 aged 20–59 years chosen randomly from the two most northerly provinces of Finland (Oulu and Lapland) participated in the epidemiological study, a response rate of 75%. The overall lifetime prevalence of prostatitis was 14.2%. The risk of having had the disease increased with age, being 1.7 times greater in the men aged 40–49 years than in those aged 20–39 years, and 3.1 times greater in those aged 50–59 years. More than a quarter of the 261 men who had or had had prostatitis symptoms (27%) suffered from them at least once a year, while 16% suffered from chronic prostatitis symptoms throughout the year. 63% of the men with prostatitis had their worst symptoms during the wintertime (November–March)

17% of the men with chronic prostatitis reported a constant fear of undetected prostate cancer. Erectile dysfunction was reported by 43% of the symptomatic men and decreased libido by 24%. Self-assessment of personality showed that the men with prostatitis were more often busy and nervous and had a meticulous attitude to life and problems than were the non-symptomatic men.

197 patients with chronic prostatitis/chronic pelvic pain syndrome participated in three clinical case-control studies during the years 1995–2000, at Oulu University Hospital, the District Hospital of Oulainen and Seinäjoki Central Hospital. The first prostatic tissue pressure measurement (PTPM) study included 34 patients and 9 controls. A novel method was developed to measure intraprostatic tissue pressure with a Stryker® intracompartmental pressure monitor. The PTPM showed a clear increase ($p < 0.001$) in the patients with symptoms of prostatitis and benign prostatic enlargement (BPE) relative to the controls and the patients with BPE but without pain symptoms. The second PTPM study included 42 patients with chronic prostatitis symptoms without significant BPE and 12 new controls. Significantly higher pressure readings ($p < 0.001$) were recorded at all three measurement points in the patients than in the controls.

48 new patients and 12 new controls were enrolled for the third PTPM study, the purpose of which was to confirm the results of the previous ones and to compare the prostatic tissue pressures of two clinical groups (IIIA and IIIB). The prostatic tissue pressure was again significantly higher in the patients with chronic prostatitis symptoms than in the controls ($p < 0.001$). An interesting finding was that prostatitis patients belonging to clinical category IIIA had significantly higher tissue pressures ($p < 0.01$) than those in category IIIB, probably reflecting more severe inflammation in the prostatic tissue.

This new PTPM method provides a more precise and/or exact tool for differential diagnosis between the forms of pelvic pain and CP/CPPS.

Keywords: epidemiology, chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), prostate tissue pressure measurement (PTPM), diagnostic method, sexual disturbances, fears

*To honour of my family
and my friends*

Acknowledgements

This study was carried out at the Department of Surgery, Oulu University Hospital, during the years 1994–2000.

I thank Professor Matti Kairaluoma, M.D., Ph.D., former Head of the Department of Surgery, and Professor Tatu Juvonen, M.D., Ph.D., its present Head (since 2000), for giving me the opportunity to carry out this work.

I own my deepest and most sincere thanks to the "Grand Old Man" of Finnish urology, Professor Olof Alfthan M.D., Ph.D. (who died in January 2000), who guided me into the interesting world of urological research in 1992 and encouraged me to look at things and problems in an unconventional way.

Warm thanks are due to Professor Matti Kontturi M.D., Ph.D., former head of the Division of Urology, who first assessed me and then warmly and silently guided me to start research into prostatitis after my graduation in urology.

I am deeply grateful to my supervisors, Docent Pekka Hellström, M.D., Ph.D., my first mentor and guide in clinical urology, and to Professor Olavi Lukkarinen M.D., Ph.D., for their support and guidance during this work and for providing constructive comments and criticism.

My sincere and special thanks go to Marjo-Riitta Järvelin M.D., M.Sc., Professor of Epidemiology at the Department of Public Health Science and General Practice in the University of Oulu, who opened my eyes to the important world of epidemiological science and guided me during this work.

I am grateful to Professor Timo Lehtonen, M.D., Ph.D., and Docent Kimmo Taari M.D., Ph.D., for their advice and criticism in connection with reviewing the present manuscript.

I must not forget to convey my special thanks to two colleagues from abroad who have deeply influenced and directed me in the field of urological research: Frans M.J. Debruyne M.D., Ph.D., Professor of Urology at Nijmegen University Hospital, the Netherlands, and James C. Nickel M.D., FRCSC, Professor of Urology at Queen's University, Kingston, Canada.

I should also express my thanks to my fellow urologists at Oulu University Hospital and all the members of "Fraternitas Urologorum Borealis".

My sincere thanks go to my co-worker, statistician Ari Sarpola, M.Sc., of the University of Oulu, for his help and guidance in the field of medical statistics. Special thanks for supporting and helping me at the beginning of my experimental work should be extended to Mr. Pentti Rantanen, technician in the surgical ward, and to Ms. Mirja Hakkarainen, nurse in the surgical ward at Oulainen District Hospital. I must also thank Ms. Marjo Kittilä, secretary of the outpatients' ward, for many hours of technical assistance with the computing in the course of analysing the results.

I also thank the staff at the Division of Urology, especially the research nurses, Mrs. Anita Tikkala and Mrs. Pirta Körkkö and all my colleagues at the Department of Surgery and the staff of the surgical ward.

I thank Mr. Malcolm Hicks, M.A., for revising the English language of this thesis.

I would also like to thank all the patients who responded to our call to participate in the prostatitis survey and thus made it possible, and who also gave the valuable information needed for this research and inspired me to continue my research in this field of urology.

Finally, I extend my warmest thanks to my family, who suffered when I should have been at home with them rather than working on this research.

August 2001

Aare Mehik

Abbreviations

BOO	bladder outlet obstruction
BPE	benign prostatic enlargement
BPH	benign prostatic hyperplasia
CNP	chronic non-bacterial prostatitis
CP/CPPS	chronic prostatitis/chronic pelvic pain syndrome
EPS	expressed prostatic secretion
HPF	high-power field
LUTS	lower urinary tract symptoms
NIH	National Institutes of Health
NIH-CPSI	National Institutes of Health Chronic Prostatitis Symptom Index
PPMT	pre-and postmassage test
PTPM	prostatic tissue pressure measurement
VB1	first voided urine
VB2	mid-stream urine
VB3	post-massage voided urine

List of original publications

This thesis is based on the following articles, which are referred to in the text by their Roman numerals:

- I Mehik A, Hellström P, Lukkarinen O, Sarpola A & Järvelin M-R (2000) Epidemiology of prostatitis in Finnish men: a population-based cross-sectional study. *BJU Int* 86: 443–448
- II Mehik A, Hellström P, Sarpola A, Lukkarinen O & Järvelin M-R (2001) Fears, sexual disturbances and personality features in men with prostatitis: a population-based cross-sectional study in Finland. *BJU Int* 88: 35–38
- III Mehik A, Hellström P, Lukkarinen O, Sarpola A & Alftan O (1999) Increased intraprostatic pressure in patients with chronic prostatitis. *Urol Res* 27: 277–279
- IV Mehik A, Hellström P, Lukkarinen O, Sarpola A & Alftan O (2000) Prostatic tissue pressure measurement as a possible diagnostic procedure in patients with chronic nonbacterial prostatitis/chronic pelvic pain syndrome. *Urol Res* 28: 316–318
- V Mehik A, Hellström P, Nickel JC, Kilponen A, Leskinen M, Sarpola A & Lukkarinen O. Chronic prostatitis/chronic pelvic pain syndrome can be characterized by prostate tissue pressure measurements. *J Urol* (in press)

Contents

Abstract	
Acknowledgements	
Abbreviations	
List of original publications	
1 Introduction	15
2 Review of the literature	16
2.1 Historical perspective of prostatitis	16
2.2 Basic anatomy, histology and physiology related to the prostate gland	18
2.3 Patho-physiological and clinical basis for tissue pressure measurement	19
2.4 Early classifications of prostatitis	21
2.4.1 The traditional classification of prostatitis	21
2.4.2 The new National Institutes of Health (NIH) classification of prostatitis	22
2.5 Epidemiology of prostatitis	23
2.5.1 Epidemiological concepts	24
2.5.2 Population-based and clinic-based studies of prostatitis	24
2.5.3 Questionnaires used in epidemiological studies so far	25
2.5.4 Practical clinical patterns followed in prostatitis studies	26
2.6 Aetiology and pathogenesis of prostatitis	27
2.6.1 Role of animal models for prostatitis research and clinical outcomes	27
2.6.2 Aetiological aspects of prostatitis	28
2.6.2.1 Histopathological aspects of prostatitis	29
2.6.2.2 Microbiological aspects of prostatitis	30
2.6.2.3 Immunological aspects of prostatitis	31
2.6.2.4 Chemical aspects of prostatitis	32
2.6.2.5 Urodynamic and myalgic aspects of prostatitis	32
2.6.2.6 Psychological aspects of prostatitis	33
2.7 Diagnostic procedures of prostatitis	34
2.7.1 Evaluation of prostatitis patients	34
2.7.2 Laboratory and related findings	35
2.7.2.1 Urine analysis and microbiological culture	35
2.7.2.2 The Meares-Stamey "four-glass test" – the golden standard	35
2.7.2.3 Nickel's pre-massage and post-massage test	36

2.7.2.4	Semen functional analysis	37
2.7.2.5	PSA (F/T ratio), PAP and cytokines	38
2.7.2.6	PCR of prostate tissue/seminal fluid: is this a new diagnostic tool?	39
2.7.3	Transrectal ultrasound examination, biopsy of the prostate gland	39
2.7.4	Urodynamic examinations	40
2.7.5	Endoscopic examinations	41
2.8	Other pathology and prostatitis	41
2.8.1	Interstitial cystitis and prostatitis	41
2.8.2	Bladder carcinoma in situ and prostatitis	41
2.8.3	Prostate cancer and prostatitis	42
2.8.4	Benign prostatic hyperplasia and prostatitis	42
3	Aims of the study	44
4	Materials and methods	45
4.1	Population-based cross-sectional epidemiological survey (I, II)	45
4.2	Technique of prostatic tissue pressure measurement (PTPM) (III–V)	46
4.2.1	Paper III: Increased intraprostatic pressure in patients with chronic prostatitis	47
4.2.2	Paper IV: Prostatic tissue pressure measurement as a possible diagnostic procedure in patients with chronic non-bacterial prostatitis /chronic pelvic pain syndrome	48
4.2.3	Paper V: Chronic prostatitis/chronic pelvic pain syndrome can be characterized by prostate tissue pressure measurements	48
5	Results	50
5.1	Population-based cross-sectional epidemiological survey (papers I–II)	50
5.2	Summary of the results of the PTPM examinations (papers III–V)	51
6	Discussion	53
6.1	Epidemiology of prostatitis (I, II)	53
6.1.1	Epidemiology of prostatitis in Finnish men: a population-based cross-sectional survey (I)	53
6.1.2	Fears, sexual disturbances and personality features of men with prostatitis (II)	55
6.2	The PTPM procedure and its clinical implications (III–V)	57
7	Conclusions	60
8	References	61
	Original publications (I–V)	
	Appendix	

1 Introduction

Doctors, especially urologists, cannot be proud of their results in dealing with and solving the clinical "puzzle syndrome" called "prostatitis". For many decades prostate cancer and benign prostatic hyperplasia have absorbed the attention of urologists, researchers, funding authorities and of course the top flight of the biomedical and pharmaceutical industries.

Prostatitis – the third part in the "round table", the "poor cousin" of benign prostatic hyperplasia and prostate cancer – is like forgotten relatives, we all remember them, but we never expect them to visit us, and when they do come, we try to get rid of them as soon as possible. For many decades we have neglected and underestimated this disease, characterized mostly by chronic pain syndrome and accompanied by variable disturbances in voiding and sexual life, not to mention the burden of mental distress and other psychological physiological factors regulating our daily lives and personal relationships. The realization that we are not always caring adequately for our prostatitis patients can lead to great frustration on both sides of the office table.

Times seemed to start to change approximately one decade ago, when a group of young scientists and clinicians restarted basic research in the field of prostatitis and opened Pandora's box. During the last five years we have been given a new, more appropriate clinical classification of prostatitis by the National Institutes of Health (NIH), and we have established an International Chronic Prostatitis Collaborative Network for the coordination of research and funding, opening up possibilities for carrying on with basic research (Nickel 1999, Nickel *et al.* 1999b). More recently, in May 1999, the NIH Chronic Prostatitis Symptom Index for measuring the severity of symptoms in prostatitis patients was published, giving some guidelines for future research (Litwin *et al.* 1999, Nickel *et al.* 1999b).

The prostatitis syndrome is no longer a faceless myth. It is a reality, and the new awareness of its importance may give new hope for patients suffering from this intractable pain syndrome (Egan & Krieger 1997, Nickel 1998a). I should close this introduction with the words of Mike Hennenfent, President of the Prostatitis Foundation: "...cancer is not the only prostate disease".

2 Review of the literature

The articles published on prostatitis between 1900 and 2000 can be divided roughly into four categories.

I. Articles written by one author and related to basic clinical knowledge, illuminating the possible role of aetiological factors (mostly bacterial), diagnostic procedures and treatment modalities, mainly comparing the treatment efficacy of different antibiotics and their clinical outcomes (1900–1970).

II. Articles related to attempts to investigate physiological and measurable functional disorders of the genitourinary tract, using instrumental-investigational approach and questionnaires (urodynamics, ultrasound investigations, endoscopic and psycho-mental mapping of problems, etc.) (1970–1990).

III. Articles related to the epidemiology of prostatitis and its relations to benign prostatic hyperplasia and/or prostate cancer (1980–1999).

IV. Articles employing very sophisticated biochemical, biomolecular, routine or specific histological and immuno-assay methods to investigate problems related to the aetio-pathology of prostatitis syndrome (1990–2000).

2.1 Historical perspective of prostatitis

The prostate gland was described in the anatomical studies of Herophilus about 350 BC and was rediscovered in the 16th century by the Venetian physician Nicola Massa. At the same time the physician Riolanus noted that bladder obstruction can be caused by swelling of the prostate gland. Prostatitis as a clinical entity/syndrome was first described in 1815 by Legneau, who noted that inflammation of the prostate gland could be a complication of urethritis (von Lackum 1928).

The first accurate description of the pathology of prostatitis in written form was presented by Verdie in 1838, and this was later confirmed and updated by Hugh Young, Gereghy and Stevens in 1903 and published in 1906 (Young *et al.* 1906, von Lackum 1928).

The time between the 1880 and 1928 was a period of searching for bacteria and confirming the postulates of Koch and Virchow related to the mechanisms of bacterial infections acting in the human body (Hitchens & Brown 1913, von Lackum 1927).

Between 1900 and 1930, the basic chemistry of prostatic fluid was studied and the role of possible pathogen bacteria cultured from the prostate gland and from prostate secretion was defined and von Lackum's theory of possible retrograde secondary infection ascending from the urethra to the prostatic ducts was clinically demonstrated by several physicians (Young *et al.* 1906, Hitchens & Brown 1913, von Lackum 1927, Nickel 1930).

The period between 1930 and 1960 was marked by an active search for aetiological factors related to prostatitis syndrome, factors that could be responsible for its chronicity and the histological changes that take place, fibrosis and scarring together with late functional disorders of the prostate gland. Despite of all these new findings, there were many internists and psychoanalysts who denied the existence of chronic prostatitis processes, and the latter group termed such symptoms "anal/rectal psychoses" (Cumming & Chittenden 1938).

Ritter and Lippow (1938) searched for an explanation for the natural history of the pathological processes involved in prostatitis, and they also described the histological findings during acute phase of inflammation as hyperaemia, oedema, cellular infiltration of polymorphonuclear leukocytes and round cells in the prostate tissue.

Grant (1938) noted that the infection was mostly located in the ducts and acini of the prostate. On the other hand, Kretschmer (1937) drew conclusions from 1000 cases that pointed to polyaetiological aspects of the disease, and also reflected on the sexual life of patients.

There was a period in the 1940s and 1950s when it was generally accepted that an important offending organism in cases of acute infectious prostatitis was gonococcus.

Henline (1943) reported that untreated gonococcal urethritis was a possible aetiological factor in over 20–30% of cases of chronic prostatitis symptoms, but Kretschmer (1937) found gonococcus to be an aetiological reason for prostatitis in only 2.4% cases.

Genitourinary tuberculosis was regarded as a specific aetiological factor between 1900 and 1960. Tuberculosis of the prostate gland as only affected genital organ was found in 12% cases in an autopsy series, and the majority of patients with upper genitourinary tuberculosis were also found to have signs of prostatic irritation (Moore 1937, Meares 1998).

In the late 1950s it was recognized and noted, especially by Campbell (1957), that chronic prostatitis may be present in the prostate gland without any clinical symptoms, and it was also realized that a disease such as prostatitis can be congestive and non-bacterial.

The active clinical research period of the 1970s and 1980s, was motivated by the findings of Meares and Stamey (1968), which pointed to a new direction in the diagnosis of prostatitis, and those of Drach *et al.* (1978), which provided a new classification of the disease. This was followed by a period of collecting clinical experience and basic knowledge on prostatitis at large, using new laboratory methods for bacterial cultures, microscopy and immunofluorescence imaging.

From the 1990s onwards a young generation of disappointed urologists who did not accept all the written data from past concerning prostatitis as a forgotten "light urological ambulatory pathology" and "not needing special urological care" started a new era in prostatitis research (Nickel 1999, Nickel *et al.* 1999b).

2.2 Basic anatomy, histology and physiology related to the prostate gland

The prostate gland, mainly consisting of a fibromuscular glandular part and the stroma, has the shape of a pyramid and lies on the pelvic musculofascial floor, being surrounded by thin layer of connective tissue (McNeal 1972, McNeal 1988, 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. The prostate is separated posteriorly from the rectum by the anterior layer of Denonvillier's fascia and is fixed anteriorly to the pubic bone with the puboprostatic ligaments, being held in the dorsal vein plexus between these structures (Dixon *et al.* 1999). 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 3 cm 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 forms about 70% of glandular part, and its ducts open into the distal prostatic urethra. The central zone forms about 25% of the glandular prostate, the ducts of which open mainly into the middle prostatic urethra. The transitional zone (about 5%) consists of two small lobes, and the ducts open almost into the sphincteric part of the urethra. The entire duct-acinar system with the exception of the main lateral ejaculatory ducts is lined by columnar secretory cells, which are separated from the prostatic stroma by a layer of basal cells belonging to the basement membrane (McNeal 1972, Blacklock 1974, McNeal 1988, Dixon *et al.* 1999).

The human prostate gland receives dual autonomic innervation from both parasympathetic (cholinergic) and sympathetic (noradrenergic) nerves in the prostatic nerve plexus, a part of the pelvic autonomic plexus that lies adjacent to the prostate gland. 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). The autonomic nerves arising from the pelvic plexus escort the vascular supply. 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 sympathetic nerves 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 acid (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 (Fair & Cordonnier 1978, Weidner *et al.* 1991a, Zaichick *et al.* 1996).

Up to 57 major protein groups, of which 27 are non-serum proteins (i.e. presumably exuded by the epithelial cells) have been identified. Major prostatic-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).

2.3 Patho-physiological and clinical basis for tissue pressure measurement

Processes of gas (oxygen vs carbon dioxide) and tissue cell metabolite exchange are constantly taking place in all parts of the human body where blood circulation is present, forming the basis for the functioning of organs and creating a working environment in the peripheral tissues in the form of interstitial pressure. All the mechanisms by which the different physiological processes function are related to the hypothesis known as "Starling's forces", based on the work of Starling (1896). This describes the physiological background to interstitial tissue pressure in terms of the hydrostatic and oncotic pressure balances inside and outside the capillary wall. This hypothesis was later confirmed experimentally by Landis in the 1920s and 1930s and subsequently in several other laboratory works (Wiederhielm 1968, Wiederhielm 1970, Guyton *et al.* 1971, Peters & Hargens 1981).

There are various normal physiological changes (blood pressure changes) or pathological changes (inflammation caused by tissue damage, releasing kinines, bacterial toxins, etc.) that take place at the level of the peripheral capillary beds, and there are also changes in the central blood circulation level (as in heart failure, hypovolaemia, anoxia etc.), which can cause severe disturbances in interstitial tissue pressure (ISTP), leading to the destruction of cells (Wiederhielm 1968, Wiederhielm 1970, Guyton *et al.* 1971, Asthon 1975).

As Asthon (1975) pointed out, the delicate structure of the capillaries and their intimate relationship to the extracellular space make them particularly vulnerable to changes in tissue pressure. The human body is composed of approximately 70% water and 30% solids, and the body fluids are distributed into three compartments: the intracellular fluid compartment, the interstitial fluid compartment and the blood. The intracellular fluid comprises about 50% of the total body weight and the blood plasma

about 5%, the remaining 15% being distributed in the interstitial space, which envelopes the cells and blood vessels in the tissue. Fluid is being exchanged continuously between the plasma and interstitial space, and between the intracellular and interstitial spaces. Despite the complexity of the fluid fluxes among different compartments, their volumes remain surprisingly constant and ensure homeostasis. Regulation of this fluid distribution is of prime importance, since it serves to maintain physical-chemical stability in the immediate environment of the cells, as required for optimal cell function and to avoid the development of oedema (Peters & Hargens 1981).

It has been confirmed in animal and human experiments that there is a relationship between blood pressure (with the main function of delivering oxygen to the cells) and tissue pressure (consisting of hydrostatic and oncotic pressure). Hydrostatic pressure means a pressure caused by fluid changes in the capillary network, and oncotic pressure that caused by fluids bound to the collagen matrix. This pressure does not equilibrate quickly, as the basic pressure rises only when the quantity of protein increases (albumin infusion, combustion, congelation, etc.). The hydrostatic and oncotic pressures together are responsible for the balancing of the physiological ISTP (Wiederhielm 1968, Guyton *et al.* 1971). The normal mean interstitial tissue pressure is 25 mmHg (range 20–30 mmHg), and if it is over 50–60 mmHg or below 10 mmHg, or below the diastolic blood pressure minus 20–30 mmHg, functional tissue changes can occur. If such a situation prevails for over 6–12 hours without interruption, irreversible tissue changes will obviously take place (Whitesides *et al.* 1975, Gelberman *et al.* 1983, Witschger & Wegmüller 1994). In other words, if the tissue pressure is between 10–60 mmHg, normal physiological exchange between the blood and tissue cells is possible, but if the pressure is below 10 mmHg or over 60 mmHg normal physiological tissue functions will cease (Wiederhielm 1968, Asthon 1975). In these circumstances the basal blood flow and the blood flow during reactive hyperaemia are considerably decreased and vascular resistance is raised. Increased transudation of fluid into the surrounding tissue during circulatory disturbances caused by inflammation, for instance, leads to an increase in tissue pressure, together with the well known later pathological tissue changes such as necrosis with scarring (Wiederhielm 1968, Guyton *et al.* 1971, Asthon 1975, Witschger & Wegmüller 1994). The sequelae of ischaemic tissue damage have been known since 1872, when Volkman described his famous findings on forearm pathology known as Volkman's contracture (Whitesides *et al.* 1975). There are several parts of the human body where functionally important structures are surrounded by non-elastic fasciae, such as the calf and forearm (muscles in several compartments) (Whitesides *et al.* 1975, Witschger & Wegmüller 1994) and also the pancreas (Ebbehøj *et al.* 1984, Ebbehøj *et al.* 1986).

Discussion has been going on since the 1970s about the compartmental syndromes caused by increased tissue pressure. The earliest sign of tissue ischaemia is pain, which is caused by increased pressure and can be measured intracompartmentally. The earliest techniques were based on the open Wick's method or the closed implanted capsule method (Wiederhielm 1968, Guyton *et al.* 1971), while the newest method is a computer-based system, the Stryker® device, with a measuring kit consisting of a monitor/pressure transducer, a needle kit and a connecting tube (Whitesides *et al.* 1975, Ebbehøj *et al.* 1984, Ebbehøj *et al.* 1986, Witschger & Wegmüller 1994). Pressure can be recorded

instantly, but continuous monitoring is also possible. A graphical method for recording forearm intra compartmental tissue pressure (ICTP) has been developed at Kuopio University Hospital in Finland by Jaroma and colleagues (2000).

2.4 Early classifications of prostatitis

From 1815 to 1838 the pathology of prostate disease was described only as acute prostatitis, as a complication either of acute septic invasion of the prostate by bacteria or of chronic inflammation of the prostate (von Lackum 1928). 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 1928).

In the 1930s Farman divided prostatitis patients into two main groups according to their bacterial aetiology: a primary group – after gonorrhoeal infections (three types: simple, true chronic and atopic prostatitis), and secondary group – without proven gonococcus – termed the focal type of prostatitis, based on the focal infection theory that attracted much attention among researchers in the 1920s (Farman 1930).

Grant (1938) proposed a classification into acute, occluded chronic and recalcitrant prostatitis, where the latter denoted persistent infection after the failure of treatment (heat, massage, vaccine, etc.), to which Henline (1943) added a group of patients with “silent prostatitis” (no clinical symptoms), as also mentioned by Kretschmer (1939).

Since the 1950s investigators have accepted that there may be a chronic process without bacterial findings (Campbell 1957).

2.4.1 The traditional classification of prostatitis

When Meares and Stamey (1968) published their article concerning suggestions for diagnosing prostatitis by the “four-glass test”, this was quickly followed by a general acceptance of the traditional classification of Drach *et al.* (1978) for clinical use, a situation that lasted for over two decades. The Meares-Stamey “four-glass test” details are given in section 2.7.2.2. Inflammation of the prostate gland was defined on the basis of the finding of leukocytes in the prostatic fluid. Meares and Stamey (1968) proposed a diagnostic value of 10 or more white blood cells per high-power field, which was also supported by Anderson and Weller (1979), while others favoured 20 or more white blood cells per high-power field, along with clumps, debris, occasional lecithin and oval fat bodies in large macrophages (Drach *et al.* 1978). Based on this description the traditional classification, as illustrated in Table 1, includes all previously accepted forms of prostatitis.

Table 1. The traditional classification of prostatitis (Drach et al. 1978).

Category	Clinical findings
I	Acute bacterial prostatitis
II	Chronic bacterial prostatitis
III	Chronic non-bacterial prostatitis
IV	Prostatodynia

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

Chronic bacterial prostatitis: should be diagnosed 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: should be diagnosed when bacteria are not found in the prostatic fluid but a significant number of leukocytes (>10 per hpf) are seen. The authors warn about the possibility of cryptic/hidden infections through trichomonas, TBC, fungi, Chlamydia or Mycoplasma, etc..

Prostatodynia: consistent pain in the prostate (pelvic pain). The diagnosis should be preferred when there are no bacteria and no signs of inflammation (leukocytes) in the prostatic fluid.

Physicians and urologists immediately adopted the concept of this classification for clinical use, and it persisted for over two decades. Real life situations nevertheless helped to point out its limitations.

The reason for the next stage in development was that in reality the majority of urologists and certainly almost all primary care physicians were refusing to use the Meares-Stamey technique routinely, and without this the classification of chronic prostatitis patients into the three traditional categories is impossible, since the diagnosis relies on findings from an expressed prostatic secretion (EPS) culture (Meares & Stamey 1968, McNaughton-Collins *et al.* 2000).

2.4.2 The new National Institutes of Health (NIH) classification of prostatitis

The meeting of the NIH Workshop on Chronic Prostatitis and the NIH-supported International Chronic Prostatitis Collaborative Research Network in Washington in December 1995 proposed a new classification of prostatitis that would be more accurate for diagnosing and characterizing the disease. 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, as presented in Table 2 was later accepted by urologists and validated by a large group of university clinics and published for clinical use in 1999 (Krieger *et al.* 1999).

Table 2. The new NIH consensus classification of prostatitis (Krieger *et al.* 1999)

Category	Clinical findings
I	Acute bacterial prostatitis
II	Chronic bacterial prostatitis
III	Chronic prostatitis/chronic pelvic pain syndrome
	A Inflammatory
	B Noninflammatory
IV	Asymptomatic inflammatory prostatitis

The new classification system is based on the results of microscopic and bacterial culture of the expressed prostate secretion (EPS, semen culture, post-prostate massage urine and biopsy of the prostate gland) (Krieger *et al.* 1999, Nickel *et al.* 1999b). As can be seen in the Table 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 pelvic pain syndrome with and without signs of inflammation (leukocytes > or < 10 per hpf). Category IV now includes patients with histologically proven chronic prostatitis without clinical symptoms of pain and/or disease at all.

This classification still has some limitations, largely related to our inadequate understanding of the relevance of white blood cells, the lack of standardization of leukocyte investigation techniques and the lack of comparable cut-off points for elevated numbers 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 microorganisms (Dominique & Hellstrom 1998). The new classification system is a clear improvement over the old one, however, and brings more effectiveness and clarity into clinical practice and research protocols (Nickel *et al.* 1999b).

2.5 Epidemiology of prostatitis

Prostatitis is an enigmatic condition that affects men at all points of their lives, a fact that nobody can overlook. It also has an impact on their health in general and it forms the third part of the prostate pathology alongside prostate cancer and benign prostate hyperplasia (Keltikangas-Järvinen *et al.* 1989, de la Rosette *et al.* 1993b, Berghuis *et al.* 1996, Wenninger *et al.* 1996, Roberts *et al.* 1997).

Prostate cancer and benign prostatic hyperplasia are two important reasons for increased healthcare costs, especially due to the need for hospitalization, and not far away is the growing group of prostatitis patients who are increasingly seeking help from modern medicine on an outpatient basis (McNaughton-Collins *et al.* 1998b, Roberts *et al.* 1998, McNaughton-Collins *et al.* 1999). There are some epidemiological studies showing that this condition is very common and that there are factors related to age, education, economic and marital status, recreational activities, sexual behaviour, infections of the

urinary tract, concomitant diseases reflecting autoimmunity, psycho-mental disturbances etc., which may provide clues to a better understanding of its aetiology (Krieger *et al.* 1993a, Alexander & Trissel 1996, Moon 1997, McNaughton-Collins *et al.* 1998a, McNaughton-Collins *et al.* 1998b, Roberts *et al.* 1998, Nickel *et al.* 2001).

2.5.1 Epidemiological concepts

Epidemiology differs from clinical medicine in that the unit of interest is the population rather than the individual. It may be defined as the study of the distribution, frequency and determinants of health problems and disease in human populations, allowing the distribution of health and illness to be described in a population, mostly by measuring the occurrence of illness. It also provides tools for comparing populations in terms of their health characteristics. Measures of disease frequency are of two basic types: incidence and prevalence (Rothman 1986).

Incidence focuses on events of a disease and represents an attempt at measuring the frequency of disease occurrence in a given population. There are several possible measures of incidence, taking account of the time elapsing before occurrence of the disease, and/or number of individuals in the population who become ill. These include the incidence proportion (or incidence at risk), cumulative incidence and incidence density (also known as incidence rate or force of morbidity) (Rothman 1986).

Prevalence focuses on disease status, and may be defined as the proportion of the population affected by disease at a given point in time, sometimes referred to as the term point prevalence (Rothman 1986).

2.5.2 Population-based and clinic-based studies of prostatitis

The prevalence of prostatitis refers to the proportion of men who suffer and/or have suffered from it at a specific point in time (point prevalence) (McNaughton-Collins *et al.* 1998b, Roberts *et al.* 1998, Nickel *et al.* 2001) or at defined period of time (period prevalence). Its incidence is the frequency of occurrence of new cases derived from the monitoring of subjects over time. The incidence data are usually obtained from retrospective and prospective cohort studies and prevalence data from cross-sectional assessments (Drabick *et al.* 1997, Moon *et al.* 1997, Roberts *et al.* 1998, McNaughton-Collins & Barry 1999, Nickel *et al.* 2001). The prevalence can be also defined from an autopsy series (Mehlhorn 1987).

The majority of studies on prostatitis are nevertheless clinical series, and their results have provided useful information and increased our clinical knowledge about to the disease and its aetiological agents (Poletti *et al.* 1985, Doble *et al.* 1989b, Weidner *et al.* 1991b, Shortliffe *et al.* 1992, Nickel & Costerton 1993, Berger *et al.* 1997).

Clinical studies are essential for the evaluation of potential treatment strategies (Schaeffer & Darras 1990, Krieger & Egan 1991, Weidner *et al.* 1991b, Nickel & Sorensen 1996), and it is these that have formed the basis for the new NIH classification of prostatitis (Moon *et al.* 1997, Krieger *et al.* 1999, Litwin *et al.* 1999).

Clinical studies have provided a valid characterization of the signs and symptoms of prostatitis (Krieger & Egan 1991, de la Rosette *et al.* 1993a, Egan & Krieger 1994, Krieger *et al.* 1996a, Egan & Krieger 1997) and future guidelines for using specific laboratory investigations, e.g. EPS (Anderson & Weller 1979, Schaeffer *et al.* 1981) and ultrasonography to judge the clinical relevance of findings in patients (Doble *et al.* 1989a, de la Rosette *et al.* 1995).

Several population-based cross-sectional surveys and series of clinical data from outpatient visits have shown that the prevalence of prostatitis symptoms is up to 25% (Moon 1997, Roberts *et al.* 1997, Pavone *et al.* 2000), whereas the prevalence based only on questionnaires and physicians' diagnoses is reported to be between 4% and 11% (Moon *et al.* 1997, McNaughton-Collins *et al.* 1998b, Roberts *et al.* 1998, Nickel *et al.* 2001) and that based on autopsy material ranges from 61% (Mehlhorn 1987) up to the 98% obtained using histopathological data from TURP chips (Kohnen & Drach 1979).

Case-control studies represent another design frequently used to collect comprehensive data related to prostatitis symptoms (Berger *et al.* 1989, Weidner *et al.* 1991a, Weidner *et al.* 1991b, Berger *et al.* 1997). This means, that the information provided is closely dependent on a very locally available "super"-selected population (a certain hospital, a certain urological clinic or a certain area in a specific country) and illuminates a very narrow part of the whole problem. The data are hard to compare and to interpret and are apt to lead to overestimation or underestimation of the real situation. All the time that the definition of prostatitis is not the same for all, our understanding of the epidemiology of prostatitis will be limited and scarce (Nickel *et al.* 2001).

2.5.3 Questionnaires used in epidemiological studies so far

Following the work of the American Urological Association (AUA) to define the symptoms associated with benign prostatic hyperplasia (BPH), several investigators have developed their own questionnaires (Brähler & Weidner 1986, Neal & Moon 1994, Alexander & Trissel 1996, Krieger *et al.* 1996b, Nickel & Sorensen 1996).

The importance of using standardized questionnaires for the evaluation of prostatitis patients is that it allows the work of different authors to be compared. And still more important is the use of standardized diagnostic criteria. This work was started under the guidance of J.C. Nickel and the International Prostatitis Collaborative Network, and was published for clinical use by Litwin *et al.* (1999).

Concerning the use of specific questionnaires to study unselected populations of men in order to collect epidemiological data, the situation among the prostatitis researchers is not very encouraging. So far only one large survey (54 questions), based on use of the Internet (Alexander & Trissel 1996), the population-based study by Roberts *et al.* (1998)

(134 questions) and a few others with up to 58 questions (Moon *et al.* 1997) have been directed at prostatitis patients or their physicians/urologists (de la Rosette *et al.* 1992a, Neal & Moon 1994, Wenninger *et al.* 1996, Moon 1997, Nickel *et al.* 1998).

2.5.4 Practical clinical patterns followed in prostatitis studies

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

When we compare these results with the surveys published by Moon (1997) and Nickel *et al.* (1998), many similarities emerge with regard to the opinions of physicians and urologists. These surveys show quite remarkable consistency from country to country, but the differences in the numbers of patients seen by doctors mainly represent differences between health care services rather than between rates of diagnosis. These surveys (de la Rosette *et al.* 1992a, Moon 1997, Moon *et al.* 1997, Nickel *et al.* 1998) 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 the results of Lowentritt *et al.* (1995) and Berger *et al.* (1997) concerning "cryptic infections" of the prostate gland.

The textbooks of urology presume that acute and chronic bacterial prostatitis are easily defined, diagnosed and treated (Meares 1998). 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.* 2000a). Additionally, when about 90% of bacterial cultures are negative, this causes a normalizing tendency, or clinical behaviour designed to avoid proper laboratory diagnostics in clinical practice, leading to an erroneous basis for reaching treatment decisions. The textbooks (Meares 1998) also suggest a possible infectious aetiology of prostatitis even when conventional cultures are negative (Lowentritt *et al.* 1995, Berger *et al.* 1997, Krieger *et al.* 2000b) and Krieger *et al.* (2000c) have found some signs of bacterial presence in prostate tissue in a case of prostatitis using a polymerase chain reaction (PCR) technique, but the clinical significance of this is still unresolved.

2.6 Aetiology and pathogenesis of prostatitis

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 even in clear instances of bacterial prostatitis (Kretschmer 1939, Krieger 1984, Meares 1984, Blacklock 1991). Anatomical/clinical examinations of prostatitis patients have shown that two factors are needed for the development of prostate inflammation: dysfunctional voiding with high pressure due to anatomical or physiological obstruction (Blacklock 1991) and intraductal reflux of urine into the prostate gland (Kirby *et al.* 1982, Barbaliás *et al.* 1983, Hellstrom *et al.* 1987, Chapple *et al.* 1990).

The causative agents in bacterial prostatitis are similar in type and prevalence to those responsible for urinary tract infections with common strains of *Escherichia coli* (Kretschmer 1939, Domingue & Hellstrom 1998), although infections caused by species of *Proteus*, *Klebsiella*, *Enterobacteria*, *Pseudomonas*, *Serratia* (Domingue & Hellstrom 1998) and lately *Chlamydia*, *Ureaplasma*, *Mycoplasma* (Weidner *et al.* 1988), *Corynebacteria* and viruses (cyto-megalo virus, human immunodeficiency virus, herpes etc.), not to mention bacterial infections in acquired immune deficiency syndrome (AIDS) patients (Leport *et al.* 1989, Staiman & Lowe 1996) and fungi (Wise *et al.* 1999) can also occur. Special interest was aroused in the 1970s and 1980s when antibody-coated bacteria were detected in immunological tests and it was hypothesized that chronic prostatitis may be a problem of altered immunity due to an antigenic stimulus (parts of bacteria and/or toxins) (Shortliffe *et al.* 1981, Fowler & Mariano 1982, Fowler 1991, Riedasch *et al.* 1991, Kumon 1992) and is under research again (Alexander *et al.* 1997, John *et al.* 2001).

2.6.1 Role of animal models for prostatitis research and clinical outcomes

Much information on the aetiology and pathogenesis of prostatitis has been gathered through the use of animal models, which have shown that immunologically or chemically mediated prostatic inflammation is the reason for hyperplastic changes (Nickel *et al.* 1990, Keetch *et al.* 1994, Takechi *et al.* 1999). *Escherichia coli* is the predominant organism causing acute and/or chronic inflammation, followed by other gram-negative pathogens. Rat and canine models have been used to confirm the importance of *E. coli* in the disease process and also to follow the distribution of antibiotics in the prostate gland (Neal *et al.* 1990, Nickel *et al.* 1990, Bahk *et al.* 2000). Experimental results have confirmed the pathophysiological mechanism of the route by which bacteria ascend from the urethra into the prostate gland through reflux. Urethral inoculation of monkeys with bacteria also resulted in similar findings to those observed in humans (Neal *et al.* 1990).

PSA behaviour in prostatitis was studied experimentally in monkeys (Neal *et al.* 1990, Neal *et al.* 1992) confirming that it takes 8 weeks for PSA to return to the base level after acute prostatitis.

The rat model used by Nickel *et al.* (1990) gave reliable and consistent results regarding the role of bacteria in acute and chronic bacterial prostatitis, showing that bacteria entering the ducts and acini of the prostate will multiply rapidly and induce a host response with infiltration of acute inflammatory cells into the ducts. Infiltrates of dead and live bacteria, and also inflammatory cells, desquamated epithelial cells and cellular debris, will block the ducts and may cause systemic clinical urosepsis. It has also been shown that infection can be eradicated with proper antibiotic treatment, but if the bacteria form small microcolonies coated with exopolysaccharide slime or glycocalyx they can "hibernate" out of range of the antibiotics. Lymphatic invasion with infiltration of plasma cells and macrophages can be seen around the colonies, leading later to fibrosis and permanent scarring (Nickel *et al.* 1990).

Naslund *et al.* (1988) showed experimentally that genetic background and hormonal imbalance with advancing age are important factors in the process of non-bacterial prostatitis. It has also been shown that prostatic inflammation is at least partially immune-mediated, explaining the close association between non-bacterial and bacterial-induced chronic inflammation (Keetch *et al.* 1994).

Experimental studies have also confirmed that bacteria can persist in the prostate tissue following treatment with antibiotics and remain undetectable in the prostate secretion. It is possible that the pharmacokinetics of the drugs may be altered by local inflammation, blockage of ducts, calculi in the acini, microabscesses and pH changes through tissue hypoxia (Klimas *et al.* 1985, Nickel *et al.* 1990, Nickel *et al.* 1995).

The rat model used by Nickel *et al.* (1990) showed that antibiotic concentrations in the inflamed glandular ducts were not significantly higher than in non-inflamed ducts, but bacterial aggregates in the slime were more resistant to normal concentrations of antibiotics and to host defence.

Fulmer and Turner (2000) showed that there is a blood-prostate barrier that restricts the movement of cells and molecules from the blood or interstitium into the prostatic ducts. This may explain the situation in which prostatitis symptoms occur but diagnostic methods fail to prove it. On the other hand, it was shown in a rat experiment that the protective barrier of the epithelium can be damaged and local resistance to cytokines/mediators reduced, possibly leading to inflammation (Lang *et al.* 2000), because otherwise harmless agents from the urine can start the inflammation process by reflux.

2.6.2 Aetiological aspects of prostatitis

Four main 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 the predisposing factors and/or host defence mechanisms.

The bacterial component is indisputable in cases of acute or chronic bacterial prostatitis, but it is questionable in cases of chronic non-bacterial prostatitis or prostatodynia (Berger *et al.* 1989, Shortliffe *et al.* 1992, Lowentritt *et al.* 1995, Berger *et al.* 1997, Krieger *et al.* 2000b).

The role of urine reflux has also been demonstrated experimentally in the human prostate gland (Kirby *et al.* 1982, Chapple *et al.* 1990, Turner *et al.* 1996) and in animal models (Nickel *et al.* 1990). A lot of evidence is available to support the importance of high voiding pressure, explaining the chronicity of symptoms in a certain group of men with prostatitis (Kirby *et al.* 1982, Barbalias *et al.* 1983, Hellstrom *et al.* 1987).

The immunological status of the host and the adherence capacity of the infective agents (Mårdh *et al.* 1979) play a role in the results of the treatment and also in development of chronic disease (Fowler & Mariano 1982, Doble *et al.* 1990, Nickel & Costerton 1992, Nickel & Costerton 1993, Nishimura *et al.* 1998).

And last but not least, the importance of mental stress has been underestimated and forgotten, but there is now agreement that psychic aspects must also be taken into account seriously when treating patients with prostatitis (Kretschmer 1937, Keltikangas-Järvinen *et al.* 1982, Miller 1988, Keltikangas-Järvinen *et al.* 1989, de la Rosette *et al.* 1993b, Egan & Krieger 1994, Berghuis *et al.* 1996).

2.6.2.1 Histopathological aspects of prostatitis

The true prevalence of histologically confirmed prostatitis in the absence of other prostatic disease is very difficult to determine, for three reasons: firstly, most studies of prostatitis have used tissue obtained from patients over 40 years of age by surgery, secondly, the prostate tissue is altered by hyperplasia or carcinoma processes which contribute to the development of inflammatory signs, and thirdly, the clinical definition of prostatitis is not uniform between various investigators (McNeal 1988, Bennett *et al.* 1993).

With certain reservations, the prevalence of histologically proved prostatitis is reported to be from 31% to 98% (Kohnen & Drach 1979, Melhorn 1987, Doble *et al.* 1989a, Nickel *et al.* 1999a, True *et al.* 1999), while Schatteman *et al.* (2000) found signs of inflammation in 100% of cases.

Considerable variation exists in the histological classification of chronic inflammation. Most pathologists agree with the basic definition characterizing the process of acute prostatitis: the presence of polymorphonuclear leukocytes (PMNL) and macrophages in the glandular ducts, the epithelium and/or the adjacent stroma. Stromal involvement varies, however, and increases with the density of intraluminal inflammation. Luminal infiltration by PMNL is accompanied by periglandular accumulation of lymphocytes and monocytes, and occasionally plasma cells. It has been speculated that the inflammation starts from the peripheral zone and spills over into the central periurethral zone (Maksem *et al.* 1988, McNeal 1988, Matsumoto *et al.* 1992, Bennett *et al.* 1993).

Histological findings based on prostatic tissue samples from clinically diagnosed chronic prostatitis patients show mononuclear cell infiltrates (lymphocytes, monocytes and plasma cells) in the stromal connective tissue around the acini or ducts, but it may also be that only focal inflammation is present. The infiltrates are most commonly multifocal (Gardner & Bennett 1992, Matsumoto *et al.* 1992, Bennett *et al.* 1993).

There is little or no correlation between the histological presence of chronic prostatitis and the clinical symptoms. The histological signs of chronic prostatitis also include distortion of the glandular ducts, disruption of the epithelium, atrophy and loss of the secretory activity of the epithelium, and hyperchromasia with polymorphism of the epithelial cell nuclei and cytoplasmic basophilia. These dysplastic changes can be misinterpreted as carcinoma of the prostate if the association with chronic prostatitis is not recognized, and this situation can be worsened by changes such as squamous metaplasia, which occurs frequently in the inflammatory areas of chronic prostatitis (McNeal 1988, Bennett *et al.* 1993).

A fine-needle aspiration (FNA) method was also developed for this purpose, but it is contraindicated in cases of acute symptomatic prostatitis due to the risk of sepsis, especially in patients with immunosuppression (Maksem *et al.* 1988, Matsumoto *et al.* 1992, Bennet *et al.* 1993).

The most common change observed in chronic prostatitis is glandular atrophy with stromal fibrosis, accompanied by a mild residual inflammation reaction occurring in several stages. Epithelial changes are frequent, ranging from squamous metaplasia to dysplastic changes (Maksem *et al.* 1988, McNeal 1988).

2.6.2.2 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 decisions and to ensure a good outcome. Laboratory findings have shown in practice that almost all standard localization cultures are negative and that success in culturing bacteria from EPS is complicated by the presence of inhibitory substances known to exist in prostate secretion and by a history of multiple previous courses of antibiotics (Fair & Parrish 1981, Nickel *et al.* 1998, Bjerklund Johansen *et al.* 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 (Kretschmer 1937, Meares & Stamey 1968, Domingue & Hellstrom 1998, Meares 1998). There can also sometimes be gram-positive uropathogens such as *Enterococcus* spp. and *Staphylococcus* spp. present (Bergman *et al.* 1989, Nickel & Costerton 1992, Nickel & Costerton 1993, Domingue & 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* (Poletti *et al.* 1985, Weidner *et al.* 1988, Bergman *et al.* 1989, Nickel & Costerton 1992, Krieger *et al.* 1993b, Ohkawa *et al.* 1993, Ostrazewska *et al.* 1998, Wise *et al.* 1999, Nickel 2000, Potts *et al.* 2000).

Acknowledged not to be pathogens so far are: Diptheroids, *Lactobacilli* and *Corynebacteria* spp. (Domingue & 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 (Shurbaji *et al.* 1988, Nickel & Costerton 1993, Berger *et al.* 1997, Domingue & Hellstrom 1998, Tanner *et al.* 1999, Hochreiter *et al.* 2000, Krieger *et al.* 2000c, Terai *et al.* 2000).

Last but not least, we must also mention 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 (Nickel & Costerton 1993, Staiman & Lowe 1996, Berger *et al.* 1997, Domingue & Hellstrom 1998, Nickel & McLean 1998, Choong & Whitefield 2000).

2.6.2.3 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 to the remnants of bacterial protein, and this local response is often different from the systemic one reflected in the serum findings. The amounts of immunoglobulins 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 & Mariano 1982, Wishnow *et al.* 1982, Fowler 1991, Kumon 1992, Meares 1998).

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* (Wishnow *et al.* 1982) and very occasionally certain enterococcus species, the role of staphylococci being more questionable (Fowler & Mariano 1982, Bergman *et al.* 1989).

On the other hand, Nickel and Costerton (1992, 1993) showed in cultures from prostate tissue that coagulase-negative staphylococci formed focal microcolonies that adhered to the walls of the prostatic ducts and were protected with glycocalyx-slime, and deduced that it was not the bacteria themselves that led to tissue damage but the immune-mediated inflammation (Nickel & Costerton 1992, Nickel & Costerton 1993).

Typical over-reactions 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 (Gardner & Bennett 1992). 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/PPS 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. John *et al.* (2001) have confirmed that T-lymphocytes have a role in the excretion of inflammatory mediators such as complements C3, C4 and IL-6 in the serum and ejaculate. They also found an increase in IgA in the ejaculate. The concentrations of these markers decreased with the relief of prostatitis symptoms.

2.6.2.4 Chemical aspects of prostatitis

Persson and Ronquist (1996) studied the chemical composition of expressed prostatic secretion (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) and by Klimas *et al.* (1985), showing that prostatic calculi are partly composed of the remains of ingredients coming from the urine by reflux (Kirby *et al.* 1982, Chapple *et al.* 1990, Turner *et al.* 1996).

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-reflecting factor (Sutor & Wooley 1974, Ramirez *et al.* 1980, Klimas *et al.* 1985, Söndergaard *et al.* 1987).

It cannot be judged what came first: anatomical structural changes or functional disorders (Blacklock 1974, Blacklock 1991). It may be that reflux comes first, leading to chronic inflammation, upon which local reactions and tissue oedema or the increased intracompartamental tissue pressure lead to voiding disturbances with more reflux of urine, sterile or infected (Kirby *et al.* 1982, Barbalias *et al.* 1983, Hellstrom *et al.* 1987, Chapple *et al.* 1990, Persson & Ronquist 1996, Turner *et al.* 1996, Theodorou *et al.* 1999).

2.6.2.5 Urodynamic and myalgic aspects of prostatitis

Measurement of urine flow rate should be an integral part of the evaluation of prostatitis patients, as most patients with prostatodynia have abnormal flowmetry parameters and distinct flow patterns (Ghobish 2000). Synchronous video-pressure-flow studies using a triple-lumen catheter with synchronous electromyography of the external urethral sphincter have demonstrated increased maximum urethral closure pressure in the proximal prostatic and membranous urethral segments as compared with controls (Barbalias *et al.* 1983, Barbalias 1990), and also decreased maximum and average flow rates. The findings were originally confirmed in patients with prostatodynia, but identical observations 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 sympathetically mediated spasm.

Increased pressure in the prostatic urethra causes reflux into the prostatic ducts and ejaculatory ducts accompanied by prostate tissue irritation (chemical reaction of urine component, seminal vesiculitis and even epididymitis in cases of infected urine) (Kirby *et*

al. 1982, Hellstrom *et al.* 1987, Chapple *et al.* 1990, Thind *et al.* 1992, Turner *et al.* 1996). It is 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 LUTS and recurrent symptoms of CP/CPPS, thus also exploring the indications for alpha-blocker treatment (Turner-Warwick *et al.* 1973, Barbalias *et al.* 1983, Hellstrom *et al.* 1987, de la Rosette *et al.* 1992b, Kaplan *et al.* 1994, Neal & Moon 1994, Kaplan *et al.* 1997, Barbalias *et al.* 1998).

Some patients with CP/CPPS 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 (Lilius & Valtonen 1972, Segura *et al.* 1979, Barbalias *et al.* 1983, Ricchiuti *et al.* 1999, Zermann *et al.* 1999). Patients also report pain and discomfort associated with sitting, running or other physical activities 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 (Lilius & Valtonen 1972, Segura *et al.* 1979).

2.6.2.6 *Psychological aspects of prostatitis*

As pointed out by Kretschmer in 1939, sexual neurasthenia can occur in a small but very definitive group of prostatitis patients in association with marital difficulties, melancholia, nervousness, irritability, depression and also suicidal tendencies (Kretschmer 1939). Psychological factors are considered to play an important role in the aetiology of chronic prostatitis, and as early as the late 1960s and the 1970s, a long time before prospective studies related to personality changes in prostatitis patients, professor Jack Lapides wrote, "...the management of the patient with symptoms and no objective findings involves a work-up as complete as that of the individual with recurrent infection and then a therapeutic regimen aimed toward support of the psyche with help from the psychiatrist if necessary" (Lapides 1976).

Urological patients with chronic complaints generally tend to exhibit psychiatric problems, and there is a widely held belief among urologists, that these patients are "neurotic" (Kretschmer 1937). In this view chronic prostatitis patients as well often tend to be characterized as having problems with their male sexual identity. Symptoms such as anxiety, depression, fear, sexual disturbances and feelings of insecurity in human relationships have been reported. Psychosomatic factors were found to be important aspects in connection with a "psychosomatic personality" and in the expression of psychological emotional problems as a whole (Keltikangas-Järvinen *et al.* 1981, Keltikangas-Järvinen *et al.* 1982, Keltikangas-Järvinen *et al.* 1989, de la Rosette *et al.* 1993b, Egan & Krieger 1994, Berghuis *et al.* 1996). Patients have reported that their symptoms greatly affect sexual or romantic relationships (Kretschmer 1937, Keltikangas-Järvinen *et al.* 1989, Egan & Krieger 1994, Berghuis *et al.* 1996.).

Psychological evaluation, relationship counselling 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 (Kretschmer 1937, Keltikangas-Järvinen *et al.* 1982, Keltikangas-Järvinen *et al.* 1989, Egan & Krieger 1994, Berghuis *et al.* 1996).

2.7 Diagnostic procedures of prostatitis

Evaluation of a patient with prostatitis is a complicated task, because the disease is defined only in terms of subjective symptoms and there is no objective, measurable parameter to divide the patients into diagnostic categories for clearly defined modes of treatment, in contrast to the treatment of other diseases of the prostate gland. Prostatitis means "inflammation of the prostate" and inflammation is an accompaniment to an infection, but not all inflammatory reactions can be explained by an infection. This condition has caused great confusion over the treatment of prostatitis, a situation that continues to apply today. Pain or discomfort is the most severe and frequent symptom (Alexander & Trissel 1996, Krieger *et al.* 1996b, Nickel & Sorensen 1996, Egan & Krieger 1997), followed by voiding complaints (Alexander & Trissel 1996, Meares 1998) and not forgetting the importance and role of sexual dysfunction in these patients (Kretschmer 1937, Keltikangas-Järvinen *et al.* 1989, Egan & Krieger 1994, Alexander & Trissel 1996, Berghuis *et al.* 1996).

The oldest "golden standard", is the four-glass test proposed by Meares and Stamey (1968). This essential test for narrowing down the diagnosis of prostatitis is known to almost everybody but unfortunately used only by a few (Moon 1997, Nickel *et al.* 1998, McNaughton-Collins *et al.* 2000).

2.7.1 Evaluation of prostatitis patients

Symptoms of prostatitis include pain in the region of the lower abdomen or in the perineal, scrotal, inguinal and penile area, also accompanied by voiding disturbances of varying severity and related symptoms. Temporary sexual dysfunction and mental distress can be present (Krieger 1984, Roberts *et al.* 1997, Meares 1998). The baseline information is obtained by taking the history of all the facts related to urinary tract infections (Lipsky 1989, Krieger *et al.* 1993a) and any previous history of possible sexually transmitted disease (STD) and relating this to the number of sexual contacts (Kretschmer 1937, Stamey 1973, Drach 1976, Krieger *et al.* 1993a, Worm & Petterson 1989, Foxman *et al.* 1997), although still more important than this can be sexual preference and the latest exposure (Krieger *et al.* 1993a, Alexander & Trissel 1996). The history of previous urological procedures can provide some explanations on which to base a clinical conclusion, and similar importance can be given to comorbidity factors reflecting on the host defence mechanisms (diabetes, immunosuppression, etc.) (Meares 1998) and patients with hematuria require cystoscopy and urinary tract imaging (Nickel 1998b).

Clinical examination should include a careful assessment of the patient's inguinal regions and scrotum (for hernias), penis for plaques suggestive of Peyronie's disease, which can cause pain in the penis, a careful inspection of the perineum for evidence of perirectal diseases and a digital rectal examination (DRE), transrectal ultrasound (TRUS), noting any tenderness or other signs confirming an inflammation process or excluding malignancy of the prostate gland (Meares 1998, Nickel 1998b).

2.7.2 Laboratory and related findings

Several laboratory and related investigational procedures, more or less used for diagnosing CP/CPPS are available and are explained in detail below.

2.7.2.1 Urine analysis and microbiological culture

The cornerstone of the laboratory diagnostic methods for prostatitis is careful bacteriological assessment of cultures from the lower urinary tract and prostate gland and/or seminal vesicles (Meares & Stamey 1968). A microscopic work-up using several staining methods and a proper microbiological urine culture will reveal uropathogens and also any candida species (Krieger 1984, Krieger & McGonagle 1989). A careful urine analysis will exclude or define signs of inflammation, with or without bacteriuria and/or haematuria (Krieger 1984). Patients with haematuria should also undergo cystoscopy and a radiographic examination of the upper urogenital tract by intravenous pyelography or CT (Nickel 1998b). Transitional cell carcinomas, especially diffuse bladder carcinoma or a carcinoma in situ can cause clinical symptoms similar to prostatitis (Solsona *et al.* 1996, Montie *et al.* 1997, Luzzi & Cranston 2000).

2.7.2.2 The Meares-Stamey "four-glass test" – the golden standard

In their famous article of 1968, Meares and Stamey launched a practical proposal for clinical differential diagnosis between several types of prostatitis (Meares & Stamey 1968). This method, which has never been validated, rose to the status of a "golden standard" and was for many decades the only method for ascertaining a diagnosis of prostatitis. This is scientifically and historically an affront to such names as Young *et al.* (1906), von Lackum (1928), Nickel (1930) and Kretschmer (1937), all of whom pointed out many times in their publications that the basis for the diagnosis and treatment of prostatitis lies in microscopy of the prostate secretion.

This "four-glass test" described by Meares and Stamey (1968), which is used to choose patients for therapy based on information received from urine and EPS samples, relies on finding excessive numbers of leukocytes in the EPS and/or post-prostatic

massage urine (VB3), relative to those found in the first voided urine (VB1) and mid-stream urine (VB2). Since normal individuals have some leukocytes in their EPS, a consensus value of 10 leukocytes per high-power field serves as an upper normal limit (Meares & Stamey 1968, Drach *et al.* 1978, Anderson & Weller 1979). EPS cannot be obtained from all patients, however, and the diagnosis requires excessive numbers of leukocytes in the VB3 as well. Over 4 leukocytes per high-power field in centrifuged VB1 and/or VB2 urine specimens examined microscopically under 400x magnification is highly suggestive of prostatitis, and results over 10 leukocytes per high-power field are clearly pathognomic (Meares & Stamey 1968, Drach *et al.* 1978, Anderson & Weller 1979, Wright *et al.* 1994).

The diagnostic difficulties lie in the fact that uncircumcised men have a rich flora of commensals around the preputial skin and in the distal urethra, which can lead to misinterpretation in localisation studies. The possibility of such problems was illuminated by Meares and Stamey (1968), who advised that the bacterial colony count for a VB3 and/or EPS sample should be at least 10-fold greater than those in the VB1 and VB2 samples.

Krieger *et al.* (2000a) have recently shown that VB1 and VB2 samples have given low sensitivity as indicators of urethral inflammation, but that in combination with properly performed EPS and VB3 assessments, the four-glass test can be of significance for detecting urethral and prostate inflammation. Ludwig *et al.* (2000) have also pointed out that if the EPS search fails, leukocytes in the VB3 sample are a diagnostically more valuable sign of inflammation.

Everyday life has shown that this procedure is well known but seldom used (McNaughton *et al.* 2000), and in order to make up for this lack of accuracy and to meet the clinical need, J.C. Nickel has proposed a new, quicker screening pre-massage and post-massage test for the diagnosis of prostatitis (Nickel 1997).

Lacquaniti *et al.* (2000) and Strohmaier and Bichler (2000), in recently published articles, have questioned the meaning and usefulness of the Meares-Stamey test for the diagnosis or categorization of different forms of CP/CPPS. Lacquaniti *et al.* (2000) proposed an easier way to achieve 90% sensitivity in bacteriological examinations, by using a semen test, which is more tolerable for the patients.

2.7.2.3 Nickel's pre-massage and post-massage test

The pre-massage and post-massage test (PPMT) is intended to be a simple, cost-effective and time-saving diagnostic tool for clinical use in cases of patients with an initial diagnosis of chronic prostatitis syndrome and with no clinical evidence of urethritis (no discharge from the urethra, no dysuria, no urethral irritation alone or in combination with dysuria). The patient gives a mid-stream urine sample (labelled pre-M) after careful cleansing of the glans penis with the foreskin retracted. A digital rectal examination is performed to assess the configuration and hardness of the prostate gland, and the prostate is massaged vigorously from the periphery towards the midline. The patient then

immediately gives another urine sample of up to 10 ml (labelled post-M). These two specimens are properly checked for quantitative culture and microscopy of postcentrifugal sediment.

In the interpretation of the test, leukocytosis over 10 per high-power field in the post-M specimen, or a one log (x10) increase in leukocytes compared with the pre-M result is taken as suggesting the probability of clinically defined prostatitis. Significant bacteriuria in the post-M specimen ($>10^3$), or a one log greater colony count/ml compared with the pre-M specimen, given that the pre-M is sterile, suggests a possibility of chronic bacterial prostatitis. Significant bacteriuria in both the pre-M and post-M specimens is suggestive of prostatic inflammation, but may be associated with bacterial cystitis or bacterial inflammation proceeding from the upper urinary tracts. Another test should therefore be performed for these patients after 3 days of nitrofurantoin or trimethoprim therapy and the results compared with the previous ones. The calculated sensitivity and specificity of the PPMT in a selected population were both 91%, and it is thus recommended for use by urologists at the first meeting with the prostatitis patients, and ideally by general practitioners at primary visits (Nickel 1997).

2.7.2.4 Semen functional analysis

The prostate gland secretes various substances, including prostate-specific antigen (PSA), prostatic acid phosphatase (PAP), citric acid, cholesterol, zinc, etc., and some investigators have suggested that measurement of these in whole semen or in EPS may provide a useful marker for diagnosing prostatic inflammation (Fair & Cordonnier 1978, Fair & Parrish 1981, Zaichick *et al.* 1996). Significant alterations in the secretory products of the prostate gland occur in patients with prostatitis. The pH of the prostatic fluid in normal men is slightly acidic, around 6.6–7.3 (Blacklock 1974, Fair & Parrish 1981), whereas in cases of bacterial inflammation an alkaline pH over 7.6 is detected (Fair & Cordonnier 1978, Huaijin *et al.* 1998).

Decreases in the citric acid concentration or in the specific gravity or zinc, spermine, cholesterol, PAF or enzyme (lysozyme) concentrations (Fair & Cordonnier 1978, Fair & Parrish 1981, Meares 1998) have been reported, but no significant differences in zinc concentrations in the semen were found between patients with prostatitis and controls by either Leib *et al.* (1994) or Zaichick *et al.* (1996). The prostate fluid contains a potent antibacterial factor named prostate antimicrobial factor (PAF), which is bactericidal to most pathogens causing urinary tract infection (UTI) (Fair & Parrish 1981), but there is still some controversy concerning the role and importance of zinc or PAF in the inflammatory process (Fair & Cordonnier 1978, Leib *et al.* 1994, Zaichick *et al.* 1996, Meares 1998). It is proposed that semen functional analysis (SFA) should be taken by masturbation after 3–5 days abstinence from sexual intercourse and after careful washing of the hands and genitalia (Weidner *et al.* 1991a, Vicari 2000).

A leukocyte count over 10 per high-power field and/or over 2×10^6 /ml in the semen may be regarded as pathognomic (Weidner *et al.* 1991a, Wolff 1995, Krieger *et al.* 1996a, Huaijin *et al.* 1998), or on some occasions only commensal (Aitken & Baker 1995).

The diagnostic sensitivity of the occurrence of bacteria or leukocytes in the seminal fluid relative to the Meares-Stamey test has been shown in a recently published prospective study (Lacquaniti *et al.* 2000) to be up to 90%. Krieger *et al.* (1996a) have pointed out that it is difficult or impossible to distinguish leukocytes from immature sperm without a specialized staining procedure, but patients have stated that giving seminal fluid is more tolerable than the Meares-Stamey test. Lacquaniti *et al.* (2000) also conclude that this diagnostic procedure is less expensive and more easily executed than the "golden standard" test.

2.7.2.5 PSA (F/T ratio), PAP and cytokines

Serum prostate-specific antigen (PSA) levels can be elevated in prostatitis (Pansadoro *et al.* 1996, Potts 2000), reducing the diagnostic value of PSA for excluding prostatic cancer. On the other hand, Hasui *et al.* (1994) showed a relationship between PSA and the histological stage of inflammation in the prostate tissue, attributing this to a leak phenomenon. A PSA increase has also been reported to be present in acute inflammation of the prostate gland in experimental studies (Neal *et al.* 1992, van Iersel *et al.* 1995). There is no evidence, however, that in inflammatory cases a better diagnostic accuracy for differentiating between benign or malign processes in the prostate can be achieved using the PSA free-to-total (F/T) ratio (Nadler *et al.* 1995), at least not entirely (Jung *et al.* 1998).

Okada *et al.* (2000) have pointed out that PMNLs are responsible for the acute inflammatory reaction in the prostate tissue, and that they constitute a significant reason for the increase of PSA. A different point of view is represented by the conclusion of Ponniah *et al.* (2000) that one possible aetiological factor or reason for CP/CPPS is an autoimmune inflammatory process, findings which confirm the results of Alexander *et al.* (1997).

Wadström *et al.* (1984) showed that increased levels of PAP can be found after prostatic massage, perhaps caused by mechanical damage to the prostatic ducts, and this was supported by Brawn *et al.* (1994), who studied the influence of prostatic tissue infarction on the levels of PSA and PAP. Both rose, but PSA was elevated more frequently than PAP, the reason possibly lying in the different molecular weights of PSA and PAP, which influence penetration from the prostate tissue into the blood circulation.

The last five years have yielded investigations into the basic behaviour of proinflammatory cytokines in the semen of patients with CP/CPPS. The cytokines are soluble proteins secreted by cells of the human immune system that principally regulate the inflammatory and immune responses of the host to microbes, and measuring the level of cytokines may give a more objective measure of disease severity in CP/CPPS patients (Alexander *et al.* 1998, Nadler *et al.* 2000, John *et al.* 2001). The production of cytokines IL-1ra and IL-1b, commonly IL-1 (secreted by macrophages) has an influence on the host response, on the severity and prolongation of the inflammatory reaction in tissues and on the response to tissue repair (Alexander *et al.* 1998, Nishimura *et al.* 1998).

Tumor necrosis factor (TNF- α) is synthesized by cell lines of monocytes / macrophages and induced by bacterial proteins, viruses and fungal antigens, and is of considerable importance for the process of inflammation and angiogenesis (Alexander *et al.* 1998, Nadler *et al.* 2000). The cytokines have a mediatory effect on nitric oxide production and through this an effect on endogenous vasodilatation and the response to inflammatory reactions, but the cytokines studied so far represent only a small part of the whole group of inflammation mediator molecules (Galley *et al.* 1997, Alexander *et al.* 1998, Nishimura *et al.* 1998, Nadler *et al.* 2000)

2.7.2.6 PCR of prostate tissue/seminal fluid: is this a new diagnostic tool?

The use of polymerase chain reaction (PCR) techniques, a highly sensitive molecular radio-assay method for bacterial detection, has opened up a "Pandora's box", showing that a situation shown to be sterile by conventional methods is actually not sterile at all. The prostate can harbour bacteria that are undetectable by traditional everyday approaches, and PCR will confirm the sterility of a tissue with a high level of confidence and can trace small numbers of microbial agents/particles and bacterial DNA sequences which may represent the presence of pathogens or parts of these (Wilson 1994, Riley *et al.* 1998, Keay *et al.* 1999, Tanner *et al.* 1999, Hochreiter *et al.* 2000, Krieger *et al.* 2000c).

The latest method, prostate-specific membrane antigen (PSMA) (measured by RT-PCR), is so sensitive that it can even detect prostate epithelial cells in the circulating blood, but we do not know the clinical relevance of this finding (Dumas *et al.* 1997).

2.7.3 Transrectal ultrasound examination, biopsy of the prostate gland

There are no transrectal ultrasound findings that are specific to prostatitis, but certain publications give a general characterization of ultrasonic patterns and their possible clinical implications, e.g. irregular internal echoes and overall alterations of the shape of the gland in cases of prostatitis, dilatation of the vessels and oedema due to acute inflammation (Veneziano *et al.* 1995, Ulleryd *et al.* 1999, Wasserman 1999).

Increased blood flow to the prostate capsule and parenchyma has been demonstrated in cases of CP/CPPS (Cho *et al.* 2000), while asymmetry and/or overdistension of the seminal vesicles may be a local sign of inflammation, and also cystic lesions in the region of bladder neck (Christiansen & Purvis 1990, Ludwig *et al.* 1994, Wasserman 1999).

The finding of prostatic stones is often taken as a basis for a diagnosis of prostatitis, but such calcifications are very common and are also present in men without symptoms of prostatitis (Wasserman 1999, Zackrisson *et al.* 2000). The usefulness of transrectal ultrasound (TRUS) lies in determining the volume of prostate gland, changes in the volume being related to inflammation, and in finding possible ejaculatory duct cysts and

ruling out possible hypoechoic lesions in the periphery of the gland that might lead to a suspicion of prostate cancer and also in diagnosing prostatic granulomas (Terris *et al.* 1997, Ulleryd *et al.* 1999, Wasserman 1999).

Targeted biopsies taken from suspicious areas and/or diagnostic/treatment procedures performed on the prostate (cyst, abscess drainage) are also very conveniently managed under TRUS control (Doble *et al.* 1989a, Doble *et al.* 1989b, de la Rosette *et al.* 1995, Aarnink *et al.* 1998, Ludwig *et al.* 1998, Wasserman 1999). In relation to biopsy and/or other invasive procedures performed with TRUS, one should not forget antibiotic prophylaxis to avoid any generalisation of possible inflammation of the prostate gland or haematogenous spread of bacteria from the rectum leading to generalized urosepsis and fatal case is also possible (Desmond *et al.* 1993, Aus *et al.* 1996, Gilad *et al.* 1999, Aron *et al.* 2000, Lindert *et al.* 2000).

2.7.4 Urodynamic examinations

The urodynamic investigation measures physiological changes in bladder and urethral sphincter function when the patient is experiencing his usual symptoms of disturbed micturition (Blaiwas 1984). The urinary flow rate can be measured with a uroflowmeter, and cystometry is a method for measuring the pressure-volume relationship in the bladder, but these investigations alone cannot give a definite diagnosis of disordered micturition, and synchronous methods (pressure-flow study) are needed (von Garrelts 1956).

Pelvic pain and voiding difficulties are symptoms commonly attributed to CP/CPPS, and incidental observations of intraprostatic reflux in voiding cystourethrography may have a causal relationship with increased urethral pressure in patients with CP/CPPS (Hellstrom *et al.* 1987, Theodorou *et al.* 1999). Indeed, many patients are misdiagnosed and treated empirically for CP/CPPS with useless antibiotic courses when they have in fact functional bladder outlet obstruction (BOO) defined by urodynamic examination (Kaplan *et al.* 1994, Kaplan *et al.* 1997, Liao *et al.* 1999, Theodorou *et al.* 1999). It has been stated that the most important part of the urodynamic examination in the case of CP/CPPS patients is the urethral sphincter profilometry (Liao *et al.* 1999, Theodorou *et al.* 1999), because behavioural changes in the external urethral sphincter include spasms and instability (Hellstrom *et al.* 1987, Liao *et al.* 1999).

Inflammatory signs may also be present in cases of obstruction caused by benign prostatic enlargement, and CP/CPPS patients can clinically have lower urinary tract symptoms (LUTS) (Kohnen & Drach 1979, de la Rosette *et al.* 1992b, Tammela & Kontturi 1993, Mayo *et al.* 1998, Nickel *et al.* 1999a).

2.7.5 Endoscopic examinations

There is no need for routine cystoscopy of patients with symptoms of CP/CPPS, but it must be born in mind that suprapubic pain with voiding complaints may be a sign of interstitial cystitis or in situ carcinoma of the bladder, and biopsies taken from several parts of the bladder must be considered in suspicious cases (Miller *et al.* 1995, Schellhammer *et al.* 1995, Solsona *et al.* 1996, Montie *et al.* 1997, Berger *et al.* 1998, Luzzi & Cranston 2000).

2.8 Other pathology and prostatitis

2.8.1 Interstitial cystitis and prostatitis

Miller *et al.* (1995) studied 20 men with prostatodynia/non-bacterial prostatitis and observed petechial haemorrhages on the bladder wall after hydrodistension under general anaesthesia. Signs of "glomerulations" on the wall of the bladder after hydrodistension are thought to be diagnostic for interstitial cystitis (IC) (Elbadawi 1997). Miller *et al.* (1995) recommended that a diagnosis of interstitial cystitis should be considered for patients with a clinical diagnosis of non-bacterial prostatitis/prostatodynia if biopsies from the bladder mucosae showed increased numbers of mast cells. The role of mast cells in IC is unclear. In a recently published article, Berger *et al.* (1998) demonstrated bladder petechiae in 58% prostatitis cases, a much higher figure than expected.

Excessive numbers of mast cells have been demonstrated in TURP chips, and the similarities between interstitial cystitis in women and prostatitis in men have led investigators to conclude that many cases of prostatitis may be misdiagnosed as interstitial cystitis (Miller *et al.* 1995, Berger *et al.* 1998). On the other hand, it is also possible that some men with refractory non-bacterial prostatitis/prostatodynia indeed have interstitial cystitis (Berger *et al.* 1998, Meares 1998).

2.8.2 Bladder carcinoma in situ and prostatitis

The exclusion criteria for CP/CPPS include the possibility of bladder cancer, and especially carcinoma in situ, with well-recognized irritative symptoms of bladder (frequency, urgency and dysuria). Involvement of the urothelium of the prostatic urethra can mimic the symptoms of chronic prostatitis, necessitating cystoscopy with proper biopsies (Schellhammer *et al.* 1995, Solsona *et al.* 1996, Montie *et al.* 1997, Luzzi & Cranston 2000).

2.8.3 Prostate cancer and prostatitis

Some speculations have been put forward concerning the possibility of prostatitis as a risk factor for prostate cancer. Serum PSA is the main diagnostic laboratory sign of a possible malignant process in the prostate gland (Polascik *et al.* 1999), but as an increase in PSA has been demonstrated in some cases of prostatitis, benign prostate hyperplasia and, of course, prostate cancer, they cannot be used as an absolute laboratory method for differentiating between these three main pathologies of the prostate gland (Nadler *et al.* 1995, Van Iersel *et al.* 1995, Pansadoro *et al.* 1996, Speights & Brawn 1996, Irani *et al.* 1997, Jung *et al.* 1998, Okada *et al.* 2000).

Prostatitis affects the more peripheral parts of the prostate (Blacklock 1974, Gardner and Bennet 1992, Bennet *et al.* 1993), and prostate cancer is also situated in the same area in most cases (Noldus & Stamey 1996). This problem was touched on by Hennenfent (1997), because there are many clinical cases suggesting a connection between prostatitis and prostate cancer, but what is missing is a population-based longitudinal survey concerning the possible higher prevalence of prostate cancer in prostatitis patients. Recently published PCR-based studies have raised speculations concerning the possible risk of prostate cancer developing out of a chronic inflammatory process (Riley *et al.* 1998, Keay *et al.* 1999, Hochreiter *et al.* 2000, Krieger *et al.* 2000c).

2.8.4 Benign prostatic hyperplasia and prostatitis

No prospective clinical studies are available to show any role of benign prostatic hyperplasia as an aetiological factor for the development of inflammation and prostatitis. The clinical knowledge available from the few published papers is based on retrospective studies and on histological findings based on prostate biopsies or surgically removed tissue (Kohnen & Drach 1974, Nickel *et al.* 1999a).

The true prevalence of histological prostatitis in the absence of other prostatic disease is very difficult to determine, for three reasons: firstly, most studies of prostatitis have used tissue from patients over 40 years old and the material has been obtained by surgery, secondly, the prostate tissue is altered by hyperplasia or the carcinoma process, which can contribute to the development of inflammatory signs in it, and thirdly, the clinical definition of prostatitis is not uniform between investigators (Gardner & Bennett 1992, Bennett *et al.* 1993). The patients referred to had never been validated by clinical means to confirm or exclude the diagnosis of prostatitis, but they had always been investigated primarily by clinical means to find obstructive symptoms or to rule out possible malignancy in the prostate gland. With certain reservations, the prevalence of histologically confirmed prostatitis has been reported to be from 31% to 98% (Kohnen & Drach 1979, Melhorn 1987, Doble *et al.* 1989a, Nickel *et al.* 1999a) and even up to 100% (Schatteman *et al.* 2000).

Prostatic inflammation may exist in hyperplastic tissue of the prostate gland, and vice versa, and patients with obvious clinical symptoms of prostatitis and pain may have also signs of LUTS with or without BOO, as reported with frequencies from 11% (Mayo *et al.* 1998) to 54% (Kaplan *et al.* 1997), but the clinical relation between these two benign histological findings still has not been proved in a prospective study (Nickel *et al.* 1999a).

3 Aims of the study

The aims of the present study were:

1. to survey the lifetime occurrence and incidence of prostatitis in a randomly chosen sample of Finnish men aged 20–59 years and to define the epidemiological status of the disease and to ascertain possible causes influencing the recurrence of prostatitis symptoms (I)
2. to assess possible fears related to prostatitis symptoms and the effects of prostatitis symptoms on the sexual life of the patient and the influence of prostatitis symptoms on the behaviour and mental well-being of the patient (II)
3. to assess if it is possible to measure intraprostatic tissue pressure (III)
4. to develop a clinical diagnostic method for prostatic tissue pressure measurement and to validate the method for clinical use (III–IV) and to compare prostatic tissue pressures between patients in chronic prostatitis/chronic pelvic pain syndrome groups IIIA and IIIB and controls (V)

4 Materials and methods

The present survey and experimental case-control studies were carried out at the Division of Surgery, Oulainen District Hospital, at the Division of Surgery, Seinäjoki Central Hospital and the Division of Urology, Department of Surgery, Oulu University Hospital, during the years 1994–2000. More detailed descriptions of the materials and methods are given in the original papers (I–V).

4.1 Population-based cross-sectional epidemiological survey (I, II)

The planning of the study was started in 1995, when a multiple-choice questionnaire was designed for use in a population-based cross-sectional survey. This comprised 102 questions and was divided into two parts: personal data, including age, marital status, education, profession, job description and outdoor activities, and information on the individual's urological history, current or past status of prostatitis symptoms and procedures carried out to diagnose and treat prostatitis.

There were 20 questions aimed specifically at finding out the extent and severity of the psycho-mental disturbances related to prostatitis symptoms. The questions were not meant to be a psychiatric investigation aimed at revealing psychic abnormalities, but we merely wanted self-assessments of the personality of males with prostatitis symptoms. Also of importance were questions related to marital life and the quality of life in general and relationship difficulties of all kinds, ranging as far as possible suicidal thinking. Questions were also asked about possible fears (prostate cancer and/or sexually transmitted disease etc.).

The questions were designed with the help of a psychologist, and an epidemiologist was also consulted. The questionnaire was constructed with consideration for local social, family, religious and community customs, and taking care to avoid causing offence or distress to the respondents.

Before mailing, a repeated answer pilot validation of the questionnaire was performed at Oulainen District Hospital (among 15 healthy men without any urological history)

giving internal consistencies of 0.86 and 0.84. The research set-up and questionnaire were approved by the Ethical Committee of Oulu University.

For the survey, an age-stratified random sample of 2500 eligible men was chosen from the National Population Register in March 1996, representing male residents of the two northernmost provinces of Finland (Oulu and Lapland) aged 20–59 years. These made up the population base for the cross-sectional study. The area has about 732 000 inhabitants, who represent well the average demographic composition of the general Finnish population.

Appropriate sample sizes were calculated for the various age strata separately (20–29, 30–39, 40–49 and 50–59 years) based on the estimated disease frequencies, a random error of 1.7% and a probable refusal rate of about 20%. The questionnaires were mailed between June 1996 and October 1997. Three repeat questionnaires were sent to those not replying. All the informants were white, and the group was genetically homogenous.

The questionnaires were double-entered to check the data before the final analysis and the data were available for analysis after October 1998. The data are described in terms of absolute numbers, proportions, odds ratios (OD) and their 95% confidence intervals (CI). The Chi-square test was used for statistical analysis. When studying the relationship between exposure and outcome, adjustment was made for age by means of logistic regression analysis.

The lifetime prevalence (current or previous possession of prostatitis symptoms) and incidence densities per 10 000 person years were calculated for the sample as a whole and stratified by age. In addition to these variables, period prevalence was chosen in order to show better the full burden arising from this recurrent complaint. As the sample was stratified for age, the lifetime prevalence in the overall population was weighted using the normal age distribution of the population.

4.2 Technique of prostatic tissue pressure measurement (PTPM) (III–V)

Before the prostatic tissue pressure measurements PSA was taken and DRE performed to exclude possible malignancy, with sextant biopsies taken in suspicious cases (PSA over 3.0). The mean prostatic volumes were measured by transrectal ultrasonography (Aloka SSD, 1700, Japan, in paper III and Medical Ultrasound Scanner, Type 2001-Leopold class I, Brüell and Kjaer Medical, Denmark with multiplane probe Type 8551/7MHz in papers IV-V).

Prostatic tissue pressure was measured with the Stryker® intracompartmental pressure monitor system (295-1 pressure monitor, 295-2 Quick Pressure Monitor Set: Bio Tec Instruments, Model DPM-1, Vinooski, Vermont, USA). The side-holed needle for the measurement of pressure was from the standard package set and was of size 18G and 6.0 cm (2.5") long.

The patient was in the lithotomy position and spinal anaesthesia was used. The perineal area was washed and prepared. The puncture needle was guided under TRUS control into the apex of the prostate, and 1 ml of sterile physiological 0.9% saline was

injected into the tissue. To eliminate the influence of the instant increase in pressure, 10 seconds were allowed to elapse before reading the results (in mmHg).

The pressure was measured in three areas for paper III: the perineal subcutaneous tissue, the paraprostatic tissue and the apex of the prostate, but only at the apex for papers IV–V (from both lobes in paper V). The tissue pressure was recorded after 10 seconds for paper III and after 10 and 60 seconds for papers IV–V, in addition to which the baseline pressure and readings 120 seconds after injection were recorded in paper V.

The same prophylactic antibiotic medication (Ciprofloxacin 500mg) was used before PTPM in all three series (papers III–V), and no infections or complications were observed after the procedure.

Statistical analyses included use of the variance test and Student's t-test with Bonferroni's corrections. The results were presented in numerical and graphical form, p values <0.05 being regarded as significant.

Contraindications for PTPM were the same as for fine-needle biopsy of the prostate gland and included bleeding disorders and acute infections of the urinary tract.

4.2.1 Paper III: Increased intraprostatic pressure in patients with chronic prostatitis

The diagnosis of chronic non-bacterial prostatitis was primarily made on the basis of a typical history, a physical examination and laboratory tests. Nickel's pre-massage and post-massage test was used for microbiological evaluation of the patients (Nickel 1997). More than 10 leukocytes per high-power field in the VB2 and EPS were required for a diagnosis. Altogether 43 patients were included in this series and were divided into the three groups.

Group A: 24 patients with chronic non-bacterial prostatitis, more than 10 leukocytes per high-power field in the VB2 and EPS and benign prostatic hyperplasia. Mean age 65.5 years, range 42–81 years, mean prostate volume 42.4 ml, range 34.0–50.9 ml, mean PSA 3.6, range 1.4–6.0.

Group B: 10 patients with benign prostatic hyperplasia without any symptoms or signs of prostatitis. Mean age 71.5 years, range 63–88 years, mean prostate volume 49.4 ml, range 33.2–65.6 ml, mean PSA 4.4, range 0.4–9.4.

Group C: 9 patients, admitted for haemorrhoid surgery without any urological history and without voiding complaints served as controls. Mean age 45.5 years, range 35–55 years, mean prostate volume 27.9 ml, range 23.4–32.4 ml, mean PSA 2.7, range 1.8–3.2.

All the patients in groups A and B underwent TURP. 100% of the chips in the group A patients showed oedema with signs of chronic inflammation and benign hyperplasia, but no malignancy was found. The histology in group B showed only benign hyperplasia without signs of inflammation or malignancy.

4.2.2 Paper IV: Prostatic tissue pressure measurement as a possible diagnostic procedure in patients with chronic non-bacterial prostatitis / chronic pelvic pain syndrome

This paper considers 54 patients and controls recruited for prostate tissue pressure measurement. They were all new patients (and controls) and had not been included in paper III.

The criteria for inclusion were very much the same as in paper III, except that all cases with voiding disturbances and/or prostate volumes over 40 ml by TRUS were excluded.

Group A (cases): 42 patients (53 measurements) with chronic non-bacterial prostatitis (IIIA and IIIB), mean age 52 years, range 33–79 years, mean prostate volume 22.3 ml, range 12.0–38.0 ml, mean PSA 2.1, range 0.6–7.0.

Group B (controls): 12 patients (15 measurements), mean age 45 years, range 35–55 years, mean prostate volume 24.9 ml, range 17.0–35.0 ml, mean PSA 2.2, range 0.3–3.2.

The PTPM procedures were performed by three urologists at three hospitals (Oulu University Hospital, Oulainen District Hospital and Seinäjoki Central Hospital).

4.2.3 Paper V: Chronic prostatitis/chronic pelvic pain syndrome can be characterized by prostate tissue pressure measurements

Again 60 new males were recruited and divided into two groups: 48 cases and 12 controls.

Group A (cases): 48 patients (96 measurements) with chronic non-bacterial prostatitis (IIIA and IIIB), mean age 55 years, range 42–81, mean prostate volume 22 ml, range 10–38 ml.

Group B (controls): 12 patients (24 measurements), mean age 44 years, range 30–65 years, mean prostate volume 21ml, range 16–38 ml.

The inclusion criteria for the patients were the same as in paper IV. A new aspect in this paper was that all the patients filled in the new NIH-CPSI questionnaire for measuring the severity of clinical symptoms. The sum score of this questionnaire was divided by the FINN IC-PPS work-group (Eskola and Tirkkonen 2001) into 4 categories: 0–10 points (category 0: such mild symptoms that patients may or may not have prostatitis), 11–20 points (category I: mild symptoms of prostatitis), 21–30 points (category II: moderate symptoms of prostatitis), 31–43 points (category III: severe symptoms of prostatitis). The duration of prostatitis symptoms was recorded and divided into 4 groups: 0–4, 5–9, 10–14 and more than 15 years. Chronic non-bacterial prostatitis was assessed in terms of the NIH classification (Krieger *et al.* 1999, Litwin *et al.* 1999), placing 18 patients (37.5%) in clinical category IIIA (>10 leukocytes per high-power field after PPMT by the method of Nickel 1997) and 30 patients (62.5%) in category IIIB (< 10 leukocytes per high-power field after PPMT). The PTPM was measured here from both apical prostate lobes, the procedure being started from the left and continued to the right.

The measurements were performed by three urologists at the same three hospitals as in paper IV. An extra semen analysis (microscopy and microbiological culture) was used to check the results of PPMT in controversial cases.

5 Results

A summary of the most important results are presented below.

5.1 Population-based cross-sectional epidemiological survey (papers I–II)

Data on a total of 1832 men who returned the questionnaire were available for analysis, giving a response rate of 75.3%. The overall lifetime prevalence of prostatitis in the sample was 14.2%. The risk of having had prostatitis at some time was higher in the older age groups, so that the men aged 50–59 years had a threefold greater risk than those aged 20–39 years. The youngest group of men (20–29 years, combined with the age group 30–39 years) had a 1.6% prevalence of prostatitis (95%CI 0.2–6.8, n=127), a significantly lower result than in any other age stratum ($p < 0.001$).

The incidence density of prostatitis for all men aged 20–59 years was 37.8 / 10 000 person years, being 6.0 in the youngest age group (20–29 years) and 43.2 in the oldest (50–59 years). 2.3% of the men aged 20–39 years, 4% of those aged 40–49 years and 5.5% of those aged 50–59 years had had prostatitis symptoms during the year in question (period prevalence) (average for all, 4%).

43% of the men (95% CI 32.5–53.7) reported that they had had prostatitis once in their lifetime, 23% (95% CI 14.9–39.1) twice, 14% (95% CI 7.8–23.2) three times and 20% (95% CI 7.0–21.9) four times or more. 27% of the men reported having had such symptoms at least once a year, while 16% had had them persistently throughout the year.

63% of the men had their worst symptoms of prostatitis in the wintertime (November–March), compared with 3% in the summertime ($p < 0.001$). 53% of the men considered the cold climate to be the main reason for their recurrent prostatitis symptoms.

The first diagnosis of prostatitis had most often been made by a GP (in 56% of cases). Hospital specialists/urologists had reached this diagnosis in 27% of cases and others (nurses, relatives, friends, etc.) had suggested the possibility of prostatitis in 17% of cases, after which it had later been confirmed by a GP or urologist.

33% of the respondents were satisfied with the information on prostatitis that they had received from their GP and/or urologist. Only one in six (16%) accepted the treatment modalities and follow-up programme proposed by their doctor, while 82% reported partially following the doctor's orders and 2% claimed never to have done so. In 65% cases the patient had asked for a second opinion. 58% of the respondents reported that regular check-ups by health care specialists (by a GP, or preferably a urologist) would be highly appropriate.

Marital status had an influence on the risk of prostatitis, in that divorced, cohabiting and single men seemed to have a lower risk than married men, but the difference was only slightly statistically significant ($p < 0.05$) after adjustment for age. Widowers had the highest risk of all, but as there were few such cases, this may merely reflect random variation.

Neither basic education nor profession showed any clear correlation with the occurrence of prostatitis, except that 36% of retired men and recipients of a pension had had prostatitis symptoms compared with 20% of the businessmen ($p < 0.001$). This difference disappeared after age adjustment, however.

48% of respondents were able to name at least one male relative with similar symptoms of prostatitis, and the difference compared with those without prostatitis (15%) was statistically significant ($p < 0.001$).

232 men with prostatitis symptoms and 1109 without such symptoms gave a subjective self-assessment of their basic personality characteristics, and analysis of the data showed that the former were more often busy, worried and meticulous than the latter.

17% of the men with prostatitis ($p < 0.001$ vs. the healthy respondents) reported a fear of undetected prostate cancer, 2.2% of possible STD ($p = 0.02$) and 3.2% some degree of suicidal thinking ($p < 0.001$).

17% of the men with prostatitis symptoms ($p < 0.001$ vs. the healthy respondents) reported some behavioural difficulties in their relationship with their wife and other relatives, and 3.5% were convinced that their illness had been a reason for their divorce. 43% reported erectile dysfunction and 24% reported a decrease in libido.

58% of the men with prostatitis preferred to be alone in a public toilet during voiding ($p < 0.001$).

The respondent's economic situation and well-being did not have any influence on the possession of current or previous prostatitis symptoms.

5.2 Summary of the results of the PTPM examinations (papers III–V)

All three papers show clearly that patients with chronic prostatitis had significantly higher tissue pressures than the controls or patients with BPE. In paper III the prostatitis patients also had prostatic hyperplasia, but patients with BPE and /or BOO were excluded from papers IV-V. Although different measurement time-points were used in the three papers, the pressure readings were made 10 seconds after injection in all cases. The results are compiled for illustrative purposes in Table 3.

In all three series the mean intraprostatic tissue pressures were significantly higher in the prostatitis patients ($p < 0.05$) than in the controls. Based on the results of the pre-massage and post-massage tests, the patients discussed in paper V were divided to the subgroups IIIA and IIIB, whereupon it was realized that the intraprostatic tissue pressures at all the measurement points (baseline, 10 sec, 60 sec and 120 sec) were higher in the patients with IIIA than in those with IIIB ($p < 0.01$). The volume of the prostate (papers IV-V), whether 20–40 ml or below 20 ml, did not have any influence on the results.

The new scoring for the NIH-CPSI questionnaire on subjective symptoms, as used in paper V, gave a mean sum of scores of 19.7, range 17.2–22.2, in the case group and 5.8, range 3.0–8.7 in the controls, the difference being statistically highly significant ($p < 0.001$). The mean pain score was 9.9, range 8.5–11.2, in the case group and 0, range 0–0.3, in the controls, the difference again being statistically significant ($p < 0.001$). The mean score for voiding disturbances was 3.3, range 2.4–4.3, in the case group and 0.3, range 0–0.6, in the controls, a further statistically significant difference ($p < 0.01$). The mean score on quality of life was 6.5, range 5.7–7.3 in the case group and 5.5, range 2.8–8.2, in the controls, the difference not being significant ($p > 0.05$). When the duration of prostatitis symptoms was divided into four categories in paper V (<5 years, 5–9 years, 10–14 years and > 15 years), 25% of the patients fell into category I, 16.7% into category II, 31.3% into category III and 27% into category IV.

Table 3. Prostatic tissue pressure 10 seconds after injection (summary of PTPM of patients in papers III–V).

Study No.	N patient	n event	Pressure mean (mmHg)	SD	95% CI	min	max
III A(CP+BPH)	24	24	85	25	75–96	36	132
B(BPH)	10	10	46	15	35–56	20	69
C (Contr)	9	9	53	15	41–65	40	78
P < 0.001 A vs C and B							
IV A (CP)	42	53	90	21	84–95	20	149
B(contr)	12	15	45	18	35–54	13	78
P < 0.001 A vs B							
V A (CP) L	48	48	71	24	64–78	24	114
B(contr)L	12	12	36	16	26–46	13	64
P < 0.001 A vs B							
V A (CP) R	48	48	79	31	70–88	19	153
B(contr)R	12	12	44	16	34–54	22	67
P < 0.001 A vs B							
Total							
V A (CP)	48	96					
B(contr)	12	24					

P < 0.05 A (right) vs. B (right), A (left) vs. B (left)

P > 0.05 A (left side vs. right side) and B (left side vs. right side)

6 Discussion

6.1 Epidemiology of prostatitis (I, II)

6.1.1 Epidemiology of prostatitis in Finnish men: a population-based cross-sectional survey (I)

The present population-based cross-sectional epidemiological survey of prostatitis in men aged 20–59 years in 1996–1997 gave an overall lifetime prevalence of 14.2% (261 with prostatitis out of 1832 respondents), and seems to be the first survey of the occurrence of prostatitis in an unselected, randomly chosen male population.

Earlier published studies have mainly derived data from questionnaire results combined with retrospective reviews of physicians' charts, giving prevalences from 4% to 11% (Moon *et al.* 1997, McNaughton-Collins *et al.* 1998b, Roberts *et al.* 1998, Nickel *et al.* 2001), or based on data concerning urological outpatient visits, giving estimates between 19% and 25% (Roberts *et al.* 1997, Pavone *et al.* 2000) or even up to 35% (de la Rosette *et al.* 1992a). These major differences between the figures have been explained in terms of study design, the ages of the patients and the indeterminate definition of prostatitis. Such reports must therefore be regarded as indicating the prevalence of prostatitis in particular series of patients seen by physicians and do not reflect its prevalence in the general population (Nickel *et al.* 2001).

The survey performed by Alexander and Trissel (1996) has also been regarded as a population-based one, although it is impossible give the prevalence of prostatitis, because the respondents were all prostatitis patients. The population was also highly selected, since it included only men having access to the Internet.

A recently published survey by Nickel *et al.* (2001) is similar in its basic setting to the present one and arrives at a prevalence of 9.7%. It must be mentioned in connection with this result, however, that their response rate was only 29%, which leaves behind a large measure of uncertainty and missing information. Also, the older respondents, those over

60 years (age range 20–74 years), may have been greatly influenced by possible BPE or prostate cancer (Bennett *et al.* 1993). Men over 60 years were excluded from the present series.

The explanatory power of the present findings relies on the high response rate (75%) and the demographically balanced distribution of the respondents (socio-economic background) over the whole area surveyed (rural and suburban aspects equally represented) and also on the number of preliminary age groups counted, to minimize the influence of sample size on the results.

The prevalence of prostatitis in northern Finland may in reality be even higher, as there were 265 men (14.5% of the 1832), who were uncertain about their symptoms. If it had been possible to interview this uncertain group personally after the survey, the prevalence might have been even higher.

27% of the men with prostatitis symptoms in the present randomly chosen population in northern Finland had prostatitis symptoms repeatedly at least once a year, which is also highly comparable with the results of up to 35% given by de la Rosette *et al.* (1992a).

Moreover, every population includes "silent" sufferers, who do not visit a doctor and will be missed if the survey is based only on health care registers or notes (McNaughton-Collins *et al.* 1998a, Roberts *et al.* 1998). It must be remembered, however, that the present survey also included men who had had only one prostatitis attack, whereas all the other published reports deal with cases of chronic prostatitis. The definition and diagnosis of prostatitis has not been uniform, however, and it is difficult to distinguish by questioning between its acute and chronic forms.

One explanation for the relatively high prevalence of prostatitis in the present survey could be the cold climate in northern Finland. The possible influence of climatic factors has not been extensively discussed, a special section of questions in the present survey was devoted to collecting data especially on this topic. Clear evidence of a seasonal influence on the initiation and worsening of symptoms of prostatitis was obtained, in that 63% of the men reported having their most severe symptoms in wintertime (November–March) and 53% considered that the cold climate was the main reason for their illness. It must be remembered, however, that the summer is short in Finland, people are on vacation and health care centres and hospitals are partially closed, all factors causing a decrease in the seeking of medical help and in its availability during the summertime.

Although it is a common belief that prostatitis is a disease of young males, the present results showed that the oldest group of men had prostatitis symptoms most often, and are in accordance with those of Roberts *et al.* (1997) and McNaughton-Collins *et al.* (1998b), whereas Nickel *et al.* (2001) found a slightly higher prevalence of prostatitis in the age group below 50 years than among men over 50 (11.5% vs 8.5%). There are studies supporting the latter finding, but these were performed on younger, selected populations, e.g. military personnel, (Drabick *et al.* 1997, Moon *et al.* 1997) and the results cannot be taken as a basis for general comparisons.

The explanation for the over-representation of prostatitis in older men may be the co-existence of BPE, as it is known that increased detrusor pressure is needed to empty the bladder in obstructive voiding, which can predispose the subject to a reflux of urine into the prostate gland (Kirby *et al.* 1982). Anyway, older men also have a longer time to develop the disease than their younger counterparts. Histopathological evidence of

prostatitis has been confirmed in up to 98% of prostatitis patients (Kohnen & Drach 1979, Doble *et al.* 1989b, Nickel *et al.* 1999a, True *et al.* 1999), and Schatteman *et al.* (2001) have reported figures of up to 100%.

Divorced and single men were found here to have a lower risk of prostatitis than their married counterparts, which is difficult to explain, but the difference could be due to married men having a higher exposure to bacterial vaginosis in their wives (Stamey 1973, Drach 1976, Worm & Peterson 1987, Berger *et al.* 1989). On the other hand, single and divorced men may have a higher frequency of random intercourse and numerous sexual partners, with a possible increased risk of sexually transmitted disease (Worm & Petersen 1989), or else they can experience only sexual excitement (Kretschmer 1937) without physiological expulsion of semen and release of intraductal pressure.

One interesting finding in the survey showed that 48% of men with prostatitis symptoms in Finland have at least one male relative with the same symptoms, while Alexander and Trissel (1996), in their data on 161 men with prostatitis, reported that about 12% had relatives with similar symptoms of prostatitis. This can be explained by the possession of similar hobbies, jobs and outdoor activities (mainly hunting in autumn and fishing around the year), along with the exposure to the influence of the cold northern climate.

6.1.2 Fears, sexual disturbances and personality features of men with prostatitis (II)

The special fears and personality features of prostatitis patients have not been studied extensively. Men with prostatitis have considerable psychic stress, and some degree of psychic difficulty (anxiety, depression, affect lability, weak masculine identity) has been discovered earlier in 80% of patients with chronic prostatitis, while signs of severe psychic disturbance have been reported in 20 to 50% of cases (Keltikangas-Järvinen *et al.* 1981, Keltikangas-Järvinen *et al.* 1982, Keltikangas-Järvinen *et al.* 1989, de la Rosette *et al.* 1992a, de la Rosette *et al.* 1993b, Berghuis *et al.* 1996).

Young *et al.* (1906) already mentioned their patients' concern over the possibility of undetected prostate cancer, and 17% of the present men reported a constant fear of prostate cancer despite proper investigations performed to exclude this possibility. McNaughton-Collins *et al.* (1998a) also reported that 22% of men were worried about their genito-urinary symptoms, which might be due to prostate cancer.

Similarly, a fear of untreated sexually transmitted disease was reported by Kretschmer (1937). This seemed not to be a problem in the present survey, however, as only 2.2% of the respondents reported such fear.

Chronic pain syndromes, including chronic prostatitis can cause psychological and physiological disability, involving depression, anxiety, sexual disorders (decreased libido and impotence) and difficulties in personal or social relationships (Kretschmer 1937, Keltikangas-Järvinen *et al.* 1981, Berghuis *et al.* 1996).

Sexual disturbances can place a great burden on human behaviour. Young *et al.* (1906) pointed out that erectile disturbances were present in 11% of cases and libido problems in 9%, and they pointed especially to premature ejaculation or sexual hypersensitivity in 20% of cases related to prostatitis. Kretschmer (1937) reported a decrease in libido in 16% of cases and total loss or decreased potency in 8% and 14%, respectively.

As reported by Keltikangas-Järvinen *et al.* (1981), sexual disturbances are common in men with chronic prostatitis, so that 52% of their prostatitis patients interviewed by a psychologist reported suffering from periodic or total impotence or decreased libido. Berghuis *et al.* (1996) reported that chronic prostatitis reduced the frequency of sexual contacts in 85% of cases, interfered with or ended ongoing sexual relationships in 67% and prevented or inhibited establishing new sexual relationships in 43%.

Alexander and Trissel (1996) nevertheless reported the prevalence of sexual disturbances to be only 6.6% (erectile dysfunctions and premature ejaculation taken together), whereas they did not ask about libido problems. In the present series, 43% of the respondents had erectile dysfunction and 24% decreased libido, which is consistent with the earlier findings of Keltikangas-Järvinen *et al.* (1981), while Pavone-Macaluso *et al.* (1991) reported reduced sexuality in 32% of cases without any further specification.

Prostatitis symptoms are mostly recurrent, causing considerable psychic stress. All this can reflect on the behaviour of patients in the long run. The importance of psychic stress, related to the chronic pain caused by prostatitis, was already mentioned by Young *et al.* (1906) and later confirmed by Kretschmer (1937). Chronic pain complaints and voiding dysfunctions were accompanied by neurasthenia and sexual disturbances, developing a burden on the social well-being and marital relationships of patients (Kretschmer 1937). Unrecognized chronic prostatitis with sexual disturbances can be a reason for suicide. The retrospective critical analysis of 1000 cases presented by Kretschmer (1937) nevertheless contained only one case of suicide after severe melancholy (0.1%). In the present survey 3.2% of the patients had some tendency for suicidal thinking, while Alexander and Trissel (1996) reported such behaviour in 5% of cases.

The personality features of men with prostatitis have been tested in a few selected contexts, and at least four pathologies have been found, i.e. psychosomatic personality, alexithymic personality, borderline personality and narcissistic personality (Keltikangas-Järvinen *et al.* 1982). De la Rosette *et al.* (1993a) suggest that it is difficult to arrive at the conclusion that there are personality features typical of men with chronic prostatitis symptoms. The personality features of prostatitis patients have not been compared earlier with those of symptomless men using a self-assessment approach, and the present results based on information given by the respondents in an unselected population-based survey rather than in a specific psychological test showed men suffering from prostatitis to be 2 to 4 times more busy, nervous and meticulous than those without this disorder. A self-administered questionnaire filled in at home may give more accurate and truthful results in this group of men, as it is easier to elicit answers concerning depression, anxiety or other mental symptoms at home, where the respondents can read and think about the questions in privacy (Rhodes *et al.* 1995, Roberts *et al.* 1996).

Keltikangas-Järvinen *et al.* (1989) showed that prostatitis patients become less cooperative with time and that their illness behaviour may be problematic, so that intensive psychic support is recommended for these men. Sometimes psychiatrists or psychologists are also consulted by urologists who feel that hidden psychological factors

may play a role in the symptomatology of prostatitis patients for whom treatment has been unsuccessful (Kretschmer 1937, Keltikangas-Järvinen *et al.* 1981, Keltikangas-Järvinen *et al.* 1989, Egan & Krieger 1994).

Chronic psychic stress may cause organic changes in certain biological systems, and these may in turn influence the individual's emotional-psychological set-up (Keltikangas-Järvinen *et al.* 1981, Addison 1984, Keltikangas-Järvinen *et al.* 1989, Berghuis *et al.* 1996, Wenniger *et al.* 1996). A new and unexpected finding of the present study never before discussed in connection with prostatitis symptoms was the need to be alone in a public urinal, a symptom generally connected with functional bladder neck dysfunction (Turner-Warwick *et al.* 1973, Barbalias *et al.* 1983, Hellstrom *et al.* 1987).

Whatever lies behind the fears of prostatitis symptoms, 69.2% of the present men wanted to have regular medical check-ups, compared with 60% of the cases reported by Nickel *et al.* (2001). Educational background and social well-being did not correlate with the degree to which the patients suffered from their prostatitis symptoms. This finding was also confirmed by Nickel *et al.* (2001).

6.2 The PTPM procedure and its clinical implications (III–V)

Tissue pressure measurement was used here for the first time to monitor the interstitial pressure of the prostate. It was postulated that pain, the leading symptom of patients with prostatitis, is caused by increased tissue pressure. In all three series, prostatic tissue pressures were significantly higher in the patients with prostatitis symptoms than in the controls.

This increased pressure may be due to local oedema in the prostate tissue, as the prostate is situated inside a compartmental system, surrounded by Denonvillier's fascia, the endopelvic fascia and the anterior surface of the surgical capsule with puboprostatic ligaments (McNeal 1972, Blacklock 1974). The stroma of the prostate is rich in blood vessels, smooth muscle and sympathetic nerve fibres connected to baroreceptors and pain receptors (Dixon *et al.* 1999).

Similar findings of pathological processes associated with increased tissue pressure and pain are available in other parts and conditions of the human body, such as anterior tibial syndrome (Whitesides *et al.* 1975, Clayton *et al.* 1977, Mabee & Bostwick 1993, Witschger & Wegmüller 1994) and chronic pancreatitis (Ebbehøj *et al.* 1984, Ebbehøj *et al.* 1986). The compartmental syndrome represents a well-documented medical phenomenon, but it requires one obligatory physiological factor, namely increased tissue pressure. Despite the different aetiological backgrounds, the main symptom in all cases is pain, through local tissue damage, inflammation and oedema (Whitesides *et al.* 1975, Clayton *et al.* 1977, Ebbehøj *et al.* 1984, Ebbehøj *et al.* 1986, Mabee & Bostwick 1993, Witschger & Wegmüller 1994, Egan & Krieger 1997, Jaroma 2000).

The reason for pain, the increased tissue pressure, can be evaluated by measuring the tissue pressure intracompartmentally, and there is consensus that if the interstitial tissue pressure reaches 40 mmHg some functional changes can be found and if it rises to 50–60

mmHg or 10–30 mmHg below the diastolic blood pressure and is present constantly over 6–12 hours, tissue damage is unavoidable (Whitesides *et al.* 1975, Gelberman *et al.* 1983, Ebbelhøj *et al.* 1984, Ebbelhøj *et al.* 1986, Witschger & Wegmüller 1994).

The present results showed that it is possible to measure intraprostatic tissue pressure with the Stryker® device without complications, and that the intraprostatic tissue pressure is high in patients with typical symptoms of chronic non-bacterial prostatitis. Pressure readings taken in the normal prostate tissue of men without symptoms 10 seconds after injection showed values below 40–50 mmHg and that for men with CP/CPPS over 60–70 mmHg. Meanwhile, the prostatic tissue end pressures after 120 seconds dropped to the physiological level (15–30 mmHg) in control men but remained higher than normal (over 40 mmHg) in the CPPS patients, thus pointing indirectly to microcirculation disturbances at some level in the capillary network of the prostatic tissue. The results showed that prostatitis patients belonging to clinical category IIIA developed a higher tissue pressure than patients belonging to category IIIB ($p < 0.001$). This may reflect more severe inflammation, leading to disturbances in microcirculation and tissue damage, with a consequent scarring process (Guyton *et al.* 1971, Asthon 1975, Clayton *et al.* 1977, Mabee & Bostwick 1993, Jaroma 2000). Inflammation disturbs the regulatory mechanisms through the production of albumin-related products, and the osmotic pressure can temporarily reach very high readings, causing oedema, with consequent pain in prostatitis patients (Krieger *et al.* 1996b, Egan & Krieger 1997). These results support the theory that reactions to microcirculation disturbances in closed compartmental spaces (including the prostate gland) can cause pain, as in other organs with a thick multilayer musculo-fibrotic capsule (Blacklock 1974, Patel & Rickards 1994, Cho *et al.* 2000). This provides an explanation for the physiological and histological changes to be found in the prostate tissue afterwards (Gardner & Bennett 1992, Bennet *et al.* 1993, Dixon *et al.* 1999).

No attempt has been made so far by others to verify the present findings of increased tissue pressure in patients with chronic prostatitis. Some indirect support can be derived from the work of Hegarty *et al.* (2000), however, who showed under cell culture conditions that increased prostate tissue pressure (over 80 mmHg) induced apoptosis of cells from BPH patients. There are also some critical points related to the PTPM approach. Proper placement of the needle in the prostate and careful setting and exact prefilling of the Stryker® device according to the manufacturer's instructions are necessary for reliable measurements. The measurement procedure must also be carried out correctly in order to avoid failures and erroneous results. The time must be followed punctually, otherwise the results will not be comparable, and the needle position must be checked by TRUS if there is any suspicion of incorrect placement. The test PTPM procedure has proved slightly invasive, and spinal anaesthesia was used in all the examinations. There is a need to develop the test so that it would be more convenient and suitable for outpatient use.

The NIH-CPSI questionnaire (Litwin *et al.* 1999) has been developed to assess reliably the severity of symptoms in CP/CPPS patients when different investigators are involved and to follow-up the efficacy of treatment. It was translated into Finnish and validated in 1999 and the results of the first experiences with its use were reported by the author at the III International Chronic Prostatitis Workshop in Bethesda, Washington in October 2000 (Mehik *et al.* 2000). So far the results of only one survey, published by Shoskes *et al.*

(1999), have been available for comparing the severity of prostatitis symptoms using this new tool. They reported total NIH-CPSI scores averaging 20.6 (range 12–39), while the average total score in the present study was 19.7 (range 17–22). Likewise, their pain score average was 8.9 (range 5–17) and the present figure 9.9 (range 8–11), their voiding score 3.0 (range 1–11) and the present score 3.3 (range 2–4), and their quality of life score averaged 7.9 (range 3–12), compared with the present 6.5 (range 5–7). We may preliminarily conclude that the patients in these two separate series had symptoms of the same subjective severities as measured in terms of their NIH-CPSI scores and could possibly be compared with each other despite their different surroundings (California, USA vs Oulu, Finland).

The present clinical-microbiological diagnosis of prostatitis by means of the Meares-Stamey four-glass test (Meares & Stamey 1968) or Nickel's pre-massage and post-massage test (Nickel 1997, Nickel 1998b, Ludwig *et al.* 2000) can assess the severity of inflammation by microscopy of the expressed prostatic secretion and/or post-voided urine, but the tests are unfortunately not 100% reliable (Krieger *et al.* 2000b, Lacquaniti *et al.* 2000, Ludwig *et al.* 2000, Strohmaier & Bichler 2000), and therefore PTPM constitutes one extra valid tool for differential diagnosis in order to confirm the laboratory findings or categorize prostatitis patients (especially to distinguish between those of types IIIA and IIIB). When laboratory findings and PTPM are normal, the patient very probably has pain originating in some other site in the pelvis. All this can reduce the use of antibiotics, which is now the norm rather the exception even without any clinical reason or any evidence of bacteria in the prostatic fluid and/or urine (de la Rosette *et al.* 1992a, Moon 1997, Nickel *et al.* 1998).

7 Conclusions

The lifetime prevalence of prostatitis in Finnish men aged 20–59 years was 14.2%, i.e. higher than the figures of 4–11% given by earlier published data. The incidence density of prostatitis was 37.8 per 10 000 person years at risk.

63% of the men in northern Finland had their worst symptoms of prostatitis during the wintertime (November–March) and 58% regarded the cold climate as a reason for their chronic symptoms of prostatitis.

17% of the men with prostatitis reported a fear of undetected prostate cancer and 2.2% of possible sexually transmitted disease, while 3.2% reported some degree of suicidal thinking.

43% of the men reported disturbances in their sexual life (temporary impotence) due to prostatitis symptoms, and 24% decreased libido.

The tissue pressure measurement method, commonly used in orthopaedics, was successfully modified for intraprostatic tissue pressure measurements.

The intraprostatic tissue pressures were found to be significantly higher in patients with chronic prostatitis than in those with BPH or controls.

PTPM made it possible to differentiate between the categories of CP/CPPS (IIIA and IIIB) and can exclude cases with pelvic pain arising outside the prostate.

8 References

- Aarnink RG, Beerlage HP, de la Rosette JJMCH, Debruyne FMJ & Wijkstra H (1998) Transrectal ultrasound of the prostate: innovations and future applications. *J Urol* 159: 1568–1579.
- Addison RG (1984) Chronic pain syndrome. *Am J Med* 10: 54–58.
- Aitken RJ & Baker HWG (1995) Seminal leukocytes: passangers, terrorists or good Samaritans? *Hum Reprod* 10(7): 1736–1739.
- Alexander RB & Trissel D (1996) Chronic prostatitis: results of an Internet survey. *Urology* 48: 568–574.
- Alexander RB, Brady F & Ponniah S (1997) Autoimmune prostatitis: evidence of T cell reactivity with normal prostatic proteins. *Urology* 50:893–899.
- Alexander RB, Ponniah S, Hasday J & Hebel JR (1998) Elevated levels of proinflammatory cytokines in the semen of patients with chronic prostatitis/chronic pelvic pain syndrome. *Urology* 52: 744–749.
- Anderson RU & Weller C (1979) Prostatic secretion leukocyte studies in non-bacterial prostatitis (prostatosis). *J Urol* 121: 292–294.
- Aron M, Rajeev TP & Gupta NP (2000) Antibiotic prophylaxis for transrectal needle biopsy of the prostate: a randomized controlled study. *BJU Int* 85: 682–685.
- Asthan H (1975) The effect of increased tissue pressure on blood flow. *Clin Orthop* 113: 15–26.
- Aus G, Ahlgren G, Bergdahl S & Hugosson J (1996) Infection after transrectal core biopsies of the prostate – risk factors and antibiotic prophylaxis. *Br J Urol* 77: 851–855.
- Bahk JY, Hyun JS, Lee JY, Kim JH, Cho YH, Lee JH, Park JS & Kim MO (2000) Concentration of ofloxacin in canine prostate tissue and prostate fluid after intraprostatic injection of biodegradable sustained-releasing microspheres containing ofloxacin. *J Urol* 163: 1560–1564.
- Barbalias GA (1990) Prostatodynia or painful male urethral syndrome? *Urology* 36 (2): 146–153.
- Barbalias GA, Meares EM Jr & Sant GR (1983) Prostatodynia: clinical and urodynamic characteristics. *J Urol* 130: 514–517.
- Barbalias GA, Nikiforidis G & Liatsikos EN (1998) Alpha-blockers for treatment of chronic prostatitis in combination with antibiotics. *J Urol* 159: 883–887.
- Bennett BD, Richardson PH & Gardner WA Jr (1993) Histopathology and cytology of prostatitis. In: Lepor H and Lawson RK (eds) *Prostate disease*, WB Saunders, p 399–413.
- Berger RE, Krieger JN, Kessler D, Ireton RC, Close C, Holmes K & Roberts PL (1989) Case-control study of men with suspected chronic idiopathic prostatitis. *J Urol* 141: 328–331.
- Berger RE, Krieger JN, Rothman I, Muller CH & Hillier SL (1997) Bacteria in the prostate tissue of men with idiopathic prostatitis inflammation. *J Urol* 157: 863–865.

- Berger RE, Miller JE, Rothman I, Krieger JN & Muller CH (1998) Bladder petechiae after cystoscopy and hydrodistension in men diagnosed with prostate pain. *J Urol* 159: 83–85.
- Berghuis JP, Heiman JR, Rothman I & Berger RE (1996) Psychological and physiological factors involved in chronic idiopathic prostatitis. *J Psychosom Res* 41(4): 313–325.
- Bergman B, Wedren H & Holm SE (1989) *Staphylococcus saprophyticus* in males with symptoms of chronic prostatitis. *Urology* 34(5): 241–245.
- Bjerklund Johansen TE, Grúneberg RN, Guibert J, Hofstetter A, Lobel B, Naber KG, Palou-Redorta J & van Cangh PJ (1998) The role of antibiotics in the treatment of chronic prostatitis: a consensus statement. *Eur Urol* 34: 457–466.
- Blacklock NJ (1974) Anatomical factors in prostatitis. *Br J Urol* 46: 47–54.
- Blacklock NJ (1991) The anatomy of the prostate: relationship with prostatic infection. *Infection* 19 (Suppl 3): 111–114.
- Blaivas J (1984) Multichannel urodynamic studies. *Urology* 23: 421–438.
- Brawn PN, Johnson EH, Foster DM, Coffield KS, Jay DW, Lind ML, Kuhl D, Karl R, Speights VO & Weaver B (1994) Characteristics of prostatic infarcts and their effect on serum prostate-specific antigen and prostatic acid phosphatase. *Urology* 44(1): 71–75.
- Brähler E & Weidner W (1986) Testpsychologische Untersuchungen zum Beschwerdebild von Patienten mit chronischer Prostatitis oder Prostatodynie. *Urologe A* 25: 97–100.
- Campbell MF (1957) The male reproductive tract: the prostate. In: Campbell MF (ed) *Principles of urology: an introductory text to the disease of the urological tract*. Philadelphia, WB Saunders, p 311–313.
- Chapple CR, Blease SCP & Rickards D (1990) What is the clinical significance of urethroprostatic reflux as a radiological finding during videocystourethrography in neurologically normal patients? *Eur Urol* 17: 296–298.
- Cho IR, Keener TS, Nghiem HV, Winter T & Krieger JN (2000) Prostate blood flow characteristics in the chronic prostatitis/pelvic pain syndrome. *J Urol* 163: 1130–1133.
- Choong S & Whitefield H (2000) Biofilms and their role in infections in urology. *BJU Int* 86: 935–941.
- Christiansen E & Purvis K (1990) Diagnosis of chronic abacterial prostatitis-vesiculitis by rectal ultrasonography in relation to symptoms and findings. *Br J Urol* 67: 173–176.
- Clayton JM, Hayes AC & Barnes RW (1977) Tissue pressure and perfusion in the compartment syndrome. *J Surg Res* 22: 333–339.
- Cumming RE & Chittenden GE (1938) Pyogenic prostatitis. *J Urol* 39: 118–122.
- de la Rosette JJMCH, Hubregtse MR, Karthaus HFM & Debruyne FMJ (1992a) Results of a questionnaire among Dutch urologists and general practitioners concerning diagnostics and treatment of patients with prostatitis syndromes. *Eur Urol* 22: 14–19.
- de la Rosette JJMCH, Karthaus HFM, de Boer Th & Debruyne FMJ (1992b) Research in "prostatitis syndromes": the use of alfuzosin (a new alpha-1-receptor blocking agent) in patients mainly presenting with micturition complaints of an irritative nature and confirmed urodynamic abnormalities. *Eur Urol* 22: 222–227.
- de la Rosette JJMCH, Hubregtse MR, Meuleman EJH, Stolk-Engelaar MVM & Debruyne FMJ (1993a) Diagnosis and treatment of 409 patients with prostatitis syndromes. *Urology* 41: 301–307.
- de la Rosette JJMCH, Ruijgrok MCM, Jeuken JMG, Karthaus HFM & Debruyne FMJ (1993b) Personality variables involved in chronic prostatitis. *Urology* 42: 654–662.
- de la Rosette JJMCH, Giesen RJB, Huynen al, Aarnink RG, van Iersel MP, Debruyne FMJ & Wijkstra H (1995) Automated analysis and interpretation of transrectal ultrasonography images in patients with prostatitis. *Eur Urol* 27: 47–53.
- Desmond PM, Clark J, Thompson IM, Zeidman EJ & Mueller EJ (1993) Morbidity with contemporary prostate biopsy. *J Urol* 150: 1425–1426.

- Dixon JS, Chow PH & Gosling JA (1999) Anatomy and function of the prostate gland. In: Nickel JC (ed) *Textbook of prostatitis*. Isis Medical Media Ltd, Oxford, UK. p 39–46.
- Doble A, Thomas BJ, Furr PM, Walker MM, Harris JRW & Witherow RO'N (1989a) A search for infectious agents in chronic abacterial prostatitis using ultrasound guided biopsy. *Br J Urol* 64: 297–301.
- Doble A, Thomas BJ, Walker MM, Harris JRW, Whiterow RO'N & Taylor-Robinson D (1989b) The role of *Chlamydia trachomatis* in chronic abacterial prostatitis: a study using ultrasound guided biopsy. *J Urol* 141: 332–333.
- Doble A, Walker MM, Harris JRW, Taylor-Robinson D & Whiterow RO'N (1990) Intraprostatic antibody deposition in chronic abacterial prostatitis. *Br J Urol* 65: 598–605.
- Domingue GJ Sr & Hellstrom WJG (1998) Prostatitis. *Clin Microbiol Rev* 11(4): 604–613.
- Drabick JJ, Gambel JM & Mackey JF (1997) Prostatodynia in United Nations peacekeeping forces in Haiti. *Mil Med* 162: 380–383.
- Drach GW (1976) Sexuality and prostatitis: a hypothesis. *J Am Ven Dis Assoc* 3: 87–89.
- Drach GW, Meares EM, Fair WR & Stamey TA (1978) Classification of benign disease associated with prostatic pain: prostatitis or prostatodynia? (Letter to the editor) *J Urol* 120: 266.
- Dumas F, Eschwége P & Loric S (1997) Acute bacterial prostatitis induces hematogenous dissemination of prostate epithelial cells. *Clin Chem* 43(10): 2007–2008.
- Ebbenhøj N, Svedsen LB & Madsen P (1984) Pancreatic tissue pressure: techniques and pathophysiological aspects. *Scand J Gastroenterol* 19: 1066–1068.
- Ebbenhøj N, Borly L, Madsen P & Svedsen LB (1986) Pancreatic tissue pressure and pain in chronic prostatitis. *Pancreas* 1: 556–558.
- Egan KJ & Krieger JN (1994) Psychological problems in chronic prostatitis with pain. *Clin J Pain* 10: 218–226.
- Egan KJ & Krieger JL (1997) Chronic abacterial prostatitis – urological chronic pain syndrome. *Pain* 69: 213–218.
- Elbadawi A (1997) Interstitial cystitis: a critique of current concepts with a new proposal for pathologic diagnosis and pathogenesis. *Urology* 49 (Suppl 5A): 14–40.
- Eskola R & Tirkkonen K (2001) Prostatitiitti vai stressin aiheuttama lihasspasmii? *Aesculapius* 2: 14–16.
- Fair WR & Cordonnier JJ (1978) The pH of prostatic fluid: a reappraisal and therapeutic implications. *J Urol* 120: 695–698.
- Fair WR & Parrish RF (1981) Antibacterial substances in prostatic fluid. In: *Prostatic cell: structure and function*. Liss AR (ed), Inc, NY, p 247–264.
- Farman F (1930) Classification of prostatitis. *J Urol* 23: 113–117.
- Foxman B, Zhang L, Tallman P, Andree BC, Geiger AM, Koopman JS, Gillespie BW, Palin KA, Sobel JD, Rode CK, Bloch CA & Marrs CF (1997) Transmission of uropathogens between sex partners. *J Infect Dis* 175: 989–992.
- Fowler JE Jr (1991) Secretory immunity of the prostate gland. *Infection* 19 (Suppl 3): 131–137.
- Fowler JE Jr & Mariano M (1982) Immunologic response of the prostate to bacteriuria and bacterial prostatitis. II. Antigen specific immunoglobulin in prostatic fluid. *J Urol* 128: 165–170.
- Fulmer BR & Turner TT (2000) A blood-prostate barrier restricts cell and molecular movement across the rat ventral prostate epithelium. *J Urol* 163: 1591–1594.
- Galley HF, Nelson SJ, Dubbels AM & Webster NR (1997) Effect of ciprofloxacin on the accumulation of interleukin-6, interleukin-8, and nitrite from a human endothelial cell model of sepsis. *Crit Care Med* 25: 1392–1395.
- Gardner WA & Bennet BD (1992) The prostate – overview: recent insights and speculations. *Monogr Pathol* 34: 129–148.
- Garrelts B, von (1956) Analysis of micturition. A new method of recording the voiding of the bladder. *Acta Chir Scand* 112: 326–340.

- Gelberman RH, Szabo RM, Williamson RV, Hargens AR, Yaru NC & Minter-Convery MA (1983) Tissue pressure threshold for peripheral nerve viability. *Clin Orthop* 178: 285–291.
- Ghobish AA (2000) Quantitative and qualitative assessment of flowmetrograms in patients with prostatodynia. *Eur Urol* 38: 576–583.
- Gilad J, Borer A, Maimon N, Riesenberk K, Klein M & Schlaeffer F (1999) Failure of ciprofloxacin prophylaxis for ultrasound guided tranrectal prostatic biopsy in the era of multiresistant enterobacteriaceae. *J Urol* 161: 222.
- Grant O (1938) Treatment of recalcitrant prostatitis by drug injection. *J Urol* 39: 150–155.
- Guyton AC, Granger HJ & Taylor AE (1971) Interstitial fluid pressure. *Physiol Rev* 51(3): 527–563.
- Hasui Y, Marutsuka K, Asada Y, Ide H, Nishi S & Osada Y (1994) Relationship between serum prostate specific antigen and histological prostatitis in patients with benign prostatic hyperplasia. *Prostate* 25: 91–96.
- Hegarty P, Watson RWG, Coffey R & Fitzpatrick JM (2000) Role of intraprostatic pressure on apoptotic resistance in a model of BPH. *BJU Int* 85 (Suppl 5): 43(abstract P67)
- Hellstrom WJG, Schmidt RA, Lue TF & Tanagho EA (1987) Neuromuscular dysfunction in nonbacterial prostatitis. *Urology* 30(2): 183–188.
- Henline RB (1943) Prostatitis and seminal vesiculitis: acute and chronic. *JAMA* 123(10): 608–615.
- Hennenfent B (1997) Prostatitis and benign prostatic hyperplasia: emerging infectious diseases? (Letter to the editor) *Emerg Infect Dis* 3(1): 77.
- Hitchens AP & Brown CP (1913) The bacteriology of chronic prostatitis. *Am J Public Health* 3: 884–891.
- Hochreiter WW, Duncan JL & Schaeffer AJ (2000) Evaluation of the bacterial flora of the prostate using a 16S rRNA gene based polymerase chain reaction. *J Urol* 163: 127–130.
- Huaijin C, Junyan Z & Naiguan C (1998) Prostate fluid and sperm examination: 106 cases preliminary study on infertility. *Acta Urol Belg* 66(1): 19–21.
- Irani J, Levillain P, Goujon J-M, Bon D, Doré B & Aubert J (1997) Inflammation in benign prostatic hyperplasia: correlation with prostate specific antigen value. *J Urol* 157: 1301–1303.
- Jaroma H (2000) Yläraajan krooninen aitiopainoireyhtymä. In: *Käsikirurgia* (ed's Vastamäki et al.), Kustannus Oy Duodecim, Hämeenlinna, p 543–548.
- John H, Barghorn A, Funke G, Sulser T, Hailemariam S, Hauri D & Joller-Jemelka HI (2001) Noninflammatory Chronic Pelvic Pain Syndrome: immunological study in blood, ejaculate and prostate tissue. *Eur Urol* 39: 72–78.
- Jung K, Meyer A, Lein M, Rudolph B, Schnorr D & Loening SA (1998) Ratio of free-to-total prostate specific antigen in serum cannot distinguish patients with prostate cancer from those with chronic inflammation of the prostate. *J Urol* 159: 1595–1598.
- Kaplan SA, Te AE & Jacobs BZ (1994) Urodynamic evidence of vesical neck obstruction in men with misdiagnosed chronic nonbacterial prostatitis and the therapeutic role of endoscopic incision of the bladder neck. *J Urol* 152: 2063–2065.
- Kaplan SA, Santarosa RP, Dálisera PM, Fay BJ, Ikeguchi EF, Hendricks J, Klein L & Te AE (1997) Pseudodyssynergia (contraction of the external sphincter during voiding) misdiagnosed as chronic nonbacterial prostatitis and the role of the biofeedback as a therapeutic option. *J Urol* 157: 2234–2237.
- Keay S, Zhang CO, Baldwin BR & Alexander RB (1999) Polymerase chain reaction amplification of bacterial 16s rRNA genes in prostate biopsies from men without chronic prostatitis. *Urology* 53: 487–491.
- Keetch DW, Humphrey P & Ratliff TI (1994) Development of a mouse model for nonbacterial prostatitis. *J Urol* 152: 247–250.
- Keltikangas-Järvinen L, Järvinen H & Lehtonen T (1981) Psychic disturbances in patients with chronic prostatitis. *Ann Clin Res* 13: 45–49.

- Keltikangas-Järvinen L, Ruokolainen J & Lehtonen T (1982) Personality pathology underlying chronic prostatitis. *Psychother Psychosom* 37: 87–95.
- Keltikangas-Järvinen L, Mueller K & Lehtonen T (1989) Illness behavior and personality changes in patients with chronic prostatitis during a two-year follow-up period. *Eur Urol* 16: 181–184.
- Kirby RS, Lowe D, Bultitude I & Shuttleworth KED (1982) Intra-prostatic urinary reflux: an aetiological factor in abacterial prostatitis. *Br J Urol* 54: 729–731.
- Klimas R, Bennett B & Gardner WA (1985) Prostatic calculi: a review. *Prostate* 7: 91–96.
- Kohnen PW & Drach GW (1979) Patterns of inflammation in prostatic hyperplasia: a histologic and bacteriologic study. *J Urol* 121: 755–760.
- Kretschmer HL (1937) Chronic prostatitis – a critical review of 1000 cases. *Ill Med J* 71: 156–161.
- Kretschmer HL (1939) Medical management of chronic prostatitis. *Wis Med J* 38(5): 363–372.
- Krieger JN (1984) Prostatitis syndromes: pathophysiology, differential diagnosis and treatment. *Sex Transm Dis* 11(2): 100–112.
- Krieger JN & McGonagle LA (1989) Diagnostic considerations and interpretation of microbiological findings for evaluation of chronic prostatitis. *J Clin Microbiol* 27(10): 2240–2244.
- Krieger JN & Egan KJ (1991) Comprehensive evaluation and treatment of 75 men referred to chronic prostatitis clinic. *Urology* 38(1): 11–19.
- Krieger JN, Ross SO & Simonsen JM (1993a) Urinary infections in healthy university men. *J Urol* 149: 1046–1048.
- Krieger JN, Verdon M, Siegel N & Holmes KK (1993b) Natural history of urogenital trichomoniasis in men. *J Urol* 149: 1455–1458.
- Krieger JN, Berger RE, Ross SO, Rothman I & Muller CH (1996a) Seminal fluid findings in men with nonbacterial prostatitis and prostatodynia. *J Androl* 17(3): 310–318.
- Krieger JN, Egan KJ, Ross SO, Jacobs R & Berger RE (1996b) Chronic pelvic pain represent the most prominent urogenital symptoms of "chronic prostatitis". *Urology* 48: 715–722.
- Krieger JN, Nyberg L Jr & Nickel JC (1999) Letter to the editor: NIH consensus definition and classification of prostatitis. *JAMA* 282: 236–237.
- Krieger JN, Jacobs RR & Ross SO (2000a) Does the chronic prostatitis/pelvic pain syndrome differ from nonbacterial prostatitis and prostatodynia? *J Urol* 165: 1554–1558.
- Krieger JN, Jacobs RR & Ross SO (2000b) Detecting urethral and prostatic inflammation in patients with chronic prostatitis. *Urology* 55(2): 186–192.
- Krieger JN, Riley DE, Vesella RL, Miner DC, Ross SO & Lange PH (2000c) Bacterial DNA sequences in prostate tissue from patients with prostate cancer and chronic prostatitis. *J Urol* 164: 1221–1228.
- Kumon H (1992) Detection of local prostatic immune response to bacterial prostatitis. *Infection* 20 (Suppl 3): 236–238.
- Lackum WH, von (1927) Clinical and experimental data on prostatic infection. *J Urol* 18: 293–306.
- Lackum WH, von (1928) The infected prostate. *Proc Staff Mtgs Mayo Clin* (Jan 11), p 14–15
- Lacquaniti S, Fulcoli V, Weir JM, Pisanti F, Servello C & Desitto A (2000) Bacterial prostatitis: urine and spermatic fluid culture. *Arch Ital Urol Androl* 72(1): 21–23.
- Lang MD, Nickel JC, Olson ME, Howard SR & Ceri H (2000) Rat model of experimentally induced abacterial prostatitis. *Prostate* 45: 201–206.
- Lapides J (1976) Prostatitis. In: Marberger H (ed), *Prostatic disease*, Alan R. Liss, Inc., NY, p 363–364.
- Leib Z, Bartoov B, Eltes F & Servadio C (1994) Reduced semen quality caused by chronic abacterial prostatitis: an enigma or reality? *Fertil Steril* 61(6): 1109–1116.
- Lepout C, Rousseau F, Perronne C, Salmon D, Joerg A & Vilde JL (1989) Bacterial prostatitis in patients infected with the human immunodeficiency virus. *J Urol* 141: 334–336.
- Liao L-M, Shi B-Y & Liang C-Q (1999) Ambulatory urodynamic monitoring of external urethral sphincter behavior in chronic prostatitis patients. *Asian J Androl* 1(4): 215–217.

- Lilius HG & Valtonen EJ (1972) Diaphragma pelvis spastica. *Duodecim* 88: 399–402.
- Lindert KA, Kabalin JN & Terris MK (2000) Bacteremia and bacteriuria after transrectal ultrasound guided prostate biopsy. *J Urol* 164: 76–80.
- Lipsky BA (1989) Urinary tract infections in men. *Epidemiology, pathophysiology, diagnosis and treatment. Ann Int Med* 110(2): 138–150.
- Litwin MS, McNaughton-Collins M, Fowler FJ Jr, Nickel JC, Calhoun EA, Pontari MA, Alexander RB, Farrar JT, O'Leary MP & The Chronic Prostatitis Collaborative Research Network. (1999) The National Institutes of Health Chronic Prostatitis Symptom Index: development and validation of a new outcome measure. *J Urol* 162: 369–375.
- Lowentritt JE, Kawahara K, Human LG, Hellstrom WJG & Domingue GJ (1995) Bacterial infection in prostatodynia. *J Urol* 154: 1378–1381.
- Ludwig M, Weidner W, Schroeder-Printzen I, Zimmermann O & Ringert R-H (1994) Transrectal sonography as a useful diagnostic means for patients with chronic prostatitis or prostatodynia. *Br J Urol* 73: 664–668.
- Ludwig M, Schroeder-Printzen I, Schiefer HG & Weidner W (1998) Diagnosis and therapeutic management of 18 patients with prostatic abscess. *Urology* 53: 340–345.
- Ludwig M, Schroeder-Printzen I, Ludecke G & Weidner W (2000) Comparison of expressed prostatic secretions with urine after prostatic massage – a means to diagnose chronic prostatitis/inflammatory chronic pelvic pain syndrome. *Urology* 55: 175–177.
- Luzzi GA & Cranston D (2000) Bladder carcinoma presenting as prostatitis syndrome (case report). *BJU Int* 85: 774–775.
- Mabee JR & Bostwick TL (1993) Pathophysiology and mechanisms of compartment syndrome. *Orthop Rev* 22(2): 175–181.
- Maksem JA, Jochenning PW & Galang CF (1988) Prostatitis and aspiration biopsy cytology of prostate. *Urology* 32(3): 263–268.
- Matsumoto T, Soejima T, Tanaka M, Naito S & Kumazawa J (1992) Cytologic findings of fine needle aspirates in chronic prostatitis. *Int Urol Nephrol* 24(1): 43–47.
- Mayo ME, Ross SO & Krieger JN (1998) Few patients with "chronic prostatitis" have significant bladder outlet obstruction. *Urology* 52: 417–421.
- McClinton S, Eremin O & Miller D (1990) Inflammatory infiltrate in prostatic hyperplasia-evidence of host response to intraprostatic spermatozoa? *Br J Urol* 65: 606–610.
- McNaughton Collins M, O'Leary MP & Barry MJ (1998a) Prevalence of bothersome genitourinary symptoms and diagnosis in younger men on routine primary care visits. *Urology* 52: 422–427.
- McNaughton Collins M, Stafford RS, O'Leary MP & Barry MJ (1998b) How common is prostatitis? A national survey of physician visits. *J Urol* 159: 1224–1228.
- McNaughton Collins M & Barry MJ (1999) The epidemiology of prostatitis. In: Nickel JC (ed), *Textbook of prostatitis*, Isis Medical Media Ltd, Oxford, UK. p 247–254.
- McNaughton Collins M, Stafford RS, O'Leary MP & Barry MJ (1999) Distinguishing chronic prostatitis and benign prostatic hyperplasia symptoms: results of a national survey of physicians visits. *Urology* 53: 921–925.
- McNaughton Collins M, Fowler FJ Jr, Elliott DB, Albertsen PC & Barry MJ (2000) Diagnosing and treating chronic prostatitis: do urologist use the four-glass test? *Urology* 55: 403–407.
- McNeal JE (1972) The prostate and prostatic urethra: a morphologic synthesis. *J Urol* 107: 1008–1016.
- McNeal JE (1988) Normal histology of the prostate. *Am J Surg Pathol* 12(8): 619–633.
- Meares EM & Stamey TA (1968) Bacteriologic localization patterns in bacterial prostatitis and urethritis. *Invest Urol* 5: 492–518.
- Meares EM Jr (1998) Prostatitis and related disorders. In: Walsh PC et al.(eds) *Campbell's Urology*, 7th ed., WB Saunders, Philadelphia, p 615–630.

- Mehik A, Hellström P, Lukkarinen O, Sarpola A & Leskinen M (2000) One year experience of using the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) for diagnosis and survey of Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS). Abstract Book of 3rd Annual International Prostatitis Collaborative Network, October 23–24, 2000, in Washington, DC, p 17.
- Mehlhorn J (1987) Die Prostatitis aus morphologische Sicht – eine Sektionsanalyse. *Z Urol Nephrol* 80: 253–258.
- Miller JL, Rothman I, Bavendam TG & Berger RE (1995) Prostatodynia and interstitial cystitis: one and the same? *Urology* 45: 587–590.
- Miller HC (1988) Stress prostatitis. *Urology* 32(6): 507–510.
- Montie JE, Wojno K, Klein E, Pearsall C & Levin H (1997) Transitional cell carcinoma in situ of the seminal vesicles: 8 cases with discussion of pathogenesis, and clinical and biological implications. *J Urol* 158: 1895–1898.
- Moon TD (1997) Questionnaire survey of urologists and primary care physician's diagnostic and treatment practices for prostatitis. *Urology* 50: 543–547.
- Moon TD, Hagen L & Heisey DM (1997) Urinary symptomatology in younger men. *Urology* 50: 700–703.
- Moore RA (1937) Tuberculosis of the prostate gland. *J Urol* 37: 372–383.
- Mårdh PA, Colleen S & Hovelius B (1979) Attachment of bacteria to exfoliated cells from the urogenital tract. *J Urol* 16(5): 322–326.
- Nadler RB, Humprey PA, Smith DS, Catalona WJ & Ratliff TL (1995) Effect of inflammation and benign prostatic hyperplasia on elevated serum prostate specific antigen levels. *J Urol* 154: 407–413.
- Nadler RB, Koch AE, Calhoun EA, Campbell PL, Pruden DL, Bennett ChL, Yarnold PR & Schaeffer AJ (2000) IL-1b and TNF-a in prostatic secretions are indicators in the evaluation of men with chronic prostatitis. *J Urol* 164: 214–218.
- Naslund MJ, Strandberg JD & Coffey DS (1988) The role of androgens and estrogens in the pathogenesis of experimental nonbacterial prostatitis. *J Urol* 140: 1049–1053.
- Neal DE Jr, Dilworth JP, Kaack MB, Didier P & Roberts JA (1990) Experimental prostatitis in nonhuman primates: II. Ascending acute prostatitis. *Prostate* 17: 233–239.
- Neal DE Jr, Clejan S, Sarma D & Moon TD (1992) Prostate specific antigen and prostatitis. I Effect of prostatitis on serum PSA in the human and nonhuman primate. *Prostate* 20: 105–111.
- Neal DE Jr & Moon TD (1994) Use of terazosin in prostatodynia and validation of the symptom score questionnaire. *Urology* 43: 460–465.
- Nickel AC (1930) The bacteriology of chronic prostatitis and seminal vesiculitis, and elective localization of the bacteria as isolated. *J Urol* 24(4): 343–357.
- Nickel JC, Olson ME, Barabas A, Benediktsson H, Dasgupta MK & Costerton JW (1990) Pathogenesis of chronic bacterial prostatitis in an animal model. *Br J Urol* 66: 47–54.
- Nickel JC & Costerton JW (1992) Coagulase-negative staphylococcus in chronic prostatitis. *J Urol* 147: 398–401.
- Nickel JC & Costerton JW (1993) Bacterial localization in antibiotic-refractory chronic bacterial prostatitis. *Prostate* 23: 107–114.
- Nickel JC, Downey J, Clark J, Ceri H & Olson M (1995) Antibiotic pharmacokinetics in the inflamed prostate. *J Urol* 153: 527–529.
- Nickel JC & Sorensen R (1996) Transurethral microwawe thermotherapy for nonbacterial prostatitis. A randomized double-blind sham controlled study using new prostatitis assessment questionnaire. *J Urol* 155: 1950–1955.
- Nickel JC (1997) The pre and post massage test (PPMT): a simple screen for prostatitis. *Tech Urol* 3: 38–43.
- Nickel JC (1998a) Prostatitis: myth and realities. *Urology* 53: 362–366.

- Nickel JC (1998b) Effective office management of chronic prostatitis. *Urol Clin North Am* 25(4): 677–684.
- Nickel JC & McLean RJC (1998) Bacterial biofilms in urology. *Infect Urol* 11(6): 169–175.
- Nickel JC, Nigro M, Valiquette L, Anderson P, Patrick A, Mahoney J, Buckley R, Corcos J & Hosking D (1998) Diagnosis and treatment of prostatitis in Canada. *Urology* 52: 797–802.
- Nickel JC (1999) Report of the 2nd International Prostatitis Collaborative Network (IPCN) Bethesda, MD, November 3–5, 1999.
- Nickel JC, Downey J, Young I & Boag S (1999a) Asymptomatic inflammation and/or infection in benign prostatic hyperplasia. *BJU Int* 84: 976–981.
- Nickel JC, Nyberg LM, Hennenfent M, for the International prostatitis Collaborative Network. (1999b) Research guidelines for chronic prostatitis: consensus report from the first National Institutes of Health International prostatitis Collaborative Network. *Urology* 54: 229–233.
- Nickel JC (2000) Chronic prostatitis: an infectious disease? *Infect Urol* 13(2): 31–38.
- Nickel JC, Downey J, Hunter D & Clark J (2001) Prevalence of prostatitis-like symptoms in population based study using the National Institutes of Health chronic prostatitis symptom index. *J Urol* 165: 842–845
- Nishimura T, Abe H, Ito H, Ikeda K, Oka F & Yamamoto M (1998) IL-1ra versus IL-1 levels in prostatic fluid from prostatitis patients. *Urol Int* 60: 92–96.
- Noldus J & Stamey TA (1996) Histological characteristics of radical prostatectomy specimens in men with a serum prostate specific antigen of 4 ng/ml or less. *J Urol* 155: 441–443.
- Okada K, Kojima M, Naya Y, Kamoi K, Yokoyama K, Takamatsu T & Miki T (2000) Correlation of histological inflammation in needle biopsy specimens with serum prostate-specific antigen levels in men with negative biopsy for prostate cancer. *Urology* 55: 892–898.
- Ohkawa M, Yamaguchi K, Tokunaga S, Nakashima T & Fujita S (1993) *Ureaplasma urealyticum* in the urogenital tract of patients with chronic prostatitis or related symptomatology. *Br J Urol* 72: 918–921.
- Ostraszewska I, Zdrodowska-Stafanow B, Badyda J, Pucilo K, Trybula J & Bulhak V (1998) *Chlamydia trachomatis*: probable cause of prostatitis. *Int J STD AIDS* 9: 350–353.
- Pansadoro V, Emiliozzi P, Defidio L, Scarpone P, Sabatini G, Brisciani A & Lauretti S (1996) Prostate-specific antigen and prostatitis in men under fifty. *Eur Urol* 30: 24–27.
- Patel U & Rickards D (1994) The diagnostic value of colour Doppler flow in the peripheral zone of the prostate, with histological correlation. *Br J Urol* 74: 590–595.
- Pavone-Macaluso M, DiTrapani D, Pavone C, Piaia F, Rocco F, Denis L, Bouffieux C, de Voogt H, Becopoulos T, Newling D & Smith PH, MRG (1991) Prostatitis, prostaticos and prostaticos. Psychogenic or organic disease. *Scand J Urol Nephrol Suppl* 138: 77–82.
- Pavone C, Calderera E, Liberti P, Miceli V, DiTrapani D, Serretta V, Porcu M & Pavone-Macaluso M (2000) Correlation between chronic prostatitis syndrome and pelvic venous disease. *Eur Urol* 37: 400–403.
- Persson BE & Ronquist G (1996) Evidence for mechanistic association between nonbacterial prostatitis and levels of urate and creatinine in expressed prostatic secretion *J Urol* 155: 958–960.
- Peters RM & Hargens AR (1981) Protein vs electrolytes and all of the Starling's forces. *Arch Surg* 116: 1293–1298.
- Polascik TJ, Oesterling JE & Partin AW (1999) Prostate specific antigen: a decade of discovery-what we have learned and where we are going. *J Urol* 162: 293–306.
- Poletti F, Medici MC, Alinovi A, Menozzi MG, Sacchini P, Stagni G, Toni M & Benoldi D (1985) Isolation of *chlamydia trachomatis* from the prostatic cells in patients affected by nonacute abacterial prostatitis. *J Urol* 134: 691–693.
- Ponniah S, Arah I & Alexander RB (2000) PSA is a candidate self-antigen in autoimmune chronic prostatitis/chronic pelvic pain syndrome. *Prostate* 44: 49–54.

- Potts JM (2000) Prospective identification of National Institutes of Health category IV prostatitis in men with elevated prostate specific antigen. *J Urol* 164: 1550–1553.
- Potts JM, Sharma R, Pasqualotto F, Nelson D, Hall G & Agarwal A (2000) Association of ureaplasma urealyticum with abnormal reactive oxygen species levels and absence of leukocytospermia. *J Urol* 167: 1775–1778.
- Ramirez CT, Ruiz JA, Gomez AZ, Orgaz RE & Del Rio Samper S (1980) A crystallographic study of prostatic calculi. *J Urol* 124: 840–843.
- Rhodes T, Girman CJ, Jacobsen SJ, Guess HA, Hanson KA, Oesterling JE & Lieber MM (1995) Does the mode of questionnaire administration affect the reporting of urinary symptoms? *Urology* 46: 341–345.
- Ricchiuti VS, Haas CA, Seftel AD, Chelimsky T & Goldstein I (1999) Pudendal nerve injury associated with avid bicycling. *J Urol* 162: 2099–2100.
- Riedasch G, Möhring K & Ritz E (1991) Do antibody-coated bacteria prove bacterial prostatitis. *Infection* 19(Suppl 3): 141–142.
- Riley DE, Berger RE, Miner DC & Krieger JN (1998) Diverse and related 16S rRNA-encoding DNA sequences in prostate tissues of men with chronic prostatitis. *J Clin Microbiol* 36(6): 1646–1652.
- Ritter JS & Lippow C (1938) Pathological and bacteriological processes present in prostatitis and tissue reaction to therapy. *J Urol* 39: 111–117.
- Roberts RO, Bergstrahl EJ, Schmidt L & Jacobsen SJ (1996) Comparison of self reported and medical record health care utilization measures. *J Clin Epidemiol* 49: 989–995.
- Roberts RO, Lieber MM, Bostwick DG & Jacobsen SJ (1997) A review of clinical and pathological syndromes. *Urology* 49: 809–821.
- Roberts RO, Lieber MM, Rhodes T, Girman CJ, Bostwick DG & Jacobsen SJ (1998) Prevalence of a physician-assigned diagnosis of prostatitis: the Olmsted County study of urinary symptoms and health status among men. *Urology* 51: 578–584.
- Rothman KJ (1986) Measures of disease frequency. In: Rothman KJ (ed) *Modern epidemiology*. Little, Brown and Co, 8th printing, Boston/Toronto, p 23–34.
- Schaeffer AJ, Wendel EF, Dunn JK & Grayhack JT (1981) Prevalence and significance of prostatic inflammation. *J Urol* 125: 215–219.
- Schaeffer AJ & Darras FS (1990) The efficacy of norfloxacin in the treatment of chronic bacterial prostatitis refractory to trimethoprim-sulfamethoxazole and/or carbenicillin. *J Urol* 144: 690–693.
- Schatteman PHF, Hoekx L, Wyndaele JJ, Jeuris W & Van Marck E (2000) Inflammation in prostate biopsies of men without prostatic malignancy or clinical prostatitis. *Eur Urol* 37: 404–412.
- Schellhammer PF, Ladaga LE & Moriarty RP (1995) Intravesical Bacillus Calmette-Guerin for treatment of superficial transitional cell carcinoma of the prostatic urethra in association with carcinoma of the bladder. *J Urol* 153: 53–56.
- Segura JW, Opitz JL & Greene LF (1979) Prostatosis, prostatitis or pelvic floor tension myalgia? *J Urol* 122: 168–169.
- Shortliffe LMD, Wehner N & Stamey TA (1981) The detection of a local prostatic immunologic response to bacterial prostatitis. *J Urol* 125: 509–515.
- Shortliffe LMD, Sellers RG & Schachter J (1992) The characterization of nonbacterial prostatitis: search for an etiology. *J Urol* 148: 1461–1466.
- Shoskes DA, Zeitlin SI, Shahed A & Rajfer J (1999) Quercetin in men with category III chronic prostatitis: a preliminary prospective, double-blind, placebo-controlled trial. *Urology* 54: 960–963.
- Shurbaji MS, Gupta PK & Myers J (1988) Immunohistochemical demonstration of chlamydial antigens in association with prostatitis. *Mod Pathol* 1(5): 348–351.
- Solsona E, Iborra I, Ricós JV, Monrós JL, Dumont R & Almenar S (1996) Extravesical involvement in patients with bladder carcinoma in situ: biological and therapy implications. *J Urol* 155: 895–900.

- Speights VO & Brawn PN (1996) Serum prostate specific antigen level in non-specific granulomatous prostatitis. *Br J Urol* 77: 408–410.
- Staiman VR & Lowe FC (1996) Prostatic disease in HIV-infected patients. *Inf Urol* 9(2): 42–47, 60.
- Stamey TA (1973) The role of introital enterobacteria in recurrent urinary infections. *J Urol* 109: 467–472.
- Starling EH (1896) On the absorption of fluids from the connective tissue space. *J Physiol* 19: 312–326.
- Strohmaier WL & Bichler KH (2000) Comparison of symptoms, morphological, microbiological and urodynamical findings in patients with Chronic Prostatitis/ Pelvic Pain Syndrome: is it possible to differentiate separate categories? *Urol Int* 65: 112–116.
- Sutor DJ & Wooley SE (1974) The crystalline composition of prostatic calculi. *Br J Urol* 46: 533–535.
- Söndergaard G, Vetner M & Christensen PO (1987) Prostatic calculi. *Acta Pathol Microbiol Immunol Scand* 95: 141–145.
- Takechi S, Yokoyama M, Tanji N, Nishio S & Araki N (1999) Nonbacterial prostatitis caused by partial urethral obstruction in the rat. *Urol Res* 27: 346–350.
- Tammela TLJ & Kontturi MJ (1993) Urodynamic effects of finasteride in the treatment of bladder outlet obstruction due to benign prostatic hyperplasia. *J Urol* 149: 342–344.
- Tanner MA, Shoskes D, Shahed A & Pace NR (1999) Prevalence of corynebacterial 16S rRNA sequences in patients with bacterial and "nonbacterial" prostatitis. *J Clin Microbiol* 37(6): 1863–1870.
- Terai A, Ishitoya S, Mitsumori K & Ogawa O (2000) Molecular epidemiological evidence for ascending urethral infection in acute bacterial prostatitis. *J Urol* 164: 1945–1947.
- Terris MK, Macy M & Freiha FS (1997) Transrectal ultrasound appearance of prostatic granulomas secondary to *Bacillus Calmette-Guerin* instillation. *J Urol* 158: 126–127.
- Theodorou Ch, Konidaris D, Moutzouris G & Becopoulos Th (1999) The urodynamical profile of prostatodynia. *BJU Int* 84: 461–463.
- Thind P, Brandt B & Kristensen JK (1992) Assessment of voiding dysfunction in men with acute epididymitis. *Urol Int* 48: 320–322.
- True LD, Berger RE, Rothman I, Ross SO & Krieger JN (1999) Prostate histopathology and the chronic prostatitis /chronic pelvic pain syndrome: a prospective biopsy study. *J Urol* 162: 2014–2018.
- Turner PJ, Eardley I & Fowler RC (1996) The use of transrectal ultrasonography in the diagnosis of urethroprostatic reflux. *Br J Urol* 77: 314–315.
- Turner-Warwick R, Whiteside CG, Worth PHL, Milroy EJJ & Bates CP (1973) A urodynamic view of the clinical problems associated with bladder neck dysfunction and its treatment by endoscopic incision and trans-trigonal posterior prostatectomy. *Br J Urol* 45: 44–59.
- Ulleryd P, Zackrisson B, Aus G, Bergdahl S, Hugosson J & Sandberg T (1999) Prostatic involvement in men with febrile urinary tract infection as measured by prostate-specific antigen and transrectal ultrasonography. *BJU Int* 84: 470–474.
- Van Iersel MP, Witjes WPJ, de la Rosette JJMCH & Oosterhof GON (1995) Prostatic-specific antigen density: correlation with histological diagnosis of prostate cancer, benign prostatic hyperplasia and prostatitis. *Br J Urol* 76: 47–53.
- Veneziano S, Pavlica P & Mannini D (1995) Color Doppler ultrasonographic scanning in prostatitis: clinical correlation. *Eur Urol* 28: 6–9.
- Vicari E (2000) Effectiveness and limits of antimicrobial treatment on seminal leukocyte concentration and related reactive oxygen species production in patients with male accessory gland infection. *Hum Reprod* 15(12): 2536–2544.
- Wadström J, Huber P & Rutishauser G (1984) Elevation of serum prostatic acid phosphatase levels after prostatic massage. *Urology* 24(6): 550–551.

- Wasserman NF (1999) Prostatitis: clinical presentations and transrectal ultrasound findings. *Semin Roentgenol* 34(4): 325–337.
- Weidner W, Schiefer HG & Krauss H (1988) Role of Chlamydia trachomatis and Mycoplasmas in chronic prostatitis. A review. *Urol Int* 43: 167–173.
- Weidner W, Jantos Ch, Schiefer HG, Haidl G & Friedrich HJ (1991a) Semen parameters in men with and without proven chronic prostatitis. *Arch Androl* 26: 173–183.
- Weidner W, Schiefer HG, Krauss H, Jantos Ch, Friedrich HJ & Altmannsberger M (1991b) Chronic prostatitis: a thorough search for etiologically involved microorganisms in 1,461 patients. *Infection* 19 (Suppl 3): 119–125.
- Wenninger K, Heiman JR, Rothman I, Brghuis JP & Berger RE (1996) Sickness impact of the chronic nonbacterial prostatitis and its correlates. *J Urol* 155: 965–968.
- Whitesides TE Jr, Haney ThC, Morimoto K & Harada H (1975) Tissue pressure measurements as a determinant for the need of fasciotomy. *Clin Orthop* 113:43–51.
- Wiederhielm CA (1968) Dynamics of transcapillary fluid exchange. *J Gen Physiol* 52: 29–63.
- Wiederhielm CA (1970) The interstitial space. In: Fung YC, Perrone N, Anliker M (eds) *Biomechanics: its foundations and objectives*. Prentice-Hall, New Jersey, p 273–286.
- Wilson KH (1994) Detection of culture-resistant bacterial pathogens by amplification and sequencing of ribosomal DNA. *Clin Infect Dis* 18: 958–962.
- Wise GJ, Talluri GS & Marella VK (1999) Fungal infections of the genitourinary system: manifestations, diagnosis, and treatment. *Urol Clin North Am* 26(4): 701–718.
- Wishnow KI, Wehner N & Stamey TA (1982) The diagnostic value of the immunologic response in bacterial and nonbacterial prostatitis. *J Urol* 127: 689–694.
- Witschger PM & Wegmüller M (1994) Apparative muskeldruckmessung beim akuten und chronischen compartmentsyndrom. *Z Unfallchir Versich Med* 87(1): 45–51.
- Wolff H (1995) The biological significance of white blood cells in semen. *Fertil Steril* 63(6): 1143–1157.
- Worm AM & Petersen CS (1987) Transmission of chlamydial infections to sexual partners. *Genitourin Med* 63: 19–21.
- Wright ET, Chmiel JS, Grayhack JT & Schaeffer AJ (1994) Prostatic fluid inflammation in prostatitis. *J Urol* 152: 2300–2303.
- Young HH, Geraghty JT & Stevens AR (1906) Chronic prostatitis: An experimental and clinical study with an analysis of 358 cases. *The John Hopkins Hosp Repts* 13: 271–384.
- Zackrisson B, Hugosson J & Aus G (2000) Transrectal ultrasound anatomy of the prostate and seminal vesicles in healthy men. *Scand J Urol Nephrol* 34: 175–180.
- Zaichick V Y, Sviridova TV & Zaichick SV (1996) Zinc concentration in human prostatic fluid: normal, chronic prostatitis, adenoma and cancer. *Int Urol Nephrol* 28(5): 687–694.
- Zermann DH, Ishigooka M, Doggweiler R & Schmidt RA (1999) Chronic prostatitis: a myofascial pain syndrome. *Infect Urol* 12(3): 84–88.

Appendix

TIEDONKERUULOMAKE
Eturauhasen tulehdus

1

Nimi: _____

Syntymäaika: _____

1. Minkälaiseksi arvioisit terveydentilasi tällä hetkellä?

en osaa sanoa	0
erinomainen	1
hyvä	2
kohtalainen	3
huono	4

2. Haluatko parannusta tämänhetkiseen tilanteeseen?

ei	0
kyllä	1
en osaa sanoa	2

3. Mielestäni olen (tärkein):

rauhallinen	1
kiireinen	2
huolestunut	3
pikkutarkka	4
välipitämätön	5
tilanteesta yli -tyyppiä	6
sisulla kestää -tyyppiä	7
en osaa sanoa	8

4. Mikä on koulutuksesi?

peruskoulu	1
ammattikoulu tai vastaava	2
opistotutkinto ja/tai lukio	3
akateeminen tutkinto	4

5. Miten pitkään olet ollut nykyisessä ammatissasi?

_____ vuotta

6. Kuinka tyytyväinen olet nykyiseen työhösi?

erittäin tyytyväinen	1
tyytyväinen	2
jokseenkin tyytyväinen	3
tyytymätön	4
erittäin tyytymätön	5

TIEDONKERUULOMAKE
Eturaubasen tulehdus

2

7. Nykyinen työtilanteesi (päätoimesi osalta)?

vakituksessa kokopäivätyössä	1
määräaikaisessa kokopäivätyössä	2
osa-aikatyössä	3
itsenäinen ammatinharjoittaja	4
yrittäjä	5
päätoiminen opiskelija	6
työtön	7
työvoimapolitiittisessa koulutuksessa tai työllistettynä lomautettuna tai lyhennetyllä työviikolla	8
eläkkeellä	9
suorittamassa varusmiespalvelusta	10
muusta syystä työelämän ulkopuolella, miksi	11
	12

8. Missä määrin työssäsi esiintyy seuraavia tehtäviä ja asioita?

(Yksi vaihtoehto jokaiselta riviltä)

	Ei lainkaan tai hyvin vähän	Harvoin	Kohtalaisesti	Usein	Hyvin usein
raskasta ruumiillista työtä (ponnisteluja, nostoja)	0	1	2	3	4
toistuvia työliikkeitä	0	1	2	3	4
seisomista paikallaan kumaria, kiertyneitä tai muuten hankalia työasentoja	0	1	2	3	4
kävelyä paikasta toiseen kantaen taakkoja	0	1	2	3	4

9. Missä määrin työympäristössäsi esiintyy seuraavia haittatekijöitä?
(Yksi vaihtoehto jokaiselta riviltä)

	Ei lainkaan	Vähän	Jossain määrin	Paljon
kylmyys	0	1	2	3
kuumuus	0	1	2	3
lämpötilan vaihtelu	0	1	2	3
kosteus	0	1	2	3
likaisuus	0	1	2	3
pölyt, savut, höyryt tai vastaavat	0	1	2	3
liuottimet (liimat, maalit, jne.)	0	1	2	3
bakteereita, homeita ja itiöitä ilmassa	0	1	2	3
tärinä kehoon	0	1	2	3
tärinä jalkoihin	0	1	2	3
veto	0	1	2	3
allergiaa aiheuttavia aineita (eläinpöly, tupakansavu)	0	1	2	3

10. Kuinka paljon seuraavat ruumiinosat rasittuvat työssäsi?
(Yksi vaihtoehto jokaiselta riviltä)

	Ei lainkaan/ hyvin vähän	Melko vähän	Kohtalaisesti	Melko paljon	Erittäin paljon
nilkat	0	1	2	3	4
polvet	0	1	2	3	4
lonkat	0	1	2	3	4
jalat yleensä	0	1	2	3	4
selkä	0	1	2	3	4
niskahartiaseutu	0	1	2	3	4

11. Kuinka paljon ammatillisessa opetuksessa oli mielestäsi tietoa ammattiisi liittyvistä terveyshaitoista?

ei ollenkaan	0
erittäin vähän	1
vähän	2
jonkin verran	3
paljon	4
erittäin paljon	5

TIEDONKERUULOMAKE
Eturauhasen tulehdus

4

12. Oletko ollut nuorena (alle 20-vuotiaana) ulkotöissä?
ei 0
kyllä 1
en osaa sanoa 2
13. Kärsitkö silloin palelusta?
ei 0
kyllä 1
en muista 2
14. Kuinka usein olet joutunut viimeisen vuoden aikana olemaan eturauhastulehduksen takia poissa työstä?
ei 0
Poissaolokertojen määrä: _____ (kertaa) 1
15. Jos olet työtön, kuinka kauan työttömyytesi on jatkunut?
_____ vuotta
16. Oletko koskaan tupakoinut elämäsi aikana?
en 0
kyllä 1
17. Missä iässä aloitit tupakoinnin?
ikä _____ v
18. Jos olet lopettanut tupakoinnin, minkä ikäisenä lopetit?
ikä _____ v
19. Tupakoitko nykyisin (savukkeita, sikareita, piippua)?
ei lainkaan 0
kyllä, säännöllisesti 1
kyllä, satunnaisesti 2

TIEDONKERUULOMAKE
Eturauhasen tulehdus

5

20. Miten paljon poltat keskimäärin päivässä? Vastaa joka kohtaan.
- | | |
|--|---|
| ei lainkaan | 0 |
| suodatinsavukkeita _____ kpl päivässä | 1 |
| ei suodatinsavukkeita _____ kpl päivässä | 2 |
| sikaria _____ kpl päivässä | 3 |
| piippua _____ kertaa päivässä | 4 |
21. Käytätkö nykyisin edes satunnaisesti mitään alkoholijuomia (esim. olutta, viiniä, väkeviä)?
- | | |
|---|---|
| kyllä, vähintään kerran kuukaudessa | 1 |
| kyllä, harvemmin kuin kerran kuukaudessa | 2 |
| en, sillä lopetin alkoholinkäytön kokonaan
_____ vuotta sitten | 3 |
| en ole koskaan käyttänyt | 4 |

22. Kuinka usein tavallisesti juot seuraavia alkoholijuomia?

en koskaan	
- olutta	0
- viiniä	0
- väkeviä	0
kerran vuodessa tai harvemmin	
- olutta	1
- viiniä	1
- väkeviä	1
pari kertaa vuodessa	
- olutta	2
- viiniä	2
- väkeviä	2
3-4 kertaa vuodessa	
- olutta	3
- viiniä	3
- väkeviä	3
kerran parissa kuukaudessa	
- olutta	4
- viiniä	4
- väkeviä	4
kerran kuukaudessa	
- olutta	5
- viiniä	5
- väkeviä	5
pari kertaa kuukaudessa	
- olutta	6
- viiniä	6
- väkeviä	6
kerran viikossa	
- olutta	7
- viiniä	7
- väkeviä	7
muutaman kerran viikossa	
- olutta	8
- viiniä	8
- väkeviä	8
päivittäin	
- olutta	9
- viiniä	9
- väkeviä	9

TIEDONKERUULOMAKE

7

Eturauhasen tulehdus

23. Minkälaista ulkoilua harrastit nuoruudessasi?
- | | |
|----------------------|----|
| yleisurheilua | 1 |
| hiihtoa, laskettelua | 2 |
| moottoripyöräilyä | 3 |
| mopoilua | 4 |
| moottorikelkkailua | 5 |
| uintia | 6 |
| metsästystä | 7 |
| kalastusta | 8 |
| pilkkimistä | 9 |
| eräretkeilyä | 10 |
| muu (mikä?) _____ | 11 |
24. Harrastatko polkupyöräilyä?
- | | |
|-------|---|
| ei | 0 |
| kyllä | 1 |
25. Milloin harrastat pyöräilyä?
- | | |
|-----------------------------|---|
| enimmäkseen vain kesäaikaan | 1 |
| ympäri vuoden | 2 |
26. Oletko huomannut pyöräilyn pahentavan oireita?
- | | |
|---------------|---|
| ei | 0 |
| kyllä | 1 |
| en osaa sanoa | 2 |
27. Onko Sinulla ollut eturauhastulehdusta tai tulehdukseen viittaavia oireita?
- | | |
|---------------|---|
| ei | 0 |
| kyllä | 1 |
| en osaa sanoa | 2 |
28. Kuka Sinulle on ilmoittanut, että sairaus on/tai saattaa olla eturauhastulehdus?
- | | |
|------------------------|---|
| terveyskeskuslääkäri | 1 |
| sairaalan lääkäri | 2 |
| urologi | 3 |
| joku muu (kuka?) _____ | 4 |

TIEDONKERUULOMAKE
Eturauhasen tulehdus

8

29. Milloin Sinulle on kerrottu, että sairaus on/tai saattaa olla eturauhastulehdus?
- | | |
|-------------------------------|---|
| ei ole ilmoitettu | 0 |
| heti vaivojen ilmetessä | 1 |
| myöhemmin vaivojen toistuessa | 2 |
| tutkimuksen yhteydessä | 3 |
30. Oletko saanut riittävästi tietoa sairaudestasi?
- | | |
|---------------|---|
| ei | 0 |
| kyllä | 1 |
| en osaa sanoa | 2 |
31. Miten kauan eturauhasvaivasi on kestänyt tai kesti?
Vastaus: _____
32. Kuinka monta kertaa Sinulla on ollut eturauhastulehdus?
- | | |
|------------------------|---|
| en osaa sanoa | 0 |
| _____ kertaa | 1 |
| vaiva on jatkuva | 2 |
| milloin viimeksi _____ | |
33. Kuinka monta kertaa vuoden aikana sairautesi uusi?
_____ kertaa
34. Kun sairautesi uusiutuu, miten pitkään kestää kivulias jakso?
_____ päivää
35. Minä vuodenaikana sairautesi on pahimmillaan?
- | | |
|----------|---|
| talvella | 1 |
| kevällä | 2 |
| kesällä | 3 |
| syksyllä | 4 |
36. Alkoiko eturauhastulehdus jo varusmiespalveluksessa?
- | | |
|-----------|---|
| ei | 0 |
| kyllä | 1 |
| en muista | 2 |

37. Minkälaisia virtsavaivoja Sinulla esiintyy?

minulla ei ole virtsavaivoja	0
tiheävirtsausuus	1
kiire virtsalle	2
heikko suihku	3
kipu/kirvely virtsatessa	4
verta virtsassa	5
jälkitiputtelu	6
aloituksen vaikeus	7
muu _____	8

38. Mikä seuraavista syistä on mielestäsi **tärkein** syy eturauhastulehdukseesi?

kylmä (työ)ympäristö	1
vetoisa paikka	2
pakkotyöasento	3
sukupuoliyhdyntään vähyys	4
sukupuoliyhdyntään runsaus	5
huono hoito alkuvaiheessa	6
lääkärin vähättelevä suhtautuminen vaivaanne	7
oireiden vähäisyys alkuvaiheessa	8
myöhästyminen hoidon aloituksessa	9
hoito-ohjeiden laiminlyönti	10
muu (mikä?) _____	11

39. Mikä on eturauhasvaivasi pahin oire? Ympyröi vain yksi kohta.

en osaa sanoa	0
kipu	1
virtsaamisvaikeus	2
muuten huono yleiskunto	3
joku muu; mikä _____	4

40. Missä alueilla Sinulla on kipua?

ei ole ollenkaan kipua	0
kiveksien alueella	1
nivustaipeissa	2
häpyluun takana tai alavatsalla	3
siittämissä	4
välilihalla	5
ristiselän alueella	6
muuten epämääräinen olo	7
muualla / missä _____	8

TIEDONKERUULOMAKE
Eturauhasen tulehdus

10

41. Onko kivun luonne (vain yksi vaihtoehto):
- | | |
|----------------------|---|
| en osaa sanoa | 0 |
| pysyvä | 1 |
| aaltoileva | 2 |
| kouristeleva | 3 |
| kirvelevä | 4 |
| polttava | 5 |
| jomottava | 6 |
| pistävä | 7 |
| tylppä | 8 |
| muu, millainen _____ | 9 |
42. Milloin kipu on pahinta?
- | | |
|--------------------------|---|
| aamulla | 1 |
| päivällä | 2 |
| iltapäivällä | 3 |
| illalla (töiden jälkeen) | 4 |
| yöllä | 5 |
43. Milloin kipu on pahinta?
- | | |
|--|---|
| juuri ennen virtsaamista, rakko täynnä | 1 |
| virtsaamisen jälkeen | 2 |
| ulostamisen jälkeen | 3 |
| yhdynnän jälkeen | 4 |
| jokun muun olotilan jälkeen, minkälaisen _____ | 5 |
44. Milloin kipu on pahinta?
- | | |
|--------------------------|---|
| ulkotoiminnan jälkeen | 1 |
| pitkän istumisen jälkeen | 2 |
| automatkan jälkeen | 3 |
| saunan jälkeen | 4 |
| muu (mikä?) _____ | 5 |
45. Onko Sinulla esiintynyt lämpöä (kuumetta) eturauhasvaivojen yhteydessä?
- | | |
|------------------|---|
| ei | 0 |
| kyllä | 1 |
| - lämpöä _____ ° | |
46. Onko Sinulla kylmäntunnetta sukuelinten alueella?
- | | |
|-------|---|
| ei | 0 |
| kyllä | 1 |

TIEDONKERUULOMAKE
Eturauhasen tulehdus

11

47. Onko Sinulla lämmöntunnetta sukuelinten alueella?
- | | |
|-------|---|
| ei | 0 |
| kyllä | 1 |
48. Onko samanlaisia eturauhasvaivoja ollut myös sukunne muilla miespuolisilla jäsenillä?
- | | |
|------------------------------|---|
| ei | 0 |
| kyllä (kuinka monella) _____ | 1 |
| en osaa sanoa | 2 |
49. Kenellä on esiintynyt (isä, veli, setä jnc.) _____
50. Kärsitkö ummetuksesta?
- | | |
|---------------|---|
| ei | 0 |
| kyllä | 1 |
| en osaa sanoa | 2 |
51. Pahentaako ummetus mielestäsi eturauhasvaivaasi?
- | | |
|---------------|---|
| ei | 0 |
| kyllä | 1 |
| en osaa sanoa | 2 |
52. Esiintyykö Sinulla jalkojen palelemista?
- | | |
|---------------|---|
| ei | 0 |
| kyllä | 1 |
| en osaa sanoa | 2 |
53. Oletko mieluummin yksin yleisessä WC:ssä virtsatessasi?
- | | |
|---------------|---|
| ei | 0 |
| kyllä | 1 |
| en osaa sanoa | 2 |
54. Oletko mahdollisesti työn luonteen tai muun takia joutunut pidättämään virtsaamista usein pitkään (kestorajoilla)?
- | | |
|---------------|---|
| ei | 0 |
| kyllä | 1 |
| en osaa sanoa | 2 |

55. Onko Sinulla esiintynyt päiväkastelua (tahaton virtsankarkailu housuihin päivällä) kuuden ikävuoden jälkeen?
- | | | |
|---------------|---|-------------------------------------|
| ei | 0 | |
| kyllä | 1 | kuinka vanhaksi: _____ (vuotiaaksi) |
| en osaa sanoa | 2 | |
56. Onko Sinulla esiintynyt yökastelua (vuoteenkastelua) kuuden ikävuoden jälkeen?
- | | | |
|---------------|---|-------------------------------------|
| ei | 0 | |
| kyllä | 1 | kuinka vanhaksi: _____ (vuotiaaksi) |
| en osaa sanoa | 2 | |
57. Pelkäätkö, että Sinulla on mahdollisesti eturauhassyöpä?
- | | | |
|---------------|---|--|
| ei | 0 | |
| kyllä | 1 | |
| en osaa sanoa | 2 | |
58. Onko Sinulla koskaan ollut tästä sairaudesta johtuen itsetuhoajatuksia?
- | | | |
|---------------|---|--|
| ei | 0 | |
| kyllä | 1 | |
| en osaa sanoa | 2 | |
59. Kuinka monen lääkärin luona olet käynyt eturauhastulehduksen vuoksi?
Lukumäärä _____
60. Miten useasti haluaisit tarkastuksen tapahtuvan vuodessa?
_____ kertaa
61. Haluaisitko säännöllisiä tarkastuksia lääkärillä, vaikka vaivoja ei olisikaan?
- | | | |
|---------------|---|--|
| ei | 0 | |
| kyllä | 1 | |
| en osaa sanoa | 2 | |
62. Sovittiinko ensimmäisen lääkärissäkäynnin jälkeen jälkitarkastus?
- | | | |
|-----------|---|--|
| ei | 0 | |
| kyllä | 1 | |
| en muista | 2 | |

63. Missä haluaisit tarkastuksen tapahtuvan?
- | | |
|-----------------------------|---|
| terveyskeskuksessa | 1 |
| aluesairaalassa | 2 |
| keskussairaalassa | 3 |
| yksityislääkärillä | 4 |
| urologian erikoislääkärillä | 5 |
| muu (mikä?) _____ | 6 |
64. Minkälaisen lääkityksen sait, kun olit lääkärin vastaanotolla ja todettiin eturauhastulehdus? Merkitse lääkkeen nimi.
- | | |
|--------------------------------|---|
| ei mitään lääkitystä / ohjeita | 0 |
| kipulääke (_____) | 1 |
| antibiootti (_____) | 2 |
| rauhottava lääke (_____) | 3 |
| ohjeet istumakylvyistä | 4 |
| joku muu, mikä? _____ | 5 |
65. Kun olet käynyt lääkärillä jälkitarkastuksessa, tehtiinkö muutoksia lääkityksessä tai hoito-ohjeissa?
- | | |
|--------------|---|
| ei | 0 |
| kyllä, mitä: | 1 |
| en muista | 2 |
66. Noudatitko lääkäriltä saamiasi muita ohjeita?
- | | |
|-------------------|---|
| kirjaimellisesti | 1 |
| soveltuvien osien | 2 |
| ei lainkaan | 3 |
| en muista | 4 |
67. Käytitkö lääkäriltä saamiasi lääkkeitä?
- | | |
|----------------------------------|---|
| täysin ohjeiden mukaisesti | 1 |
| osittain ohjeiden mukaisesti | 2 |
| ei ollenkaan ohjeiden mukaisesti | 3 |
| en muista | 4 |
68. Milloin tilanne alkoi helpottaa lääkityksen aloittamisen jälkeen?
- | | |
|----------------------------|---|
| heti (1 - 2 päivää) | 1 |
| myöhemmin (yli 3 päivää) | 2 |
| ei merkittävää selvää apua | 3 |

Eturauhasen tulehdus

69. Kuinka kauan olet käyttänyt kipulääkettä yhtäjaksoisesti eturauhasvaivaasi?
_____ päivää
70. Oletko käyttänyt rauhoittavia lääkkeitä ennen sairastumistasi (krooniseen) eturauhastulehdukseen?
- | | |
|---------------------|---|
| ei | 0 |
| kyllä (mitä?) _____ | 1 |
| en osaa sanoa | 2 |
71. Joudutko käyttämään sairautesi takia unilääkettä?
- | | |
|---------------|---|
| ei | 0 |
| kyllä | 1 |
| en osaa sanoa | 2 |
72. Oletko käyttänyt jonkinlaisia kotikonsteja kivun helpottamiseksi?
- | | |
|-------------|---|
| ei | 0 |
| kyllä | 1 |
| mitä? _____ | |
73. Onko mielestäsi sairausloma tarpeellinen eturauhastulehduksessa?
- | | |
|---------------|---|
| ei | 0 |
| kyllä | 1 |
| en osaa sanoa | 2 |
74. Miten pitkä mielestäsi sairausloman pitäisi vähintään olla?
Päivien lukumäärä: _____
75. Kun olet ollut sairauslomalla, onko tilanne helpottunut?
- | | |
|---------------|---|
| ei | 0 |
| kyllä | 1 |
| en osaa sanoa | 2 |
76. Kun olet saanut hoitoa, onko tilanne helpottunut?
- | | |
|---------------|---|
| ei | 0 |
| kyllä | 1 |
| en osaa sanoa | 2 |

77. Onko Sinulle tehty leikkauksia tai toimenpiteitä rakon, alavatsan tai peräsuolen alueella ennen sairastumistasi eturauhastulehdukseen?

ei	0
kyllä	1
mitä? _____	
en muista	2

78. Onko tehty kroonisen eturauhastulehduksen hoidoksi leikkaustoimenpiteitä sairaalassa?

ei mitään	0
eturauhashöyläys	1
rakon kaulan halkaisu	2
paikallinen antibioottiruiskutus peräsuolen kautta	3
lämpöhoito, millainen _____	4
joku muu hoitotoimenpide, mikä _____	5

79. Onko tehty eturauhastulehdusta hoidettaessa ja tutkittaessa toimenpiteitä:

ei	0
verikokeita	1
virtsakoe	2
eturauhasen tutkiminen peräsuolen kautta	3
ultraäänitutkimus vatsanpeitteiden läpi	4
ultraäänitutkimus peräsuolen kautta	5
virtsarakon tähytys	6
virtsarakon toiminnan tutkimus sairaalassa	7
eturauhasnesteen näytteenotto hieromalla peräsuolen kautta	8

80. Onko virtsarakkoosi jouduttu laittamaan katetria (letkua)?

ei	0
kyllä	1
en muista	2

81. Onko annettu eturauhasen hierontaa peräsuolen kautta?

ei	0
kyllä	1
kuka? (lääkäri, vaimo, joku muu) _____	2

TIEDONKERUULOMAKE
Eturauhasen tulehdus

16

82. Oletko naimisissa ja kuinka kauan?
- | | |
|----------------------------|---|
| ei | 0 |
| kyllä (_____ vuotta) | 1 |
| avoliitossa (_____ vuotta) | 2 |
| leski (_____ vuotta) | 3 |
| eronnut (_____ vuotta) | 4 |
83. Kuinka monta lasta Sinulla on?
_____ lasta
84. Millainen on perheesi/taloutesi taloudellinen toimeentulo?
- | | |
|----------------|---|
| erittäin hyvä | 1 |
| melko hyvä | 2 |
| tydyttävä | 3 |
| melko huono | 4 |
| erittäin huono | 5 |
85. Jos et ole naimisissa tai avoliitossa, seurustelko vakituisesti?
- | | |
|-------|---|
| en | 0 |
| kyllä | 1 |
86. Oletko ollut nuoruudessasi sukupuolisesti aktiivinen?
- | | |
|---------------|---|
| ei | 0 |
| kyllä | 1 |
| en osaa sanoa | 2 |
87. Minkä ikäisenä aloitit säännöllisen sukupuolielämän?
_____ vuotiaana
88. Oletko harrastanut ja/tai harrastatko itsetydytystä?
- | | |
|---|---|
| ei | 0 |
| kyllä | |
| - säännöllisesti (miten useasti?) _____ | 1 |
| - satunnaisesti | 2 |
| en ota kantaa | 3 |
89. Harrastatko satunnaisia sukupuolisuhteita?
- | | |
|---------------|---|
| ei | 0 |
| kyllä | 1 |
| en ota kantaa | 2 |

TIEDONKERUULOMAKE
Eturauhasen tulehdus

17

90. Jos Sinulla on satunnaisia sukupuolisuhteita, käytätkö suojausta (kondomia)?
- | | |
|---------------|---|
| ei | 0 |
| kyllä | 1 |
| en ota kantaa | 2 |
91. Sairastuttuasi krooniseen eturauhastulehdukseen oletko huomannut vaikutusta sukupuoli-elämääsi?
- | | |
|-----------------------------|---|
| ei muutosta | 0 |
| haluttomuus lisääntynyt | 1 |
| kyvykyys heikentynyt | 2 |
| joku muu muutos, mikä _____ | 3 |
| en osaa sanoa | 4 |
92. Onko sukupuolinen halukkuutesi alentunut sairauden aikana?
- | | |
|---------------|---|
| ei | 0 |
| kyllä | 1 |
| en osaa sanoa | 2 |
93. Onko Sinulla ollut sairauden aikana
- | | |
|--|---|
| kipua sukupuoliyhdyntä aikana | 1 |
| verta siemennesteessä | 2 |
| impotenssia (sukupuolista kyvyttömyyttä) | 3 |
94. Oletko sairautesi aikana joutunut pidättäytymään yhdynnästä kivun tai muun syyn vuoksi?
- | | |
|---------------|---|
| ei | 0 |
| kyllä | 1 |
| en osaa sanoa | 2 |
95. Vaikuttaako säännöllinen sukupuoliyhdyntä mielestäsi kiputilaan?
- | | |
|---------------|---|
| ei vaikutusta | 0 |
| pahentaa | 1 |
| helpottaa | 2 |
| en osaa sanoa | 3 |
96. Onko sairauden aikana siemennesteen määrä vähentynyt?
- | | |
|---------------|---|
| ei | 0 |
| kyllä | 1 |
| en osaa sanoa | 2 |

TIEDONKERUULOMAKE

18

Eturauhasen tulehdus

97. Onko mielestäsi eturauhastulehdus haitannut keskinäistä suhdetta puolisoasi kanssa?

ei	0
kyllä	1
en osaa sanoa	2

98. Onko kumppanisi kiinnittänyt huomiota eturauhasvaivaasi?

ei	0
kyllä	1
en osaa sanoa	2

99. Kumppanin huomautukset olen kokenut?

ei kokemuksia	0
tukena	1
moitteena	2
en osaa sanoa	3

100. Jos olet eronnut, onko sairautesi ollut syynä eroon?

ei	0
kyllä	1
en osaa sanoa	2

101. Onko Sinulla ollut sukupuolitauti?

ei	0
kyllä	1
en osaa sanoa	2

102. Pelkäätkö, että Sinulla on mahdollisesti sukupuolitauti?

ei	0
kyllä	1
en osaa sanoa	2