EPIDEMIOLOGICAL AND PATHOPHYSIOLOGICAL ASPECTS OF BENIGN PROSTATIC HYPERPLASIA

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EPIDEMIOLOGICAL AND PATHOPHYSIOLOGICAL ASPECTS OF BENIGN PROSTATIC HYPERPLASIA.

(EPIDEMIOLOGISCHE EN
PATHOFYSIOLOGISCHE ASPECTEN VAN
BENIGNE PROSTAATHYPERPLASIE).

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CONTENTS

INTRODUCTION AND SCOPE OF THE THESIS.

In the "old" days, an open prostatectomy was only performed in those benign prostatic hyperplasia patients who had severe symptoms and very large prostates and in those with urinary retention and severe life-threatening complications such as hydro-uretero-nephrosis, sepsis and haemorrhage. There was little or no doubt about the correctness of the diagnosis, inasmuch as it was usually made at a late point in the natural history of the disease and because it was based on very clear physical signs.

With the advent of transurethral resection of the prostate, that is the introduction of the Stern-McCarthy resectoscope in the early 30's and the Hopkins lens system, trained urologists could perform the operation quickly and with minimal morbidity and mortality [1]. This has resulted in a first shift in the indications for invasive treatment. The purpose of treatment has evolved from the preservation of lives to the relief of discomforting symptoms and the improvement of quality of life [2]. Basically, this was a good development: patients could now be treated well before severe life-threatening problems occurred. However, another result of these developments was the fact that the diagnosis was less clear in many instances, depending on how early one would like to start treating these men.

Nowadays, patients present to their doctors with a set of complaints, which are often not accompanied by clear physical signs. In modern allopathic medicine, clearly established diagnoses are formulated in anatomical and pathophysiological terms. A work-up is necessary to achieve this goal. If this shift in the indications and its consequences is not recognized, a patient with minimal or moderate complaints of prostatism will be approached as if he were a patient of the type that was typically treated in an operative fashion some decades ago. The recent interest in the use of symptom scores in the assessment of these patients is a potentially dangerous development, particularly because there is little or no correlation between symptoms and objective anatomical and physiological findings in clinical BPH patients [3].

A second shift in the indications for invasive treatment has recently taken place with the advent of many new minimally invasive treatment modalities. The patient himself can now be involved in the decision making process and in the choice of the treatment modality. Some investigators advocate the use of a patient preference algorithm [4, 5]. The basis for this philosophy is the idea that patients with minor complaints would accept a treatment modality with a smaller chance of success but with a minimal risk of complications. It becomes increasingly important to make a refined and correct diagnosis before treatment options are discussed. To make a correct anatomical and pathophysiological diagnosis, it is necessary to have a good working knowledge of "what is normal".

The first part of this thesis is therefore devoted to these aspects:

Can prostate volume as measured by transrectal ultrasound be compared to published autopsy data or are different reference values more appropriate? Which are the reference values for prostate specific antigen in the community? What is the prevalence of symptoms of BPH in the community and how are symptoms correlated with age and anatomical and physiological measures for BPH? Can an operational definition for clinical BPH be developed and what is the prevalence of BPH in the community based on such (a) definition(s)?

The second part of this thesis is devoted to pathophysiological aspects of benign prostatic hyperplasia. Changes in urethral resistance and bladder contraction strength are the most important urodynamic sequelae of BPH [6]. The relationship between benign prostatic enlargement and outflow obstruction in urodynamic terms needs further clarification. Some challenging questions that have important implications for daily practice have been addressed:

How does suboptimal prostate volume reduction, as seen in modern alternative treatment modalities, such as medical and laser treatment of BPH, affect urethral resistance? Why is the correlation between prostate volume and urodynamically determined urethral resistance parameters so weak? How does voiding efficiency quantitatively relate to age, bladder contractility and urethral resistance? Can acute retention be predicted in any way, based on urodynamic measurements?

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CHAPTER I

The Pathogenesis of benign prostatic hyperplasia.

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ABSTRACT.

The pathogenesis of benign prostatic hyperplasia (BPH) remains largely unresolved. Three major groups of theories have evolved over the years, each emphasising a possible causative mechanism. The first group of theories is based on hormonal mechanisms, such as oestrogen/androgen synergism and the dihydrotestosterone hypothesis, which is based on the failure of BPH to develop in men castrated prior to puberty. The second, the stem cell theory postulates the development of BPH through an increase in the number of stem cells or through an abnormal increase in clonal expansion of amplifying or transit cells or through a decreased rate of cell death of the mature cells. The third group of theories relates to stromal-epithelial interactions with possible roles for growth factors, the basement membrane and embryonic reawakening, which assumes a reawakening of the embryonic induction potential of prostatic stroma. These mechanisms may act in concert.

INTRODUCTION

From a clinical perspective , much interest attaches to the pathogenesis of the clinical syndrome attributed to benign prostatic hyperplasia (BPH). The first step in unravelling this problem is to understand the pathogenesis of the histopathological abnormalities of BPH.
The histological changes of nodular hyperplasia constitute various combinations of glandular and stromal proliferation, almost always accompanied by some degree of atrophy and involution. In any case, either glandular or stromal proliferation may predominate, whereas areas of atrophy and involution occur so commonly that they can be considered part of the process [1].
The clinical syndrome of BPH, is characterized by so-called obstructive and irritative symptoms also known as the symptoms of "prostatism", prostatic enlargement and bladder outflow obstruction [2]. Although almost every man who lives long enough will develop microscopic BPH, only about 50% will go on to develop macroscopic BPH, and only about 50% of the patients who develop macroscopic BPH will actually develop the clinical syndrome [3]. Decreasing the size of the prostate will not necessarily lead to fewer symptoms of prostatism. Bosch et al. have shown that the use of cyproterone acetate or the luteïnizing hormone releasing hormone agonist buserelin, leads to a 30% decrease in volume of the prostate, but that no clinically important improvement in symptoms occurred [4]. Furthermore, a spontaneous decrease in subjective symptoms does occur in about one third of patients followed for 3 years [5]. Because prostate size does not usually decrease spontaneously, it is possible for symptomatic improvement to occur even without reduction in prostatic volume. Therefore, it cannot be size alone that determines the development of the clinical syndrome. Unravelling the aetiology of pathological BPH does not necessarily mean that we will understand prostatism. However, the development of histopathological BPH is apparently the first step on the path to benign prostatic enlargement which may eventually lead to the clinical syndrome of BPH.
The pathogenesis of histopathological BPH has remained largely unresolved. Over the years, 3 major approaches that emphasize different possible causative mechanisms have evolved; these mechanisms may act in concert. There is no direct proof that any of these theories is correct with respect to the human male. These approaches are: (1) theories based on hormonal mechanisms; (2) the stem cell theory; and (3) theories relating to stromal-epithelial interactions.

THEORIES BASED ON HORMONAL MECHANISMS

The dihydrotestosterone hypothesis.

That BPH does not develop in men castrated prior to puberty points to a testicular dependence of BPH. Because androgen withdrawal leads to a reduced prostate volume, androgens, most notably dihydrotestosterone (DHT), appear to be implicated in the development and/or maintenance of BPH.
DHT is the major intracellular androgenic metabolite in the human prostate. Wilson et al. [6, 7] suggested that the development of BPH was related to an increase in prostatic DHT content, which was thought to increase with age. However,Walsh et al. [8] showed that DHT levels are no higher in BPH tissue than in normal prostatic tissue. They contended that previous reports stating the opposite were actually based on artefacts. Furthermore, abnormal prostatic growth in dogs continues despite declining serum testosterone and tissue DHT levels. Therefore, DHT is

needed for the development and maintenance of BPH but cannot be the only factor involved in its induction.

Oestrogen / androgen synergism.

For many years the synergism between oestrogen and androgen has been hypothesized as a mechanism to induce BPH. Oestrogens are produced in the male by aromatization of androstenedione (forming oestrone) or testosterone (forming oestradiol). Data on the role of oestrogens in BPH were summarized by Walsh [9]. Some of the more important arguments against oestrogen/androgen synergism as a pathogenetic factor are that BPH tissue contains fewer oestrogen receptors than does normal prostate tissue and that age-related alterations in oestrogen/androgen production are minor and definitely occur only after the onset of the pathologic process. However, the induction by oestrogen of the androgen receptor in dogs and the elevated level of nuclear androgen receptor in human BPH argue for the oestrogen/androgen synergism in a sense that oestrogens possibly sensitize the ageing prostate. In dogs with established benign prostatic hyperplasia, it has not been possible to decrease prostate size by treatment with an aromatase inhibitor [10].

In general, there is no evidence for the steroid-induced pathogenesis of BPH in the human.

THE STEM CELL THEORY

Isaacs and Coffey have proposed the stem cell theory [11]. A stem cell is defined as a cell type capable of extensive renewal despite physiologic or accidental removal or loss of cells from the population. From experimental data, these researchers concluded that the development of stem cells is androgen-sensitive until their full number has developed. This number defines the maximally attainable prostate size and is determined by testicular androgen influence during prostate development. In the rat, the full number is reached at 5% of the total life span; in the dog at 20%. Animals castrated before that number has been reached, will not show full prostate regrowth after androgen supplementation, in contrast to animals castrated after the critical period. Thereafter, the stem cells are androgen-insensitive.

Transiently proliferating cells or amplifying cells originate from stem cells and proliferate for only a limited number of cell divisions. They lead to a major amplification of the total number of cells present. Amplifying cells do not depend on hormones for their survival, but can be stimulated by androgens to clonal expansion, forming mature cells. The mature functional epithelial cells or transit cells become the majority of cells present in the prostate; these mature cells are programmed to die. The growth or size of the prostate at a particular point in time is also determined by the balance between cell growth and cell death [12]. Studies by Barrack and Berry [13] have shown that canine BPH prostates may have a lower rate of DNA synthesis although the size of these prostates is much larger than normal. These investigators also showed that oestrogens inhibit the rate of cell death in the presence of androgens.

According to these concepts, BPH could develop in 3 ways: (1) through an abnormal increase in the number of stem cells and/or (2) through an abnormal increase in clonal expansion of amplifying or transiently proliferating cells and mature cells and/or (3) a decreased rate of cell death of the mature cells. Isaacs and Coffey based their theory on data on growth rates during the development of the prostate to normal adult size, and growth rates during spontaneous development of BPH

and restoration of prostate size, after discontinuation of androgen withdrawal. The restoration rate of human BPH after discontinuation of androgen withdrawal is more than threefold faster than the growth rate during spontaneous development of BPH [11]. Furthermore, the biochemical and morphometric difference of BPH tissue from normal prostatic tissue suggests that an increased total number of cells cannot be the only mechanism operating in the pathogenesis of BPH. An abnormally increased total number of cells would only result in an enlarged prostate, i.e., more tissue but not phenotypically different from that of the normal prostate.

THEORIES RELATING TO STROMAL-EPITHELIAL INTERACTION

Embryonic reawakening.

Mc Neal [14] observed that the primary lesion of BPH was not the formation of stromal nodules, but a glandular budding and branching mechanism that gives rise to new alveoli in a small periurethral area of the prostate which he called the transition zone. He considers this acinar formation to be the expression of the reawakened "embryonic" capacity of the tissue. He further theorizes that some stromal-humoral factor might induce epithelial proliferation.
In embryonic development, androgens induce budding of the prostatic ducts into surrounding stroma. In experiments in which either intact embryonic urogenital sinus tissue or only its epithelial or mesenchymal components were implanted in adult mice prostates, Chung [15] has shown that only the mesenchyme has an inductive potential. Cunha [16] found that the mesenchyme is the target for androgenic stimulation and mediates this effect to the epithelium. However, no evidence as yet supports the idea that adult smooth muscle cells or fibroblasts have retained the capacity to induce glandular growth.

Growth factors.

Several scenarios have been postulated to explain reawakened proliferation of stromal or epithelial tissues. Lawson [17] proposes a role for basic fibroblast growth factor (bFGF), the major growth factor found in the human prostate. This factor is present in higher concentrations in BPH tissue than in normal prostate tissue. It can be modulated by androgens, oestrogens, and steroids, as well as by transforming growth factor ß (TGF-ß). Stromal cells can produce bFGF, which can bind to heparan sulfate, a glycosaminoglycan in the basement membrane. TGF-$ß_2$ and bFGF synergistically induce stromal cells to become mesenchymal-like cells. bFGF stimulates stromal and epithelial cell growth and TGF-$ß_2$ stimulates stromal cells but inhibits epithelial cells [18]. Theoretically, stromal and glandular hyperplasia could be induced by increased cellular release of these substances, either through secretion or from injured cells. Alternatively, bFGF might be released from the basement membrane by action of the enzyme heparinitase on the heparan/ bFGF complex. In tissue culture stromal cells proliferate in response to bFGF suggesting an autocrine effect [17].
Another growth factor named keratinocyte growth factor (KGF) is also produced by prostate stromal cells and is a paracrine stimulator of the growth of prostate epithelial cells [19].

Basement membrane.

Another scenario places more emphasis on the basement membrane itself; the glycosaminoglycan heparan and related substances have been shown to inhibit smooth muscle cell proliferation in

vivo and in vitro. This scenario is derived from possible analogies with fibromuscular proliferation in arterial blood vessels. Endothelial damage and removal of the antiproliferative glycosaminoglycan layer in these blood vessels leads to fibromuscular proliferation. It is therefore conceivable that an altered or declining production of extracellular matrix molecules could lead to a reduced inhibitory effect. This again could be the initiating step for fibroblast or smooth muscle cell proliferation.

DISCUSSION.

Although the aforementioned theories seem to differ in their explanation of the development of BPH, it is not unlikely that hormonal changes and aberrations in stromal-epithelial interactions act in concert in the aetiology of this disease. Although androgens are certainly needed for the maintenance of prostate epithelial cell function, there is no hard evidence that androgens alone play a direct key role in the aetiology of benign prostatic hyperplasia.
Most of the present concepts of the development of BPH have been developed on the basis of results obtained in animal research. These concepts are now being tested in human BPH. The DHT hypothesis has led to human trials of androgen withdrawal in BPH and the use of a 5-alpha-reductase inhibitor which blocks the transformation of testosterone into DHT. The fact that androgen withdrawal leads to a reversible decrease in prostate size [4], proves that androgens play some role in the development or maintenance of human BPH. Therefore, treatments aimed at reducing plasma testosterone or inhibiting androgen metabolism inside the prostate cell may be of value. If oestrogen/androgen synergism is a mechanism of importance, treatments such as aromatase inhibition, which aim at reducing oestrogen levels, should have some effect on prostate size in humans. This does, however, not seem to be the case.
Clinical research in the form of well-designed trials will have to prove or disprove these concepts in humans. Prostate size will be only one of the variables of interest in such trials. In a clinical setting, symptoms and objective measures of voiding function are even more important variables in the determination of treatment success. Future clinical research will have to establish whether a strong relation exists between volume increase and voiding dysfunction, or whether the voiding dysfunction is caused (in part) by factors unrelated to volume increase of the prostate.
Despite many years of research, the pathogenesis of histopathological BPH has remained obscure. The only two factors that are definitely known to be of importance in its onset are the presence of testes and advancing age. Direct proof is lacking regarding a definite association between BPH and any or all of the mechanistic theories postulated thus far. However, such theories do provide interesting avenues for research into the development of new treatment modalities.

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CHAPTER II

THE NATURAL HISTORY AND PREVALENCE OF BENIGN PROSTATIC HYPERPLASIA: A REVIEW

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DEFINITION OF BPH

Although the term "benign prostatic hyperplasia" was originally meant to describe histopathological changes in the prostatic gland, clinicians now use it to describe a clinical syndrome. Despite many years of research, the pathogenesis of BPH has remained obscure. The only two factors that are definitely known to be of importance in its onset are the presence of testes and advancing age [1]. In other words, one has to be a man to acquire BPH and the chances are bigger when one is older. Although there is agreement that age is the dominant determinant of BPH [2], there is no consensus on a clinical case definition. Pathologically, BPH has been characterized as a combination of atrophy and proliferation in both glands and stroma which is a result of involution of the ageing prostate that depends on trophic hormones for its maintenance [3]. It has been postulated that men with the clinical disease represent florid examples, that is individuals situated at the extreme of the gaussian distribution, of the normal ageing process of this organ. If this hypothesis is correct, clinical prostatism may be a nonselective process with a random distribution in the population at risk [3]. However, data suggesting preliminary evidence for the heritability of benign prostatic disease have been presented. In one study the pairwise concordance rate for monozygotic twins was 14.7% as opposed to 4.5% for dizygotic twins [4]. In another study, first degree male relatives of young men with BPH had a 66% cumulative lifetime risk of prostatectomy for BPH as compared to 17% among first degree relatives of control probands [5]. The small sample size in the latter study did not permit rigorous exclusion of non-genetic models. Many other factors, such as blood type, coital frequency, smoking, alcohol consumption, socio-economic status, cardiovascular status, hypertension, abnormal body mass index, diabetes mellitus and liver cirrhosis have been implicated but their role in the aetiology of BPH remains unconfirmed [6].
The most important properties of clinical BPH can be summarized as follows [7] symptoms of "prostatism", prostatic enlargement and signs of bladder outflow obstruction.

Table 1.

Symptoms included in the different published symptom score systems.

Boyarsky	Madsen-Iversen	Fowler	Danish	AUA-IPSS.
frequency	frequency	frequency	frequency	frequency
weak stream	weak stream		weak stream	weak stream
emptying	emptying		emptying	emptying
intermittency	intermittency	intermittency		intermittency
hesitancy	hesitancy		hesitancy	
	straining	straining	straining	straining
nocturia	nocturia		nocturia	nocturia
urgency	urgency		urgency	urgency
dribble	dribble	dribble		
dysuria.		dysuria	dysuria	
		incontinence (2x)	incontinence	

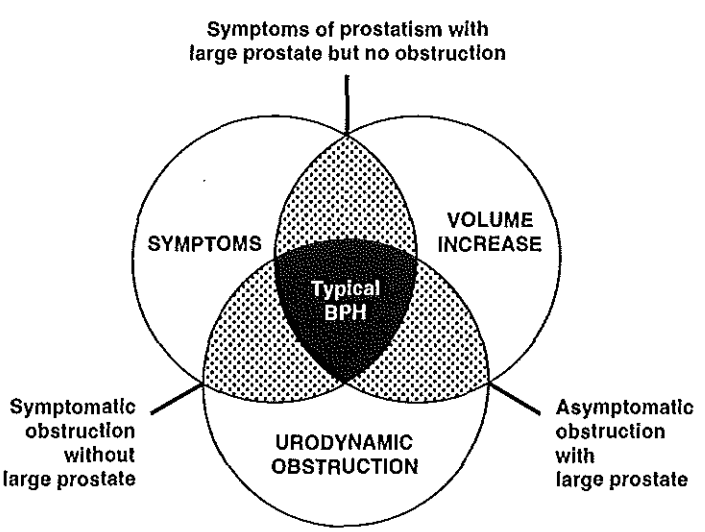
The first of these properties is a collection of the non-specific, socalled symptoms of prostatism which may or may not be caused by benign prostatic hyperplasia. Symptoms can be assessed by the use of symptom scores such as those proposed by Boyarsky [8], Madsen and Iversen [9], Fowler [10] and the Dan(ish)-Prostate symptom score [11] or the American Urological Association-International prostate symptom score [12, 13] (Table 1).

Symptoms that are used in at least 4 of these scoring systems are: weak stream, a feeling of incomplete emptying, intermittency, hesitancy/straining, nocturia and urgency. Surprisingly, urinary frequency is the only symptom used in all 5 of these well known scoring systems.

The second property is benign prostatic enlargement. Prostatic enlargement can be studied by the determination of prostate volume, for example by transrectal ultrasonometry [14, 15] or by simple estimation on digital rectal examination. Benign prostatic enlargement is often, but not always due to benign prostatic hyperplasia [16].

The third property is bladder outflow obstruction which may or may not be due to benign prostatic enlargement [7]. The best way to quantify bladder outflow obstruction is to determine urethral resistance parameters during pressure/flow studies [17]. Bladder outflow obstruction can be quantified indirectly by the urinary flow rate, although it must be realized that a decreased flow rate may be due to bladder outflow obstruction, poor detrusor contractility or a combination of these [18]. Therefore, any value of the peak flow rate may or may not be associated with obstruction. A peak flow rate of less than 10 ml/s is associated with obstruction in 88 % of the cases, whereas a peak flow rate of more than 15 ml/s is associated with obstruction in only 25 to 41 % of the cases [19, 20]. Furthermore, the test-retest reliability of the peak flow rate is poor [21].

Figure 1.
The Hald-rings show the relationship between symptoms of prostatism, prostatic enlargement and bladder outflow obstruction in men with clinical BPH.



The correlations between symptoms and prostate volume [22], symptoms and urethral resistance [23, 24, 25, 26, 27] and symptoms and other physiological measures of BPH such as peak flow rate and residual urine volume [22] are poor in men with a clinical diagnosis of BPH.

Only a minority of the patients who are treated with a clinical diagnosis of BPH, show all the aforementioned properties. It is clear that different combinations of these properties can result in a wide spectrum of clinical pictures: this is illustrated by the Hald-rings [7] in **figure 1**. Most probably these clinical pictures should not all be treated in the same fashion.

PREVALENCE OF BPH AND ITS PROPERTIES.

Definition of prevalence.

The prevalence rate of a disease is the number of current cases (old and new) of a specified disease during a specified time period divided by the estimated mid interval population at risk. Point prevalence refers to a specific point in time, and period prevalence refers to a given time interval. Prevalence rates are influenced by the incidence and the duration of a disease [28]. Since there is no agreement on a case definition for BPH, prevalence rates have been determined in various ways.

Prevalence of histopathological BPH.

Autopsy studies have looked at the occurrence of microscopic and macroscopic BPH in a histopathological sense. Berry et al. [29] have summarized the results of 5 autopsy studies that originated from various countries and found that the prevalence of microscopic pathological BPH in these populations rose steadily from less than 10 % around the age of 35 to more than 85 % around the age of 85. These data indicate that the histopathological changes that are attributed to BPH may be part of a normal ageing process rather than being due to a disease process.
Isaacs and Coffey [30] have studied the age-specific prevalence of macroscopic BPH. They summarized data from autopsy studies in which BPH was defined as an enlarged gland on macroscopic inspection and from a study that had defined BPH as an enlarged prostate on digital rectal examination. Again a gradual rise of the age-specific prevalence was found: from 2 % around the age of 35 to 53 % around the age of 85. This collective data shows that almost every man will eventually be diagnosed with microscopic BPH, provided that he attains an age that is high enough. However, only about half of the men with microscopic BPH will develop macroscopic enlargement of the gland.
In the Veterans Administration Normative Ageing Study (VANAS) [31], a cumulative incidence of prostatectomy of 29 % was found for men between 40 and 80 years. Therefore, it seems that only about half of the men with macroscopic BPH will eventually be treated by prostatectomy.

Prevalence of symptoms of prostatism.

The prevalence of the so-called symptoms of "prostatism" with or without taking bother scores into account, has been studied in several countries. An enlarged prostate does not necessarily lead to symptoms and/or bladder outflow obstruction. These individual symptoms or combinations of these symptoms are aspecific and non-pathognomonic for BPH [32] and are even found in women [33, 34]. In table 2, the age-specific prevalence rates of men with moderate to severe symptoms of prostatism in community-based population samples originating from various countries, are

summarized [35-39]. These data seem to indicate that the prevalence of moderate to severe symptoms is below 30% before the age of 55. There are considerable differences among countries; these differences may be due to population sample bias or may represent true regional differences. The results of the French community survey [38] attract attention because of the low percentage of moderately to severely symptomatic men. Sampling bias is a possible explanation for this finding; due to its novel design the true response rate in that study is unknown. Although the prevalence of symptoms may differ from one country to another, there are indications that men from different countries are bothered to the same degree by these symptoms [40].

Table 2.

Prevalence of men with moderate to severe symptoms of prostatism in studies evaluating community-based population samples of various ages.

Country	Denmark Sommer [35]	Canada Norman [36]	USA Chute [37]	France Sagnier [38]	Holland Wolfs [39]
Symptom-score	Modified Madsen	AUA-7	Rescaled AUA-7	Modified AUA-7	Modified Boyarsky
Age	20-79	50-70+	40-80	50-80	55
N	368	508	2119	2011	1692
30-39	2%				
40-49	7%		24%		
50-59	18%	15%	31%	8%	
55-59					
60-64					
55-64					25%
60-69	23%	27%	36%	14%	
65-69					
70-74					
65-74					27%
70-79		31%	44%	27%	
75					27%

Prevalence of poor flow.

The peak flow rate (Q_{max}) as a function of age was determined in a community based sample of men from Olmsted county in Minnesota, USA [41]. These data indicate that 39 % of the men between 40 to 79 years have a Q_{max} of less than 15 ml/s. This percentage increases from 24 % in men 40 to 44 years old to 69 % in men older than 75 years. More than 50 % of the men older than 65 years had peak flow rates of less than 15 ml/sec. The percentage of men failing to achieve a peak flow rate of 10 ml/s ranges from 6 to 35 %.

K-M. Jensen et al. [42] studied uroflowmetry variables in a sample of males, aged 50 years or older, drawn from the population registry. The average maximum flow rates of men without complaints

of prostatism was 13.5 (range 3.5-26.5) ml/s as opposed to 10.5 (range 4-29.5) ml/s in symptomatic males. These values were statistically not different. In a Scottish community study [43] the average Q_{max} in men between 40 to 79 years was 20.3 (SD 9) ml/s. Of 40 to 49 year old men, 14 % had a Q_{max} of less than 15 ml/s. This figure rose to 48 % among men 60 to 69 years old.
Community-based studies of the prevalence of bladder outflow obstruction in urodynamic terms, that is assessed by pressure/flow studies, have not yet been performed.

Prevalence of prostatic enlargement.

The prevalence of benign prostatic enlargement or prostate volume increase in living subjects can be assessed either by digital rectal examination (DRE) or by transrectal ultrasound. Lytton reported the age distribution of prostatic enlargement in 6975 men who underwent rectal examination in relation to life insurance examinations [44]. The prevalence of prostatic enlargement rose from 8 % between 40 to 49 years to 43 % between 70 to 79 years (see also Table 4). In the Baltimore Longitudinal Study of Ageing, the prevalence of prostatic enlargement as judged by rectal examination was somewhat higher and increased from about 20% at age 50 to about 60% at age 80 [45]. Jakobsen et al. [16] studied prostate volume by transrectal ultrasonometry. These authors found that the total volume of the prostate increased from 23.9 cm^3 between 31 to 40 years to 25.7 cm^3 between 41 to 50 years. Prostatic enlargement does not always indicate benign prostatic hyperplasia; even prostates with large volumes of up to 39.1 cm^3 can be free of histopathological signs of BPH [29], whereas small prostates can harbour adenomas [16].

Prevalence of clinical BPH.

Several studies, often based on debatable definitions have been done. These studies as follows are on:

1) Prostatectomy rates.

In the Veterans Administration Normative Ageing Study a cumulative prostatectomy rate of 29 per cent was found for men between 40 and 80 years [31]. However, prostatectomy rates are a dubious criterion: there are large differences in rates among different countries and among different areas in one country [46, 47]. These differences are determined by differences in accessibility and utilization of health care facilities, as well as differing treatment algorithms among surgeons.

Table 3.

The increase in the number of prostatectomies and the number of men older than 55 years between 1985 and 1989 in The Netherlands.

	Number prostate operations (TURP + Open prostatectomy)	Number of men >55 yrs. (x 1000)
1985	14605	1373
1989	18181	1425
Increase	24,5%	3,8%

In the Netherlands the number of prostate operations showed an increase of 24.5% between 1985 and 1989 (Table 3). This increase is not easy to explain because the percentage of men

older than 55 years increased by only 3.8% in the same time interval. Alternative explanations may be changing treatment algorithms or a lower threshold in the health care seeking behaviour of the men of this age interval. An indication that the latter alternative has been important, is found in the results of the "IMS-urologen studie" which showed that the number of first outpatient visits for BPH in urology practices showed an increase of 71% between 1982 and 1989 [48]. Another explanation may be a more pronounced increase of the number of men with a very old age.

2) *The prevalence of clinical BPH.*

Such studies usually combine multiple parameters. In the Baltimore longitudinal study of ageing (BLSA) the diagnosis of BPH was based on history and physical examination; however, the definition of BPH remains vague and unclear in this study. The prevalence of clinical BPH rose from 26.5% between 41 to 50 years to 85% above the age of 80 [45].

The criteria used in the Veterans Administration Normative Ageing Study (VANAS) were an enlarged prostate on physical examination or the presence of symptoms of prostatism if these could not be explained by another diagnosis than BPH. In this study the cumulative probability that a 40 year old man who is initially free of benign prostatic hyperplasia and lives to age 80 will develop symptoms or a physical finding was 77.7% [31].

Recently, Garraway et al [43] studied men between 40 to 79 years who were registered with a health centre in the town of Bridge of Allen (Scotland). These men were asked to complete a symptom score questionnaire and to void in a flow meter. Those with a symptom score of 11 or more points on a scale of 48 (modified Fowler scoring system) and / or a Q_{max} of less than 15 ml/sec and those who did not manage to void a volume of at least 150 ml on three different occasions, were invited to attend a clinic for a transrectal ultrasound examination of the prostate. If a prostate volume of more than 20 ml was found, a diagnosis of BPH was made. In this study a high prevalence of BPH was found: it rose from 13.8 % in men between 40 to 49 years to 40% between 70 to 79 years.

In a follow-up study [49] involving a second health centre, the same authors confirmed the high prevalence of BPH and divided the men in three groups:Men "who did not need treatment" (39.5%), men "with whom treatment options were discussed" (50.5%) and men "who were advised to seek treatment for BPH" (10%). A TURP was performed in 12.9% of the men in the second group and in 83.3% of the men in the third group. This means that an operation was eventually performed in only 2.4% of the original population of 2497 men. The latter figure contrasts sharply with the reported prevalence rates.

Table 4.

Age-specific prevalence of "BPH" based on various definitions.

Country Pop.type Criteria	Scotland [43] Community Symptoms $\pm Q_{max}$ (+TRUS)	USA [44] Life Insurance DRE	USA [45] Community Symptoms +DRE	Various [28] Autopsy Pathology
50-59	24	20	50	42
60-69	43	35	69	71
70-79	40	43	79	82

Age-specific prevalence rates based on various definitions are summarized in table 4. The rates for clinical BPH from the Baltimore Longitudinal study of Ageing [45] were generated using a vague definition that combined history and physical examination and almost exactly matched the prevalence of microscopic BPH.
An enlarged prostate on digital rectal examination as the only criterion for BPH, which was used in life insurance examinations [44], resulted in rates that matched autopsy rates for macroscopic BPH [30].

HOW TO STUDY THE NATURAL HISTORY OF A DISEASE.

The natural history of a disease outlines its evolution without medical intervention. The following premises should ideally be fulfilled when studying the natural history of a disease [50]:

1. There should be agreement on the definition of a "case".
2. An age close to, but prior to the usual onset of the disease has to be defined.
3. A community-based cohort, based on that age, has to be created.
4. That cohort then has to be followed prospectively, without medical intervention.
5. During this follow-up regular standardized evaluations should be done.

Since there is no generally accepted definition for benign prostatic hyperplasia (BPH), it is difficult to describe its natural history and determine its true prevalence and incidence.

NATURAL HISTORY OF BPH AND ITS PROPERTIES.

Studies in community-based cohorts.

Natural history of symptoms of prostatism.

In 1993 Garraway and co-workers reported on the one year follow-up of 266 men with untreated BPH [51]. These men had been part of their original BPH-prevalence study in a Scottish community that was published 2 years earlier [43]. Improvements in individual symptoms were seen in 8 to 26% of the men depending on the symptom. Symptomatic deterioration was seen in 18 to 35% of the men, again, depending on the symptom. One quarter of the men was bothered less and about half of the men had the same level of overall bother after one year. (table 5)
Another community study is being conducted in Olmsted county, Minnesota.Men included in this study, were sent follow-up questionnaires after an average of 18 months after the initial evaluation [52]. Overall, symptom frequency scores had decreased slightly in younger men and had increased slightly in men over 70. However, as in the Scottish study, bother scores did not change significantly with time.

Natural history of poor flow.

The peak flow rate as a function of age was determined in a community based sample of men from Olmsted county in Minnesota, USA [41]. The decrease in peak flow rate per decade was about 2 ml/sec on average. These data are cross-sectional and do not represent changes with time in individual men. In the Scottish community study [43] the decrease per decade was between 0.3 and 1.7 ml/sec. A peculiar finding in the follow-up examination of the Scottish men was that 36% of the men who initially had a Q_{max} of less than 15 ml/s raised their peak flow above this

cut-off point after one year follow-up [51]; this finding emphasizes the cross-sectional nature of the age-specific flow rate data. These authors had previously defined BPH as an enlargement of the prostate gland above a volume of 20 ml in the presence of moderate to severe symptoms and / or a peak flow rate of less than 15 ml/sec. It is important to note the last part of the definition : "symptoms and/or a low flow rate". This means that men were classified as BPH cases if the flow rate was less than 15 ml/sec, even if they had less than moderate symptoms. Therefore, if the prevalence rates for BPH would have been recalculated after one year the prevalence rates most certainly would have dropped.

Natural history of prostatic enlargement.
One study on the longitudinal evolution of prostate volume [53] has been reported in Japanese men. This study involved only 16 men who were followed for 7 years. There seemed to be a subgroup of men (3 out of 5 men) between 55 to 70 years who showed a rapid growth of the prostate. In all other men no clear growth could be detected in this time interval.

Natural history of clinical BPH in the community.
The natural history of clinical BPH has not been studied in community-based cohorts.

Studies in clinical cohorts.

Natural history of symptoms of prostatism and clinical BPH.
Spontaneous fluctuations in the severity of symptoms have been reported in clinical cohorts just as in the community-based cohorts. Elderly patients followed in a "watchful-waiting" protocol by Diokno et al. have shown spontaneous improvement in a considerable percentage. Of patients with severe, moderate and minor symptoms, 10%, 13.2% and 37.5%, respectively, have been reported to be asymptomatic after one year of follow-up. Symptomatic progression from minor to severe and from moderate to severe complaints was seen in 12.5% and 31.6% of the cases, respectively [54]. The symptomatic outcome in 3 other clinical cohorts is summarized in table 5.

Table 5.
Symptomatic outcome in a community-based cohort [51] and in 3 clinical cohorts [55, 56, 57] of men with symptomatic "BPH" followed without treatment.

Author	N	Fol-up (yrs.)	Better	Same	Worse
Garraway [51]	266				
a. indiv. symptoms		1	8-26%	44-71%	18-35%
b. overall bother		1	25%	48%	27%
Craigen [55]	123	4-6	26%	28%	46%
Ball [56]	107	5	29%	47%	24%
Barham [57]	107	1-9	12%	66%	22%

In 1969 Craigen [55] reported on a prospectively studied, but highly selected group of BPH patients, 123 of these men had symptoms of prostatism at baseline. These men were followed for 4 to 6 years. Although the patients were poorly described, this study suggested that a certain percentage of men may improve without treatment. This was later confirmed in a study by Ball and associates [56] who followed 107 BPH patients who did not undergo surgery on poorly defined clinical grounds. Half of these patients were obstructed urodynamically. These men were followed for 5 years. Recently Barham reviewed patients who had been on a waiting list for TURP for an average of 3 years [57]. After reassessment, 29% of the patients were discharged from the waiting list. These collective data indicate that only 25 to 50% of the men with clinical BPH deteriorate with long-term follow-up.
In addition, some preliminary 1 year follow-up data from the VA co-operative study that compares watchful waiting and TURP in patients with moderate symptoms, are available [58]. These data indicate that urinary symptoms, urodynamic parameters and quality of life do not worsen in men who delay this operation for one year. TURP, however, had a higher efficacy than watchful waiting, but 5 of 6 men treated with watchful waiting did not fail this treatment.

CONCLUSIONS.

Despite the fact that there is no generally accepted case definition of BPH and that the prevalence is probably somewhat overestimated in many studies, it is clear that this is an important health problem. To determine the true impact on health care facilities it is necessary to develop (a) better case definition(s) in order to make a better estimate of the number of men that truly needs therapeutic intervention. As a first step towards this goal, the normal values of several parameters associated with BPH must be determined in community-based samples of men.

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PART A.

EPIDEMIOLOGICAL ASPECTS OF BENIGN PROSTATIC HYPERPLASIA.

CHAPTER III

PARAMETERS OF PROSTATE VOLUME AND SHAPE IN A COMMUNITY-BASED POPULATION OF MEN 55 TO 74 YEARS OLD.

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ABSTRACT.

Parameters of prostate volume and shape were determined in a community-based population of 502 men between 55 to 74 years old who had not undergone a previous prostate operation and did not suffer from prostatic cancer. The volumes of the total prostate and of the central relatively hypoechoic part of the prostate were determined. Of all men in this age range 95% had a total prostate volume of more than 20 cm^3. Moderate correlations between age and both volume measurements were found ($r=0.26$, $p<0.0001$ and $r=0.34$, $p<0.0001$, respectively). The percentage increase per year of central hypoechoic volume (3.5%) was higher than that of total prostatic volume (2%). The average doubling time of total prostatic volume and central hypoechoic volume was calculated to be 35 and 20 years, respectively. The roundness of the prostate as expressed by width-to-height ratio at the largest transverse section of the prostate correlated poorly with age ($r= -0.13$; $p=0.004$). The average total prostate volumes as measured by transrectal ultrasound were 21-28% higher than reported average volumes measured at autopsy in men in the same age range.

INTRODUCTION.

Our knowledge about the natural history of benign prostatic hyperplasia (BPH) and age-related growth of the human prostate is limited.Most of the available information originates from the review of multiple autopsy studies [1]. Although valuable data have been generated by this approach, these studies do not represent community-based samples of men. Furthermore, the values for prostate volume derived from autopsy studies are a questionable reference in the study of living men. At autopsy, prostate weights or volumes might differ significantly from the volumes determined by transrectal ultrasonometry in living men. Reference values for prostate volume must be established by the technique that currently represents the standard in prostate volume determination, that is by transrectal ultrasound.Such studies can also expand our knowledge of the natural history of BPH.

A few studies have addressed the determination of prostate volumes in groups of living men. Jakobsen et al. [2] studied 175 men by transrectal ultrasound: 115 were randomly selected from the population registry, whereas the other 60 were studied prior to vasectomy. In that study volumes were mainly measured in men between 30 and 50 years old (only 16 men were older than 50 years and only 14 men were younger than 30 years). Collins et al. [3] measured volumes in 430 men 40 to 79 years old by transrectal ultrasound. Unfortunately, the men in the latter study were selected on the basis of the presence of moderate to severe symptoms of prostatism and/or a maximum flow rate of less than 15 ml/s. Therefore, these data do not accurately reflect the actual situation in a community-based population. We [4] and others [5] reported preliminarily on data from a community-based sample of men.

When prostate volumes and weights are measured as an aid in the determination of the prevalence of clinical BPH, it should be realized that an increased prostate volume or size alone is not sufficient for the diagnosis of BPH. Prostates as large 40 gm can be histologically normal [1] whereas those as small as 15 gm may show evidence of pathological BPH [1], and there is a considerable overlap in size between normal and adenomatous prostates [1,6].

In the Netherlands 96% of all patients who are hospitalized with BPH as the main diagnosis are older than 55 years [7]. From this age on the problem apparently becomes clinically important, although the development of microscopic evidence of BPH may have started much earlier [1].

We describe prostate volume and shape in a community-based sample of men aged 55 to 74 years old.

MATERIAL AND METHODS.

Study design.

The community-based data on prostate volume and shape presented in this chapter were collected as part of a randomized pilot study of the value of screening versus no-screening for prostate cancer.

After taking care of the appropriate legal regulations, the municipal authorities of the city of Rotterdam created a database based upon the population registry, that contained the information necessary to contact all men 55 to 74 years old residing in 4 different districts of the city. Subsequently, invitations were sent by mail.Of the men who were invited, 1186 agreed to participate in the study. The response rates for the 4 five-year age intervals between 55 and 74

years varied between 33 to 36.3%, resulting in a community-based population with a slight overrepresentation of men between 60 to 64 years old and a slight underrepresentation of men 55 to 59 years old. (Table 1) Part of this effect is explained by ageing of the original data base.An enquiry among participants and non-participants which was conducted at the end of this study by the department of epidemiology of the community health services of the City of Rotterdam, has shown that participants were not more symptomatic or less symptomatic than non-participants [8].

Table 1.

Frequency distribution of men in 4 consecutive age groups of 55-74 years in the general population of Rotterdam at creation of the database and in the population of participants at the time they were actually seen for the study.

Age (yrs.)	% Total population	% Participants
55-59	25.8	20.9
60-64	27.9	32.0
65-69	25.6	26.1
70-74	20.7	21.0
Totals	**100**	**100**

In all of these men demographic and other data pertinent to the screening study were recorded. A serum prostate specific antigen (PSA) determination (Hybritech assay.) was used as a pre-screening tool. If the PSA value was greater than 10 ng/ml, a diagnostic evaluation was advised because of the high probability of prostate cancer [9] and the person was excluded from randomization. This was the case in 30 out of 1186 men (2.5% of the total study-population; 15 of these 30 men were ultimately diagnosed with prostate cancer).

The remaining 1156 men were randomly assigned to a screening or a no screening group. In the latter group no further studies were done. The 554 men assigned to the screening group were further examined by digital rectal examination and transrectal ultrasound of the prostate. If the findings on digital rectal examination and / or transrectal ultrasound were abnormal, prostate biopsies were taken. Height and body weight were recorded and the body mass index was calculated according to the formula: body weight/height^2 (kg/m^2). An index of 20 to 25 kg/m^2 is considered to be normal, while a value greater than 25 kg/m^2 indicates overweight. Men who subsequently had biopsy proved prostatic cancer (10), those who had undergone a prostate operation in the past (39) and men who refused transrectal ultrasound examination (3) were excluded from the present evaluation. Thus, a community-based population of 502 persons in whom prostate cancer had been excluded with reasonable certainty and who had not previously undergone a prostate operation was established.

Procedures:

Prostate volume and shape.

A 7 MHz Bruel and Kjaer multiplane sector scanning probe was used to measure prostate volumes with the transrectal planimetric technique [6]. This method involves measuring the surface area of transverse sections taken through the prostate at 5 mm intervals. The average of two surface areas multiplied by 5 mm provides the volume for each step and the cumulative volume allows the total prostatic volume (cm^3) to be derived. Because the specific gravity of prostatic tissue is 1.050 [10], the prostatic volume in cubic centimetres as determined by the ultrasound method was directly compared to prostate weight in grams when comparisons were made with studies that used weight as the parameter for prostate size. The same technique was used to determine the volume of the central prostate. The reliability of this method was shown in a previous study of the intra-observer and inter-observer error of the planimetric technique [11]. The ultrasound image of the prostate does not correspond exactly to the zone description of McNeal [12]. Villers et al. reported that the McNeal central and peripheral zones cannot be easily demarcated as separate regions on transrectal ultrasound images of the prostate, and that these 2 glandular areas are ultrasonically of a lighter shade of grey than the transition zone [14]. They also found that the peripheral and the central zones are clearly of a lighter shade of grey than the preprostatic sphincter, the periurethral glands and the fibromuscular stroma. The peripheral area of the gland (peripheral zone plus central zone) is therefore, relatively hyperechoic compared to the elements of the central area of the gland (transition zone, preprostatic sphincter and periurethral glands)[13]. Others have claimed that in the normal prostate, the transition zone is ultrasonically incorporated in the relatively hyperechoic peripheral area and that in men with prostatic adenoma the periurethral glandular area blends ultrasonically with the adenoma tissue [2, 6, 14, 15].

To circumvent this potential source of confusion we named the relatively hypoechoic area the central part of the prostate, with its volume being referred to as central hypoechoic volume. A further separation of this central part in the transition zone and periurethral glandular area is not relevant from a clinical viewpoint because both areas will be enucleated together during retropubic prostatectomy. Furthermore, McNeal stated that BPH arises in the transition zone (lateral lobes) and in the periurethral glands of the proximal urethral wall (median lobe)[12]. Therefore, when studying the development of BPH and volume increase in the population, it is appropriate to measure the volume of the entire central area of the prostate, as opposed to the total volume of the prostate and volume of the peripheral area. In 47 of the 502 subjects the volume of the central portion was not determined separately due to an aselect temporary deviation from the protocol by one of the ultrasonographers.

We also measured the width and height at the area of greatest transverse diameter in the axial plane. The ratio of width to height was used to describe the shape of the prostate and its possible change with increasing age [6].

Statistical analysis:

Least squares regression analysis was used to evaluate the relationships among age, body mass index and prostate volume parameters. In this analysis the volume parameters were logarithmically transformed to obtain approximate normal distributions. The Chi-square test for trend was used to assess whether percentages increased or decreased in relation to an ordered classification (that is age groups). The level of statistical significance was set at p=0.05 (two-tailed).

RESULTS.

The frequency distribution of the total prostate volumes is skewed towards larger volumes (fig. 1A). The volumes appeared to be roughly log normally distributed (fig. 1B). The same pattern is noted for the volume of the central prostate: a skewed distribution to the right and again an approximately normal distribution of the logarithmic values of the volumes (fig. 1C and 1D). The mean and median values of the total prostate volume and the central prostate volume for the different age groups are summarized in table 2.

Although the mean volumes for the various age groups show an increase with increasing age, the correlation between volume of the total prostate and age is not strong ($r=0.26$; $p<0.0001$, fig. 2A). An equally moderate correlation is found between volume of the central hypoechoic prostate and age ($r=0.34$; $p<0.0001$, fig. 2B). Only 11% ($r^2=0.11$) of the variation in volume of the central prostate can be attributed to the variation in age.

Figure 1.

A. Frequency distribution of total prostate volume (Vol_T).2.5% and 97.5% limits are 18.1 and 76.8 cm^3, respectively.
B. Frequency distribution of log total prostate volume.
C. Frequency distribution of volume of the central prostate (Vol_C).
D. Frequency distribution of log central prostate volume.

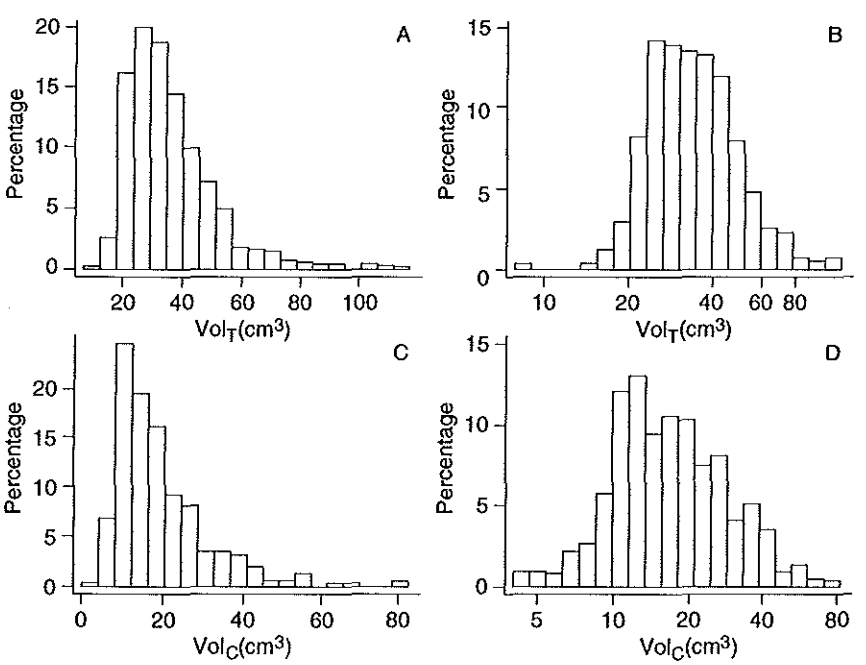


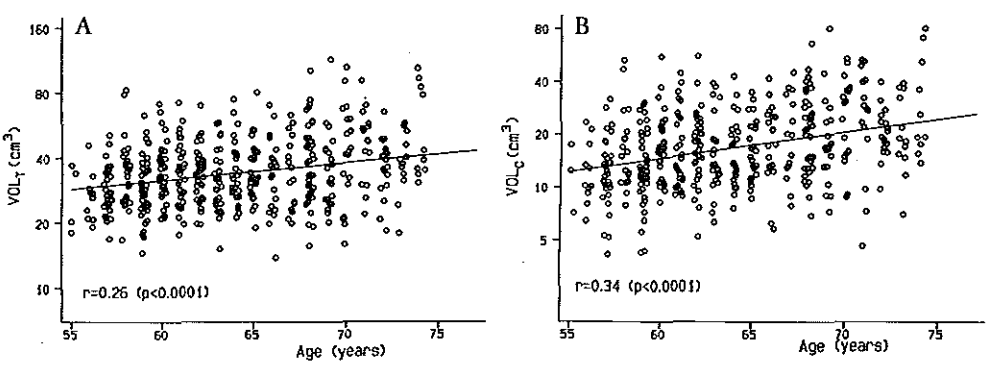
Table 2.

Mean and median values (± Standard deviation) by age for volume of the total and central prostate.

Age (yrs.)	Total prostate			Central prostate		
	N	Vol. (cm^3)		N	Vol. (cm^3)	
		Median	Mean±SD		Median	Mean±SD
55-59	124	28.1	30.9±10.9	109	12.2	14.5± 7.9
60-64	162	33.3	35.3±11.6	149	15.8	18.1± 9.2
65-69	132	33.0	37.9±16.1	118	17.5	21.0±11.8
70-74	84	41.6	44.9±20.6	79	21.9	26.5±15.0

Figure 2.

Scattergrams of prostate volumes versus age, with least squares regression lines.
A. total prostate volume (Vol_T).
B. volume of the central portion of the prostate (Vol_C).



The volume of the peripheral zone was calculated by subtracting central hypoechoic volume from total prostatic volume. Volume of the peripheral zone did not significantly correlate with age (r=0.07; p=0.12). Therefore, it appears that the observed increase in total prostatic volume with advancing age is mainly due to an increase in volume of the central hypoechoic prostate.
From the slope of the regression lines (fig. 2) the average per cent increase of total prostatic volume and the volume of the central hypoechoic part of the gland per year can be calculated. In men 55 to 74 years old the average per cent increase per year of the volume of the central hypoechoic part of the prostate is 3.5% and is about twice as high as the 2% increase per year of the total prostatic volume. The average doubling times for the volume of the total prostate and the central portion of the prostate were calculated to be 35 and 20 years, respectively.
Almost all men (95%) 55 and 74 years old have a prostate volume of greater than 20 cm^3. Therefore, the percentage of all men with a prostate volume of greater than 20 cm^3 does not

increase significantly with age. However, the percentage of all men with a volume of greater than 30 cm^3 significantly increases with age as well as the percentage of all men with volumes of greater than 40 and 50 cm^3 (table 3).

Table 3.

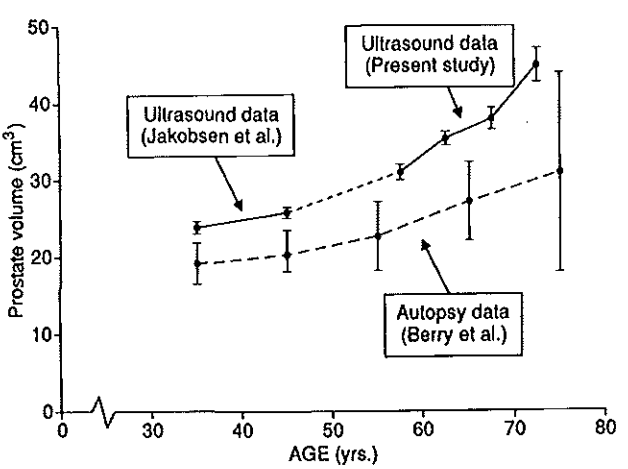
Percentages of all men with total prostate volume more than 20, more than 30, more than 40, and more than 50 cm^3, respectively, per 5-year age group.

	% with volume (cm^3):			
Age (yrs.)	more than 20	more than 30	more than 40	more than 50
55-59	93	43	15	5
60-64	98	62	28	12
65-69	96	63	36	17
70-74	94	76	55	33
Totals	95	60	31	15
p-value	0.77	<0.0001	<0.0001	<0.0001

P-values refer to test for trend.
For numbers of patients in whom total prostatic volume was determined per age group see table 2.

Figure 3.

Age-related average volumes of the prostate based on autopsy studies (data from Berry et al. [1]) compared to average volumes based on transrectal ultrasound measurements (data from Jakobsen et al. [2] and present study). Error bars indicate standard error of mean.



If the average prostate volumes determined in this study are plotted against age as has been done by Berry et al. [1] for average prostate weights determined at autopsy (fig. 3), it is apparent that the 2 curves diverge and that prostate volumes measured by transrectal ultrasound in living men are on average larger than the volumes measured at autopsy. Data from the study of Jakobsen et al. [2] (table 4) are added in this figure to show that this difference is also present in the age range of 30 to 50 years. The absolute difference between average volumes measured at autopsy and by transrectal ultrasound is not constant over the entire age range (table 4).

Table 4.

Mean prostate volumes/weights (± standard error of mean) by age-group.

Transrectal ultrasound data / Total Prostate			Autopsy data* / Total prostate		
Age (yrs)	No.	Vol.(cm^3)$	Age (yrs.)	No.	Weight (gm)$
31-40	75#	23.9 ± 0.8	31-40	130	19.1 ± 2.7
41-50	70#	25.7 ± 0.7	41-50	130	20.2 ± 3.2
			51-60	161	22.6 ± 4.5
55-59	124	30.9 ± 1.0			
			61-70	141	27.1 ± 5.1
60-64	162	35.3 ± 0.9			
65-69	132	37.9 ± 1.4			
			71-80	105	30.9 ± 13.0
70-74	84	44.9 ± 2.2			

Total prostate weights in grams as measured at autopsy are compared to total prostate volume in cm^3 as measured by transrectal ultrasound.

* Data from Berry et al. [1]. # Data from Jakobsen et al. [2]. $ Mean ± Standard error.

An average difference of about 5 gm in the 31 to 40 years old group has been found [2], while this difference amounts to about 12 gm in men older than 70 years in our study. The differences in volume between measurements at autopsy and at transrectal ultrasound over the entire age range vary only moderately between 21 and 28%. This difference could be explained by desiccation or by the fact that there is no blood circulation in the prostate in the post-mortem situation. Alternative explanations may be the poor condition of the subjects just before post-mortem examination (autopsy selection bias) or the ultrasonographic technique per se.

It has been reported that the normal prostate in young men exhibits a more or less triangular shape on transverse section [16,17]. It also has been reported that the prostate becomes more rounded and ellipsoid in shape as it enlarges because the anterior-posterior diameter (height) increases more than the transverse diameter (width)[16]. The ratio of width-to-height should, therefore, decrease with age if a change in shape of this type is related to an age-dependent volume increase. On regression analysis a negative correlation between width-to-height ratio and age is found but this correlation is weak (r=-0.13; p=0.004). The correlation between prostate volume and volume of the central prostate with the body mass index is weak as well (r=0.14, p=0.001 and r=0.12, p=0.008, respectively). Less than 2% of the variation in volume is explained by the variation in body mass index.

DISCUSSION AND CONCLUSIONS.

Our study represents to our knowledge the first analysis of total and central prostate volumes and prostate shape in a community-based population of men without prostate cancer and without a history of a prostate operation. Men with such a history had to be excluded from the analysis inasmuch as the natural history had been interrupted.It would have been interesting to know the resected weights and the exact dates of the operations because the necessary exclusion of these men may have introduced some bias in the determination of normal volumes. Of the initial group of 554 screened men 39 (7%) had previously undergone a prostate operation.

Our study shows that prostatic growth with age is a complex process. The average growth rates can be calculated for the total prostate volume and for the central portion of the gland, which shows that the central portion of the gland on average grows faster (3.5% per year) than the total prostate (2% per year) among men 55 to 74 years old. This finding is compatible with the theory that the transition zone is the area where BPH mainly occurs [12]. The average doubling times for the volume of the total prostate and the central prostate were calculated to be 35 and 20 years, respectively. The growth rates reported by Jakobsen et al. [1] in men who where mainly 30 to 50 years old are slower, with a rate of 0.8% per year for the total prostate and 1.5% per year for the central portion of the gland, respectively. These combined data suggest that on average there is an acceleration of prostatic growth in men older than 55 years.

Average weights of prostatic tissue removed at operation as reported by Berry et al.[1] amounted to 26.3, 39.5, 42.8 and 45.1 gm for the age groups of 55 to 59, 60 to 64, 65 to 69 and 70 to 74 years, respectively. These amounts are almost twice as high as the volumes of the central prostate in all corresponding age intervals of men living in the community (**table 2**). These volumes are generally even higher than the average total prostate volumes in men of corresponding ages in the community. Therefore, it is obvious that the surgically treated prostates were much larger than those of men in the general population.

Average growth rates cannot be applied to the individual patient. Prospective studies with longitudinal measurements are needed to determine which proportion of men might have a faster than average growth rate of the prostate. When comparing the average volumes of the central prostate found in our study to the average weights of tissue removed at operation in corresponding age groups, [1] it would seem likely that men with a faster growth rate are also more likely to eventually undergo surgery. This assumption, however, must be proved in a prospective study. During a 7-years period Watanabe et al. [16] followed the prostate volumes as determined by transrectal ultrasound in a group of 16 men, of whom 9 were approximately 70 years old or older at the start of the study and their prostates did not grow. The 2 men who were 50 to 55 years old at the start also did not experience growth of their prostates. However, 3 of 5 men between 55 to 65 showed a rapid volume increase. The final prostate volumes of those 3 men did not appear to be significantly larger than the initial and final volumes of the other 13 men in that study. Therefore, these results are not conclusive because too few men in the younger age range were followed for a long enough interval. Data presented by Berry et al [1] support the aforementioned assumption: a histologically normal prostate had an average weight of approximately 20 gm regardless of age and one with histopathological signs of BPH showed a steady volume increase with increasing age.

Figure 3 shows that with increasing age, the age-related curve for average volumes determined by transrectal ultrasound diverges from that determined at autopsy; the difference in average volume

measured by transrectal ultrasound in living men and at autopsy amounts to up to 12 cm^3 in men older than 70 years. Reference values for prostate volumes or weights that are derived from autopsy data should not be used for comparison without correction in studies using transrectal ultrasound as the method for volume determination in living men. A study correlating the planimetrically determined volume with prostate weights determined immediately after operative removal (radical prostatectomy or cystoprostatectomy) showed that the planimetric method on average underestimated the weight by 9.4 gm [18]. Therefore, it is unlikely that the higher volumes measured with ultrasound compared to prostate weights determined at autopsy can be attributed to the ultrasound technique per se.

The relationship between prostate volume and body mass index was also studied. Several investigators reported on the relationship between body mass index and the diagnosis of BPH [19, 20, 21]. It has been reported that a low body mass index is associated with the "clinical diagnosis of BPH" [19], which in that study (the normative ageing study) was defined as "diffuse enlargement" of the prostate on digital rectal examination. In another study a low body mass index was independently associated with an elevated risk of prostatectomy [20]. In contrast to these studies, Daniell [21] found that obesity was associated with prostatic enlargement but not with "obstruction" inasmuch as the resected weights at transurethral resection in obese men were larger, whereas the body mass index in men who underwent transurethral resection was not larger than this index in office controls. Our study shows that there is a weak correlation between total prostate volume and body mass index ($r=0.14$, $p=0.001$) and between volume of the central prostate and body mass index ($r=0.12$, $p=0.008$). The variation in prostate volume is determined by the variation in body mass index by only 2 %. Therefore, body mass index is hardly associated with prostate size in a community-based population.

In summary, the frequency distribution of prostate volumes in men between 55 to 74 years is skewed towards larger volumes. An approximately normal distribution is found when the logarithmic values for volume are considered. The average growth of the total prostate volume in this cross-sectional study is 2% per year among men 55 to 74 years old, resulting in an average doubling time of the total prostate volume of 35 years. The average growth of the central portion of the prostate in this cross-sectional study is 3.5% per year among men 55 to 74 years old, resulting in an average doubling time of the volume of the central part of the prostate of 20 years. There is only a minor increase of the peripheral zone volume with advancing age. Prostate volumes measured by transrectal ultrasound in living men are larger than volumes measured at autopsy. The absolute difference increases from 7 cm^3 among men 55 to 59 years old to 12 cm^3 among those 70 to 74 years old, whereas the percentage difference varies between 21 to 28% for the same age ranges. The shape of the prostatic area of greatest transverse diameter in the axial plane (increased roundness), which is expressed by the ratio width-to-height, correlates poorly with age. Body mass index is hardly associated with prostate size in a community-based population. A longitudinal study of prostate volume in a community-based sample of men is needed to determine the proportion of men who have a faster than average growth of the prostate. Such a study is planned in relation to rescreening for prostate cancer.

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CHAPTER IV.

PROSTATE SPECIFIC ANTIGEN IN A COMMUNITY-BASED SAMPLE OF MEN WITHOUT PROSTATE CANCER: Correlations with prostate volume, age, body mass index and symptoms of prostatism.

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ABSTRACT.

The correlation between both prostate specific antigen levels (PSA) and prostate specific antigen density (PSAD) and age, prostate volume parameters, body mass index and the International Prostate Symptom Score (IPSS) were studied in a community-based population.A sample of 502 men aged 55 through 74 years was evaluated, excluding those with a serum PSA above 10 ng/ml, those with biopsy proven prostate cancer and those who had previously undergone a prostate operation.

PSA and PSAD did not correlate with the body mass index. Weak correlations were found between PSA and age ($r=0.25$; $p<0.001$), PSAD and age ($r=0.17$; $p<0.001$) and between PSA and the total prostate volume ($r=0.58$;$p<0.001$). PSA did not correlate independently with age after adjustment for volume ($p=0.22$). The finding that PSAD correlates with age ($r=0.17$; $p<0.001$) is partly explained by the incomplete volume adjustment of PSAD which is proved by the positive correlation between PSAD and prostate volume ($r=0.26$; $p<0.001$).

In the main target age-range for prostate cancer screening there is a poor basis for the use of age-specific reference values or volume adjustment for PSA levels in order to increase the clinical usefulness of this serum marker. Comparison of the results of the present study and studies conducted in others regions shows that there may be significant differences in PSA values per age stratum.Further studies are needed to clarify the reasons for these differences.

INTRODUCTION.

Prostate specific antigen (PSA) is a serine protease produced by the epithelial cells of the prostate [1]. The upper range of normal for the monoclonal prostate specific antigen level as recommended by the manufacturer is 4 ng/ml (Hybritech). However, it has been shown that benign prostatic hyperplasia (BPH) can be associated with elevated prostate specific antigen levels in 21-53% of the patients [2, 3, 4, 5]. Although Stamey et al [6] have shown that the serum PSA level is elevated by 0.310 ± 0.25 ng/ml per gm of BPH tissue (polyclonal Yang-assay) others [7, 8] have not been able to find a clear relationship between serum PSA levels and the amount of hyperplastic BPH tissue. In spite of the results of the latter studies, attempts have been made to increase the specificity of the PSA assay by prostate volume adjustment [9, 10].

Several studies have correlated serum PSA with age and with the total prostate gland volume, as measured by transrectal ultrasound [10, 11, 12, 13] in men in whom prostate cancer has been excluded with a reasonable level of certainty. Two of these studies were done in a community-based population [12, 13]. The men included in the study by Collins et al. [13] were however preselected on the basis of the presence of moderate to severe symptoms of prostatism and/or a flow rate below 15 ml/sec. The results of these studies were contradictory as to the aspect of association between serum PSA levels and age.

Kane et al. [10] evaluated 1695 men with no likelihood of clinically significant prostate cancer between the ages of 55 to 70 years. These men had no history of prostatic surgery. In this study a relationship was observed between serum PSA and prostate gland volume but not between age and PSA levels or between symptoms of prostatism and PSA levels independent of gland volume.

Babaian et al. [11] studied 343 self-referred men and 65 physician-referred men because of an abnormal digital rectal examination or transrectal ultrasound or an elevated serum PSA. These men had a median age of 62 years (range 29 to 84 years). This study showed significant and independent associations between prostate gland volume and PSA level and between age and PSA level.

Oesterling et al. [12] studied 471 men aged 40-79 years who were randomly selected from the community.In this study a relationship was found between PSA and both prostate volume and age.

Collins et al. [13] reported data from a community-based population of 472 men aged 40-79 years in whom prostate cancer had been excluded.An independent relationship between PSA and both age and prostate volume was observed in this study.

The present evaluation was performed to further clarify the relationship between both PSA and PSAD and age, prostate volume, symptoms of prostatism and body mass index in a community-based population of men 55 to 74 years old, who had no history of prostate surgery and in whom prostate cancer had been excluded with reasonable certainty. It was not the purpose of this study to evaluate the relative importance of PSA, DRE and TRUS in a prostate cancer screening program.

MATERIAL AND METHODS.

Study design:

The community-based data for this study were collected as part of a randomized pilot study of the value of screening versus no-screening for prostate cancer.

Based upon the population registry and after taking care of the appropriate legal regulations the municipal authorities of Rotterdam created a database containing the information necessary to contact all men aged 55 through 74 years of age residing in 4 different districts of the city. After being invited by mail, 1186 men agreed to participate in the study. The response rates for the 4 five-year age-groups between 55 and 74 years, varied between 33 and 36.3%, resulting in a community-based population with a slight overrepresentation of men between 60 to 64 years of age and a slight underrepresentation of men aged 55 to 59 years of age (table 1). Part of this effect is explained by ageing of the original database between the time of its creation and the time that the men were actually evaluated. An enquiry among participants and non-participants which was conducted at the end of this study by the department of epidemiology of the community health services of the City of Rotterdam, has shown that participants were not more symptomatic or less symptomatic than non-participants [14].

Table 1.

Frequency distribution of men in 4 consecutive age-groups between 55-74 years of age in the general population at the time of creation of the database and in the population of participants at the time they were actually seen for the study.

Age	Total population	Participants
55-59	25.8%	20.9%
60-64	27.9%	32.0%
65-69	25.6%	26.1%
70-74	20.7%	21.0%
Total	100 %	100 %

In all of these men demographic and other data pertinent to the study, including the IPSS or International Prostate Symptom Score [15], were recorded. A serum PSA (ng/ml; Hybritech-assay) determination was used as a pre-screening tool. If the PSA value was above 10 ng/ml, a work-up was advised because of the high probability of prostate cancer [16] and the person was excluded from randomization. This was the case in 30 of 1186 men (i.e. 2.5% of the total study-population; 15 of these 30 men were subsequently found to have prostate cancer).

The remaining men (N=1156) were randomized between a screening and a no-screening group.In the latter group no further studies were done. The 554 men assigned to the screening group were further examined by digital rectal examination (DRE) and transrectal ultrasonography (TRUS) of the prostate.

Height (H) and body weight (BW) were recorded and the body mass index was calculated according to the formula: BW/H^2 (kg/m^2). An index of 20-25 kg/m^2 is considered to be normal; a value above 25 kg/m^2 indicates overweight. Those who were subsequently found to have prostatic cancer (N=10), those who had undergone a prostate operation (N=39) and the few men who refused the transrectal ultrasound examination (N=3) were excluded from the present evaluation. A community-based population of 502 persons in whom prostate cancer had been excluded with reasonable certainty and who had not previously undergone a prostate operation was thus established.

Procedures:

Symptoms:

The questionnaire used is the AUA-7 symptom index [17] which has been adopted by the WHO as the International Prostate Symptom Score (IPSS) [15]. According to AUA scoring conventions the men were grouped in three categories of symptom severity: those with minor symptoms (IPSS 0-7),those who were moderately (IPSS 8-19) and those who were severely (IPSS 20-35) symptomatic [17].

Prostate evaluation:

A 7 MHz Bruel and Kjaer multiplane sector scanning probe was used to measure prostate volumes with the transrectal planimetric technique [18]. This involves measuring the surface area of transverse sections taken through the prostate at 5 mm intervals. The average of two surface areas multiplied by 5 mm gives the volume for each step, and the cumulative volume allows the total prostatic volume (cm^3) to be derived. The same technique was used to determine the volume of the central prostate. The reliability of this method in our hands was shown in a previous study of the intra- and inter-observer error of the planimetric technique [19]. The transrectal ultrasound image of the prostate does not correspond exactly to McNeal's description [20] of zones. In this study the relatively hypoechoic central part of the prostate, including adenoma tissue if present, has been defined as the central part of the gland and should not be confused with Mc Neal's central zone. Its volume is referred to as VolC as opposed to VolT for total volume of the prostate and VolP (VolT-VolC) for volume of the peripheral part of the prostate. In 47 of the 502 subjects VolC was not determined separately due to an aselect temporary deviation from the protocol by one of the ultrasonographers. The prostate specific antigen density (PSAD) [9] was calculated by dividing the PSA value by the total prostate volume.

If the findings on DRE and/or TRUS were abnormal, prostate biopsies were taken. In case of an elevated PSA level alone (i.e. 4 < PSA < 10 ng/ml) in combination with normal findings on digital rectal examination and transrectal ultrasound, a biopsy was not performed. Of the original 554 men included in the screening group, 51 (9.2%) had a PSA value between 4 and 10 ng/ml. Prostate biopsies were performed in 9 of these 51 men because of abnormal findings on DRE and/or TRUS. Prostate cancer was found in 5 of these 9 men, resulting in a cancer detection rate of 9.8% in men with a PSA value between 4 and 10 ng/ml. This is lower than the detection rate of 17.7% as reported by Catalona et al. [16] who used a more liberal biopsy protocol. If a similar detection rate would have been applicable in our population, this would have resulted in the diagnosis of prostate cancer in 4 additional men implying that 4 additional men should have been excluded from the present evaluation. The impact of this number on a total of 502 men is negligible.

Statistical analysis:

Spearman correlation coefficients (r) were used to evaluate the relations between PSA or PSAD and age, IPSS, body mass index and prostate volume parameters.

The Kruskal-Wallis test was used to compare the levels of PSA and PSAD between the three IPSS-groups. If this test indicated significant differences it was followed by Mann-Whitney's test for pairwise comparisons of the median levels.

Multivariate analysis was used to evaluate various factors simultaneously. In this latter analysis serum PSA and prostate volume parameters were analysed after logarithmic transformation to reduce skewness of distributions. This transformation was also used in the calculation of the

coefficients of determination (r^2).
The level of statistical significance was set at p=0.05 (two-tailed).

RESULTS.

Figure 1 shows the cumulative frequency distribution of the PSA values. Two features of this frequency distribution are noteworthy. Firstly,this distribution is skewed towards the higher PSA values. Secondly, a relatively high percentage of men has a PSA-value of 0.1 ng/ml (3%) or less (5%). Seven percent of the men had a PSA value between 4 and 10 ng/ml.

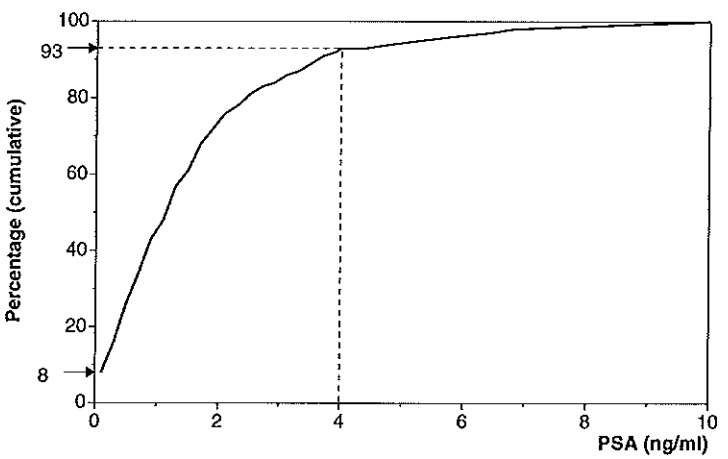

Figure 1. Cumulative frequency distribution of serum PSA values in 502 men without prostate cancer or a previous prostate operation.Men with a serum PSA level above 10 ng/ml had been excluded.

Figure 2 shows the cumulative frequency distribution of the PSAD values. Of the men studied, 95% had a PSAD below 0.117 and 97.5% below 0.145. The median PSAD value of the study population was 0.033 whereas 30% of the men had a PSAD value above 0.050 and 7% above 0.100.

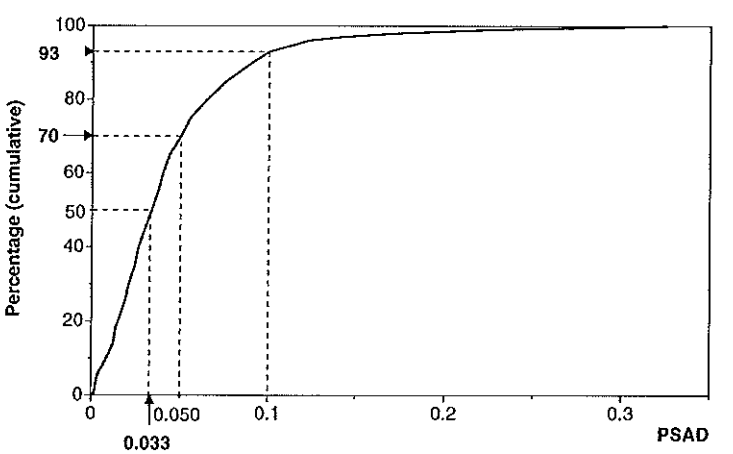

Figure 2. Cumulative frequency distribution of PSAD values in 502 men without prostate cancer or a previous prostate operation.Men with a serum PSA level above 10 ng/ml had been excluded.

Descriptive statistics of PSA and PSAD for the different age strata are shown in table 2.

Table 2.
Descriptive statistics of PSA (ng/ml) and PSAD values (ng/ml/cm^3) for consecutive 5 year age-groups of men without prostate cancer and without previous prostate operation.Men with a PSA value above 10 ng/ml had been excluded.

Age	55-59	60-64	65-69	70-74
N	124	162	132	84
PSA-value.				
mean.	1.2	1.5	1.8	2.4
median.	0.8	1.0	1.4	1.7
minimum.	<0.1	<0.1	<0.1	<0.1
maximum.	7.9	7.3	8.4	10
SD.	1.3	1.5	1.6	2.2
PSAD-value				
mean.	0.035	0.041	0.046	0.055
median.	0.030	0.029	0.038	0.043
minimum.	0.002	0.001	0.002	0.001
maximum.	0.173	0.200	0.326	0.309
SD.	0.030	0.034	0.042	0.053

Total prostate volume is positively correlated with age (r=0.26; p<0.001). The correlations between PSA and age, IPSS, body mass index and prostate volume parameters and the correlations between PSAD and age, body mass index and IPSS are summarised in table 3. There is a weak but statistically significant correlation between PSA and age (r=0.25; p<0.001). This is also reflected by the increase in mean PSA in advancing 5 year age-groups (table 2). An equally weak correlation is found between PSA and IPSS (r=0.16; p<0.001).

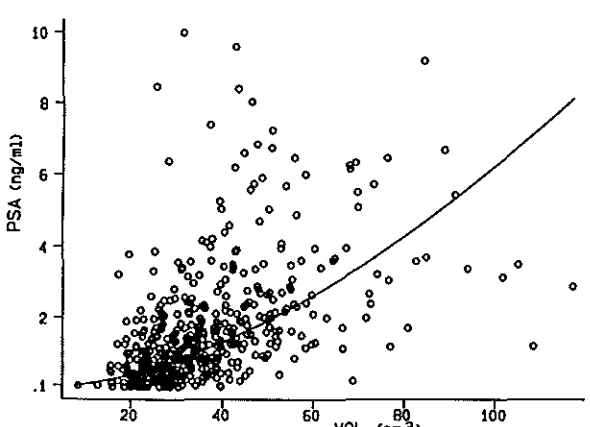

Figure 3.
Scattergram of PSA values (ng/ml) versus total prostate volume (VolT; cm^3). Drawn line [log(PSA) = -2.61 + 1.70.log (VolT); r^2 = 0.30; p<0.001] corresponds to least squares regression line after logarithmic transformation of both axes.

Table 3.
Spearman correlation coefficients (r) between PSA or PSAD and age, IPSS, body mass index and between PSA and prostate volume parameters in men aged 55-74 years without prostate cancer and without previous prostate operation.Men with a PSA value above 10 ng/ml had been excluded.Coefficient of determination is indicated by r^2.

	r	r^2	p-value.
Parameters correlated with PSA			
Body mass index	-0.01	0.00	0.89
Age	0.25	0.06	<0.001
IPSS	0.16	0.03	<0.001
VolT	0.58	0.34	<0.001
VolC	0.58	0.34	<0.001
VolP	0.33	0.11	<0.001
Parameters correlated with PSAD			
Body mass index	-0.07	0.00	0.10
Age	0.17	0.03	<0.001
IPSS.	0.09	0.01	0.04

All correlations are statistically significant except those involving the body mass index.

PSA and PSAD did not correlate with the body mass index. The correlations between PSAD and age (r=0.17; p<0.001) and PSAD and IPSS (r=0.09; p=0.04) are both weak. There is a slight increase in mean PSAD in advancing 5 year age-groups (table 2). Calculation of the coefficient of determination shows that only 6% of the variation in PSA and 3% of the variation in PSAD respectively can be explained by the variation in age.
PSA correlates moderately with VolT (r=0.58; p<0.001) and with VolC (r=0.58; p<0.001). The correlation between PSA and VolP (r=0.33; p<0.001) is weaker. Figure 3 shows the scattergram of PSA values versus total prostate volume (VolT).

Using multivariate analysis it was found that each doubling of VolP, with constant VolC, leads to an average increase of 31% (p=0.007) of PSA. Each doubling of VolC, with constant VolP, however leads to an average increase of PSA of 108% (p<0.001). Adjusted for both volume parameters there was no significant correlation anymore between PSA and age (p=0.22).

Figures 4 and 5 show the cumulative frequency of serum PSA levels and PSAD respectively, in 502 men without prostate cancer and PSA<10 ng/ml by international prostate symptom score subgroups. The men were grouped as those with no or minor complaints (IPSS 0-7; N=318), those with moderate complaints (IPSS 8-19; N=120) and those with severe complaints (IPSS 20-35; N=30). This grouping by IPSS resulted in significant differences (p=0.002) in median PSA values, whereas the median PSAD did not significantly differ (p=0.17) between IPSS-groups. Further analysis showed that the median PSA value in the group with no or minor complaints

(1.1 ng/ml) differed significantly (p=0.005) from the median value in the group with moderate complaints (1.3 ng/ml) and also significantly (p=0.02) from the median value in the group with severe complaints (1.8 ng/ml). The median PSA values in the latter two groups did not differ significantly (p=0.36) from each other. The group of men with severe complaints, however, only consists of 30 men.

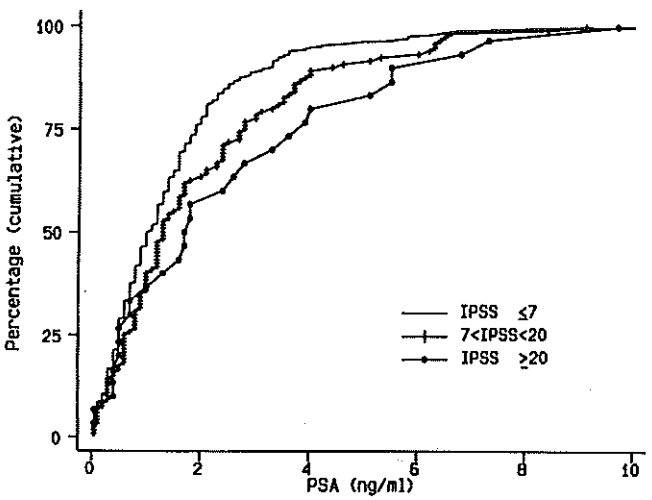

Figure 4.
Cumulative frequency of serum PSA levels in 502 men without prostate cancer or a previous prostate operation by International prostate symptom score-groups. Scores are grouped as no or minor complaints (IPSS 0-7; N=352), moderate complaints (IPSS 8-19; N=120) and severe complaints (IPSS 20-35; N=30). Men with a serum PSA level above 10 ng/ml had been excluded.

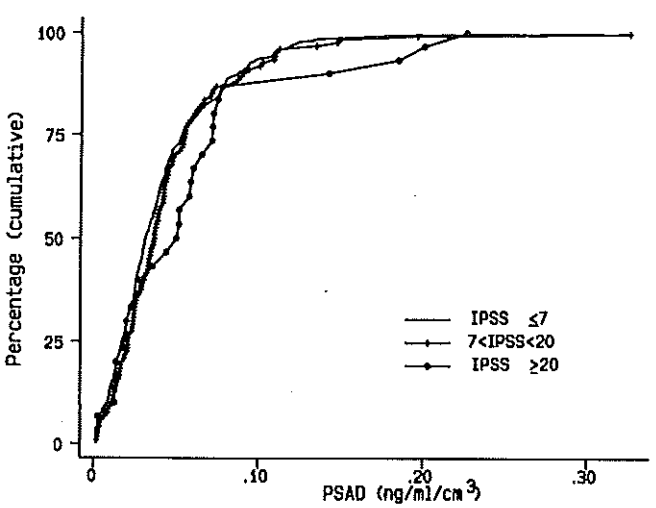

Figure 5.
Cumulative frequency of PSAD values in 502 men without prostate cancer or a previous prostate operation by International prostate symptom score-groups. Scores are grouped as no or minor complaints (IPSS 0-7; N=352), moderate complaints (IPSS 8-19; N=120) and severe complaints (IPSS 20-35; N=30). Men with a serum PSA level above 10 ng/ml had been excluded.

DISCUSSION.

The correlations between PSA level and the volume of the central (r= 0.58) and peripheral part of the prostate (r=0.33) that were found in this study, support the idea that more PSA is produced in the central (hyperplastic) than in the peripheral part of the prostate. These findings are also in agreement with the fact that elevated PSA levels can be found in men without prostate cancer but with an enlarged prostate due to BPH.

The positive correlation between PSA and age may be due to the fact that prostate volume increases with age. Multivariate analysis indeed showed that age is not an independent factor after adjustment for volume. This is at variance with the results of other studies that found independent effects of age and volume [11, 12, 13].

Babaian at al [11] claimed an independent effect of age and volume with the significance of one not being dependent on the other. The fact that these authors studied men over a wider age range (29-84 years) may be an explanation for this finding. Oesterling et al. [12] found that the serum PSA level was correlated with both age ($r=0.43$; $p<0.001$) and prostate volume ($r=0.55$; $p<0.001$) and proposed age-specific reference ranges for serum PSA. Their results indicated that 30% of the variation in PSA could be attributed to the variation in prostate volume, but that age accounted for an additional 5% ($p<0.001$) of the variation in PSA. Their study population was younger, with about half of the 471 men below the age of 55 years, and consequently represented a wider age range (40-79) than the age range in our study population.

Dalkin and associates [21] also determined age-specific reference ranges for men between 50 and 79 years old. Compared to the values determined by Oesterling et al. [12] their reference values were higher for men 60 to 69 years old (5.4 as opposed to 4.5 ng/ml) and lower for men 70-79 years old (6.3 as opposed to 6.5 ng/ml). The men included in the evaluation of Dalkin et al. did not represent a community-based population but were recruited by advertisements in newspapers.

The percentages of men with a PSA >4 ng/ml by age-group in the Olmsted county population [12] can be compared with these percentages in the present population, if the population of men included in the present study is adjusted by the secondary inclusion of half of the 15 men with a PSA >10ng/ml but no prostate cancer: 5.1% of the men between 55-59 years in the present population and 2% of the men between 50-59 in the Olmsted county population have a PSA >4ng/ml. The difference is even larger between 60-69 years with 13% in Olmsted county as compared to 7.3% in the present series. The median prostate volumes for the men between 60-69 years in Olmsted county and Rotterdam are comparable (34.6 and 33.2 cm^3 respectively). It should be noted however that prostate volumes were not determined in the men with a PSA >10 ng/ml making it impossible to exactly adjust the median prostate volume, but the addition of half of the 7 men without prostate cancer and a PSA >10 ng/ml between 60-69 years is unlikely to change the difference between the median prostate volumes very much. Between 70-74 years we find a percentage of 15.8% as compared to 19% for the group of 70-79 in Olmsted county. Since the biopsy protocol was more liberal in the Olmsted county population, these differences cannot be due to a different percentage of men excluded because of a diagnosis of prostate cancer; If a more liberal biopsy protocol had been employed in our study we would most probably have found some more cancers in the group of men with a PSA >4ng/ml. This would have resulted in the exclusion of a few more men with a PSA >4 ng/ml from the population of 502, resulting in an even lower percentage of men with a PSA >4 ng/ml but without prostate cancer per age stratum.

Collins et al [13] found a significant and independent correlation between both PSA and age (r=0.37; p<0.001) and PSA and total prostate volume (r=0.56; p<0.001) but concluded that "because of the non-linearity of these interrelationships, PSA may be best employed using absolute cut-off levels". Comparing the mean PSA values of the Scottish population and the present population (after correction for the men with PSA >10 ng/ml but without prostate cancer as described above) shows that there are again considerable differences by age-group: The mean PSA value between 60-69 years is 1.8 ng/ml in the present population as compared to 3.1 ng/ml in the Scottish study. The mean prostate volume in these two population does not differ for the age-group between 60-69 years. (36 versus 36.5 cm^3).

Theoretically, the correlation between PSA and age could have been influenced by the exclusion of men with a PSA >10 ng/ml but without prostate cancer. If all men would have been included, 15 of the 30 men with a PSA >10 ng/ml would have been randomized for screening and consequently half of these (i.e. about 7) would have been free of prostate cancer. Proportionately, 1, 2, 1 and 3 men with a PSA >10 ng/ml would have to be added to the 4 respective advancing 5 year age-groups between 55 and 74 years. These numbers would have a negligible influence on the correlation between PSA and age.

The lack of an independent correlation between age and PSA indicates that there is a weak basis for the proposal of age-specific reference ranges in the population of men between 55 to 74 years. Another factor that should be taken into account is the finding that comparative data from Rotterdam, Olmsted County and Scotland seem to indicate differences in PSA values per age-group despite the use of the same method of serum PSA determination (Hybritech). These differences may be due to population sample biases. To fully understand the reasons for these differences a more detailed epidemiological analysis would be necessary including for example an analysis of data on types of BPH, incidence of prostatitis and instrumentation rates. Until such information is available it is prudent to realize that reference ranges determined for one particular region or country may not necessarily be valid for another area. Furthermore, the proposed age-specific reference ranges have not yet been tested in actual clinical practice.

In the present study it was found that only 6 % of the variation in PSA can be attributed to the variation in age. However, 34% of the variation in PSA can be attributed to the variation in volume.

The correlation coefficient between PSA and total prostate volume observed in the present study (r=0.58) is almost identical to the data presented by Oesterling et al. [12] (r=0.55) and by Collins et al. [13] (r=0.56). The correlation coefficients between PSA and age show considerable differences: r=0.25 in the present study and r=0.37 and r=0.43 in the studies reported by Collins et al. [13] and Oesterling et al. [12] , respectively. The major difference between these studies is the age range of men included which was 55 to 74 years in the present study and 40 to 79 in both other studies. It would be interesting to study the correlation coefficient between age and PSA in both other samples of men after exclusion of those who are not between 55 to 74 years of age. This may be important because the main target age-range for prostate cancer screening does not include men between 40 and 55 years of age unless a hereditary factor is suspected: only 2% of all prostate cancers in United States white men occur in those 55 years or younger whereas the hereditary form of prostate cancer accounts for 43% of the cases with an onset below 55 years of age [22].

Based on the fact that there is a positive correlation between PSA values and volume, the idea of defining reference values for different volume classes or to adjust PSA for volume has been introduced [9, 10]. The correlation coefficient between PSA and total volume in the present study

however is only moderate. Furthermore, only 34% of the variation in PSA is explained by the variation in volume of the central part of the gland. These results do not support the usefulness in clinical routine and screening programs of PSA reference values for different volume classes, even if the volumes of the central or peripheral part of the gland are considered specifically.
Of the men in the present study only 2% had a PSAD greater than 0.15, whereas 97.5% had a PSAD below 0.145. In their original paper on PSAD Benson et al [9] found that none of their 20 BPH patients had a PSAD value above 0.117. In the present study 95% of the men had a PSAD below 0.117.
Interesting is the finding that although PSA does not correlate independently with age (i.e. after adjustment for volume), PSAD still correlates ($r=0.17$; $p<0.001$) with age. Since prostate volume is also positively correlated with age ($r=0.26$; $p<0.001$), a possible explanation for this finding may be that PSAD provides an incomplete volume adjustment. Indeed, the correlation between PSAD and total prostate volume in this study amounts to $r=0.26$ ($p<0.001$), which proves that PSAD does not provide a full volume adjustment. An alternative explanation for the correlation between PSAD and age, could be the possible influence with increasing age of other factors than volume such as elements of prostatitis or infarction. If this were true one could reason that men with prostatitis or infarction would possibly be more symptomatic and that consequently PSAD values might differ significantly between IPSS groups. This is however not the case. Statistical analysis shows that although median PSA values differ significantly between IPSS-groups ($p=0.002$) there is no significant difference of median PSAD values between IPSS-groups ($p=0.17$) (see **fig. 5**). Other factors that frustrate prostate volume correction of serum PSA levels are the findings recently reported by Mandell et al [23]. They found marked variations in stromal to epithelial ratios in BPH patients and an absence of correlation between PSAD and grams of epithelium and stromal to epithelial ratio. They also found an age dependent decrease in PSA production per gram of epithelium.

Summary.

1. Prostate volume adjustment with the intention to increase the specificity of serum PSA values in the detection of prostate cancer has been proposed either with specific volume ranges or with the use of PSAD. The moderate correlations between PSA and prostate volume parameters and the incomplete volume adjustment that is provided by the use of PSAD, do not support the clinical usefulness of PSA reference values for different volume classes, even if the volumes of the central or peripheral part of the gland are considered specifically.
2. Age specific reference ranges for serum PSA values have been proposed for use in screening for prostate cancer. The lack of an independent correlation between age and PSA in the present study does not support the clinical usefulness of this approach in men between 55 and 74 years old.
3. There may be significant regional differences in PSA values per age-group. Further studies are needed to clarify the reasons for these differences.
4. The positive correlation between PSAD and age can be explained in part by the incomplete volume adjustment of PSAD. An increase with age of prostatic abnormalities such as prostatitis or infarctions, could be an alternative explanation. The present study does not support this latter possibility since there is no significant difference in PSAD between groups of men with different levels of symptom severity.
5. There is no correlation between PSA or PSAD and body mass index.

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CHAPTER V

THE INTERNATIONAL PROSTATE SYMPTOM SCORE IN A COMMUNITY-BASED SAMPLE OF MEN BETWEEN FIFTY-FIVE AND SEVENTY-FOUR YEARS OF AGE.

-Prevalence and correlation of symptoms with age, prostate volume, flow rate and residual urine volume.-

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ABSTRACT.

The study of the prevalence of symptoms of prostatism in the community and the correlations between these symptoms and age, prostate volume, flow rate and residual urine volume was the objective of this evaluation.

The International Prostate Symptom Score (IPSS) was administered to a community-based population of 502 men between 55 to 74 years of age with no prostate cancer and with no history of a previous prostate operation. Prostate volume parameters, flow rate variables and post void residual urine volume were measured.

Overall, 6 % and 24 % of the men were severely and moderately symptomatic respectively. The results of a detailed questionnaire such as the IPSS (only 12% of the men scored 0) contrast with the men's global perception of their voiding function (82% of the men claimed to have "no voiding complaints"). A good correlation between the total symptom score and the single disease-specific quality of life question that is included in the IPSS ($r=0.74$; $p=0.001$) was found. There is a weak correlation between the IPSS and total prostate volume ($r=0.19$; $p<0.001$) and between the IPSS and physiologic measures such as peak flow rate ($r=-0.18$; $p<0.001$) and post void residual urine volume ($r=0.25$; $p<0.001$). There is a very weak correlation between the IPSS and age ($r=0.09$; $p=0.04$).

The different parameters used to characterize BPH should be considered independently because no predictions about the value of a certain parameter can be made by knowing one of the other parameter values. Symptom scores should therefore not be used as a preselection criterion in the determination of the prevalence of clinical BPH without taking other measures into account. The interpretation of the parameter values in a clinical setting should take the lack of correlation and the variability of the parameter values into account.

INTRODUCTION

Only a limited number of studies evaluating the prevalence of symptoms of prostatism in community-based population samples have been performed [1, 2, 3, 4, 5]. These studies are difficult to compare because of the different age ranges of the men studied and the use of different scoring systems with different wording of the symptom questions, different scaling and different numbers of symptom questions included and differences in importance that is attached to obstructive and irritative symptoms. Some scoring systems put an emphasis on the frequency with which a particular symptom is experienced (AUA-7 symptom index [6], MMAP score [7]), whereas other systems include items with an emphasis on severity as well as items with an emphasis on the frequency of a symptom (Boyarsky [8] and Madsen-Iversen [9]).
The AUA-7 symptom index has been adopted by the World Health Organization (WHO) as the International Prostate Symptom Score (IPSS) after addition of one disease-specific quality of life question as a means of assessing the global impact of BPH on quality of life [10]. On validation [6], the AUA-7 index has been shown to have an excellent test-retest reliability and is internally consistent. Furthermore, it discriminates between subjects with a clinical diagnosis of BPH and office control subjects and it is sensitive to change.
It is not recommended to use the AUA-7 index as a screen for BPH [6]. In spite of this caution, symptom scores have been used as a preselection criterion in studies of the prevalence of BPH [11].
It was the aim of this analysis to study the prevalence of urinary symptoms as measured by the IPSS, to correlate these scores with age, the single disease specific quality of life question, the men's global perception of their urinary condition and with other measures used to diagnose BPH in a clinical setting such as prostate volume, flow rate and post void residual urine volume. These community-based data provide information on the potential of this symptom index to indicate a disease such as clinical BPH.

MATERIAL AND METHODS.

Study design.

The community-based data on symptoms and signs of BPH presented in this paper was collected as part of a randomized pilot study on the value of screening versus no-screening for prostate cancer. The municipal authorities of the city of Rotterdam created a database containing the information necessary to contact all men aged 55 through 74 years residing in 4 different areas of the city.
Subsequently, invitations to participate in this randomized pilot study were sent by mail and 1186 men agreed to participate. The response rates for the 4 five-year age intervals between 55 and 74 years, varied between 33 and 36.3%, resulting in a community-based population with a slight overrepresentation of men between 60 to 64 years of age and a slight underrepresentation of men aged 55 to 59 years of age (Table 1).
In all of these men demographic and other data pertinent to the screening-study were recorded, including the IPSS [10]. A serum PSA (ng/ml; Hybritech-assay.) determination was used as a pre-screening tool. If the PSA value was above 10ng/ml, a work-up was advised because of the high probability of prostate cancer [12] and the man was excluded from randomization. This was the case in 30 of 1186 men (2.5% of the total study-population; 15 of these 30 men were found to

have prostate cancer).
The remaining men (N=1156) were randomly assigned to a screening or a no-screening group. The 554 men assigned to the screening group were further examined by digital rectal examination and transrectal ultrasonography of the prostate to detect lesions indicative of prostate cancer and prostate volume measurement. Those men in whom positive biopsies subsequently showed prostatic cancer (N=10), those who had undergone a prostate operation in the past (N=39) and the men who refused the transrectal ultrasound examination (N=3) were excluded from the present evaluation. The proportion of men per 5 year age-group who had previously undergone a prostate operation is indicated in Table 1.

Table 1.
Frequency distribution of men in 4 consecutive age-groups between 55 to 74 years of age in the general population at the time of creation of the database and in the population of participants at the time they were actually seen for the study.Percentage of men per 5-year age-group who had previously undergone a prostate operation.

Age	Total population	Participants	Previous prostate surgery in participants
55-59.	25.8%	20.9%	0.8%
60-64.	27.9%	32.0%	3.2%
65-69.	25.6%	26.1%	7.1%
70-74.	20.7%	21.0%	12.0%
Total.	100 %	100 %	5.6%

A community-based population of 502 persons in whom prostate cancer had been excluded with reasonable certainty and who had not previously undergone a prostate operation was thus established.
Among several planned peripheral studies was this study of signs and symptoms of BPH; the parameters studied included uroflowmetry and the determination of residual urine by transabdominal ultrasound. These tests were done in 494 and 326 consecutive men respectively.

Procedures:

Symptoms:
The questionnaire used is the AUA-7 symptom index [6] which has been adopted by the WHO as the international prostate symptom score (IPSS) after addition of one disease-specific quality of life question [10]; the latter question results in a separate quality of life score. This numerical symptom scoring system grades the presence of 7 symptoms on a discrete scale of 0 (symptom never present) to 5 (symptom always present). The 7 symptoms graded can be described as incomplete emptying, increased frequency, intermittency, urgency, weak stream, hesitancy and nocturia. The disease-specific quality of life question was phrased as follows: "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel

about that?", and the answering scale ranged from 0 (delighted) to 6 (terrible).
The professionally translated English source text of the questions of the index was reviewed and amended by 2 urologists and an epidemiologist. Minor textual changes were made to improve clarity of the questions after the questionnaire had been administered to a pilot population of 20 men. The questionnaire was basically self administered but the men completed it in the presence of a data manager who was available for clarifications and who checked the form for completeness. Based upon correlations between the symptom index and bother scores it has been suggested to create three subclasses for the resulting total score:minor (IPSS 0-7),moderate (IPSS 8-19) and severe (IPSS 20-35) symptoms [6].

Urodynamic parameters:
Uroflowmetry (ml/s) was done using a Dantec Urodyn 1000 flowmeter. The following parameters were noted: peak flow rate (Q_{max}), average flow rate (Q_{ave}), delay time (T_{delay}), total voiding time (T_{100}), total flow time (T_Q) and voided volume. The percentage of the total voiding time that the men were actually passing urine (flow time) was calculated by the fraction T_Q/T_{100}. In case of clear artefacts, the flow rate readings were corrected manually. The men were not specifically asked to come to the clinic with a full bladder but were instructed to wait for the flowmetry and not void before that time. Of the 494 persons asked to void in the flowmeter 62 (13%) were unable to do so at the time.
The post void residual urine volume (ml) was computed using an Aloka machine with a 3.5 MHz handheld probe using the formula /6x(width)x(height)x(depth) [13]. The determination of residual urine by ultrasound was not performed in those persons who could not void.
The initial pre-micturition bladder volume was determined by adding the voided volume and the residual urine volume. The initial bladder volume was 100 ml or more in 83% of the men and 150 ml or more in 62% of the men. No flow rates were discarded because of relatively low initial bladder volume.
Prostate volume:
Transrectal ultrasonometry with a 7 MHz Bruel and Kjaer multiplane sector scanning probe was performed to measure volumes. The planimetric technique of volume measurement was used [14]. This involves measuring the surface area of transverse sections taken through the prostate at 5 mm intervals. The average of two surface areas multiplied by 5 mm gives the volume for each step, and the cumulative volume allows the total prostatic volume (cm^3) to be derived. The volume of the central part of the gland (VolC) which in this study was defined as the relatively hypoechoic central area including adenoma tissue if present, was determined by the same technique.

Statistical analysis:
Spearman correlation coefficients (r) were used to evaluate the relations between the total IPSS and age, prostate volume parameters, post void residual urine volume, peak flow rate and for evaluation of correlations between individual symptoms and residual urine volume and flow rate parameters.
The Chi-square test for trend was used to assess whether percentages increased or decreased in relation to an ordered classification (age intervals or symptom score classes).
The Kruskal-Wallis test was used to compare IPSS levels between groups.
The level of statistical significance was set at p=0.05 (two-tailed).

Results.

Total score and correlation with age and quality of life:

On the basis of the IPSS a subdivision of men into three symptom classes has been proposed [6], resulting in groups with minor (IPSS 0-7), moderate (IPSS 8-19) and severe (IPSS 20-35) symptoms. The relevance of this subdivision is confirmed by the relation between the total IPSS sub-groups and the results of the disease-specific quality of life question in the present analysis. (see Table 2).

There was a good correlation between the total IPSS and the score of this single quality of life question (r=0.74; p=0.001). The results also showed that 31% of men were "delighted", 24% were "pleased", 29% "mostly satisfied" and 10% felt "about equally satisfied and dissatisfied" about their urinary condition. Few men were "mostly dissatisfied" (5%) or felt "unhappy" (1%). No man scored 6 i.e. "terrible".

During an intake interview, answers to questions of demographic nature and the medical and surgical history were recorded; the participants were also asked whether they had any voiding complaints and if so whether this was a reason to participate in the study. The median IPSS of the men who answered yes or no to the question whether they had any voiding complaints was 13.5 and 3.0 respectively (p<0.0001).

Table 2.

Relationship between severity of symptoms and results of disease-specific quality of life question. Values are numbers of patients with percentages (row-wise) in parentheses. No participant scored 6 (maximum) on the quality of life scale.

	Score on Quality of Life scale.					
Total IPSS	0	1	2	3	4	5
0	44 (75)	12 (20)	3 (5)			
1-7	109 (37)	93 (32)	83 (28)	7 (2)	1 (0)	
8-19	5 (4)	10 (8)	56 (47)	35 (29)	13 (11)	1 (1)
20-35		3 (10)	2 (7)	10 (33)	9 (30)	6 (20)
Total	158 (31)	118 (24)	144 (29)	52 (10)	23 (5)	7 (1)

The quality of life score of the men who answered yes or no to the question whether they had any voiding complaints was 3.0 and 1.0 respectively (p<0.0001). Overall, 82% of the men gave a negative answer to the first part of this question (table 3). This contrasts with the results of the more detailed symptom questionnaire (IPSS). Only 12% of the men had a score of 0 i.e. they were asymptomatic. The percentage of men who gave a positive answer to the global question whether they had any voiding complaints did not increase significantly with age (p=0.19).

The cumulative frequency plot of the total symptom score (fig. 1) shows that the percentages of men with minor (IPSS 0-7), moderate (IPSS 8-19) and severe (IPSS 20-35) symptoms were 70%, 24% and 6% respectively.

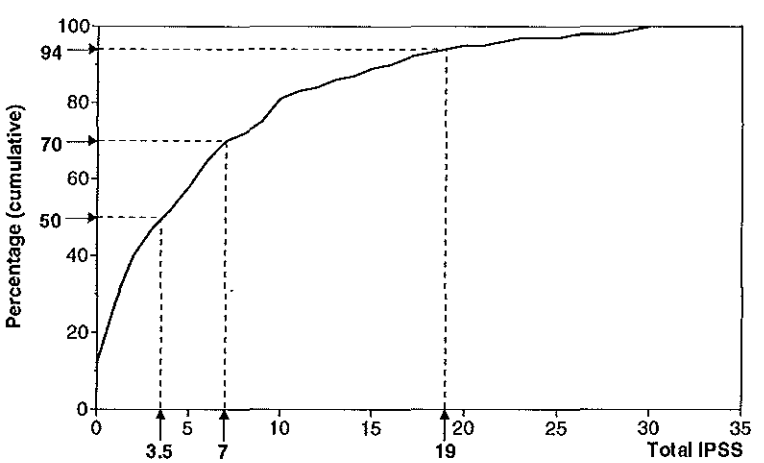
Table 3.

Percentages of men who answered "yes" to the global question whether they had any "voiding complaints" and the percentage of those men with voiding complaints who stated that the presence of complaints was a reason to participate in the study. Means, medians and interquartile ranges for IPSS by age category. P-values for the items "voiding complaint" refers to test for trend; p-value for the comparison of IPSS between the age groups refers to the Kruskal-Wallis test.

Age	N	"Voiding complaints"	"Voiding complaints" as reason to participate	IPSS		
				Mean (±SE)	Median	Interquart. range
55-59	124	20%	58%	6.1 (±0.7)	4.0	1.0-9.0
60-64	162	14%	61%	6.1 (±0.5)	3.0	1.0-9.0
65-69	132	17%	76%	6.1 (±0.5)	4.0	1.0-9.8
70-74	84	24%	63%	7.5 (±0.8)	6.0	2.0-10.0
p-value		0.19	0.57		0.09	

Figure 1.

Cumulative frequency distribution of the total symptom score (IPSS) in a community-based group of men 55 to 74 years old with no prostate cancer and no history of a prostate operation. The median value and the percentages of men with IPSS up to 7 and up to 19 are indicated.



Overall, the IPSS correlated poorly with age (r=0.09; p=0.04). The mean and median values and the interquartile ranges of the IPSS per consecutive 5 year age group are shown in table 3. The variation per 5 year age group is not significant (p=0.09). If the men between 60 to 69 years are taken together as one group there is a statistically significant variation with age (p=0.04). But

Mann-Whitney's test for comparison of the median levels does not show a significant difference between the men aged 55 to 59 and the men aged 60 to 69 years (p=0.34).
The percentage of men with severe complaints showed only a small variation around 6% (5.3 - 6.5%) between 55 and 74 years.

Scores for individual symptoms:
If the presence of a symptom is defined as having a score of 1 or more for that particular symptom, then the 7 symptoms in the total group of men between 55-74 years, were present in the following order of frequency: Nocturia: 75%; Increased frequency: 60%; Weak stream: 47%; Urgency: 31%; Incomplete emptying: 30%; Intermittency: 28%; Hesitancy: 15%.
When results of the scores on the individual questions are subdivided into 3 classes of severity i.e. slight, moderate and severe on the basis of a score of 0-1, 2-3 and 4-5, respectively, for that particular symptom, then the percentages of men suffering moderately and severely, respectively, from one particular symptom are as follows: Weak stream 14% and 18%; Increased frequency 21% and 11%; Nocturia 25% and 4%; Urgency 11% and 8%; Intermittency 10% and 7%; Incomplete emptying 8% and 7%; Hesitancy 5% and 4%. In general there are more men who complain moderately than men who complain severely of a particular symptom except for the symptom "weak stream".

Figure 2.
Histogram of the percentages of men suffering moderately and severely from each individual symptom of the IPSS per 5 year age interval from 55 to 74 years.

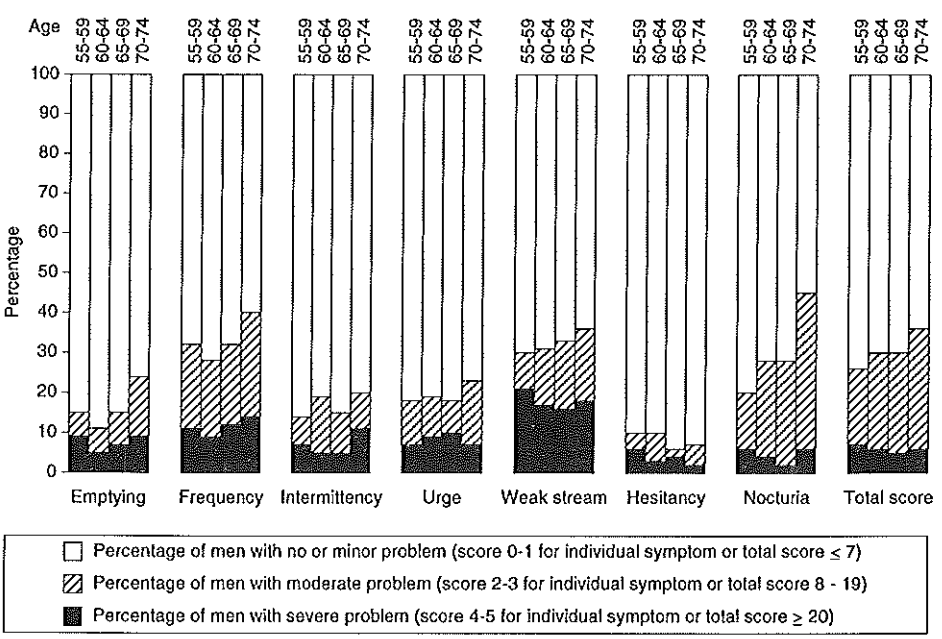


Fig. 2 shows the percentages of men suffering moderately and severely from each individual symptom per 5-year age-group. It is interesting to note that for all symptoms except urgency the prevalence of men suffering severely from one particular symptom is higher in the age group of 55 to 59 years than in the group of 60 to 64 years. Nocturia is a very prevalent symptom:the percentage of men who wake up to void at least once every night rises from 63% between 55 to 59 years to 83% between 70 to 74 years of age (with an average of 75% between 55 to 74 years). In the age group of 55 to 59 years 14% have to get up to void 2 or 3 times and 6% 4 or more times every night. Of the men aged 70 to 74 years 39% get up 2 or 3 times and 6% 4 or more times per night.
The individual questions of the IPSS were examined for their relationship to age. Although the prevalence of nocturia, increased frequency, weak stream and incomplete emptying seems to increase somewhat with age only the prevalence of nocturia increases significantly with age between 55 to 74 years (p=0.002).
Surprisingly, the prevalence of the symptom hesitancy decreases, although not significantly, with age.

Total IPSS in relation to other parameters:
Table 4 shows the correlations between the total IPSS and prostate volume parameters, age, post void residual urine volume and peak flow rate. There is only a weak correlation between the IPSS and any of these parameters (all statistically significant).

Table 4.
Spearman correlation coefficients of international prostate symptom score with age, total prostate volume (VolT), volume of the central part of the prostate (VolC), postvoid residual urine volume (PVR) and peak flow rate (Q_{max}) respectively.

Parameter	N	r	p-value
Age:	502	0.09	0.04
VolT:	502	0.19	<0.001
VolC:	455	0.24	<0.001
PVR:	326	0.25	<0.001
Q_{max}:	432	-0.18	<0.001

Scores on individual questions correlated with the physiologic parameter where it is assumed that it measures the same variable:
The "feeling of incomplete emptying" was poorly correlated with residual urine volume (r=0.14; p=0.01). This question however may be difficult to interpret. An increased frequency may give the person the false impression that he has not emptied his bladder sufficiently because he has to void again soon after the previous micturition. Five percent (14/271) of the men without a significant post void residual urine volume (PVR 50 ml) claim to hav e a feeling of incomplete emptying more than half of the time or almost always.
Intermittency was weakly correlated with total flow time divided by total voiding time (r=-0.20; p<0.001).

The symptom weak stream was weakly correlated with the peak flow rate ($r=-0.19$; $p<0.001$), with the average flow rate ($r=-0.22$; $p<0.001$). Nine percent (9/105) of the men with a peak flow of more than or equal to 15 ml/s claimed to have a weak stream more than half of the time or almost always.
Hesitancy was poorly correlated with the time before flow actually commenced after the patient had been informed that the flow recorder was recording ($r=0.13$; $p=0,0081$).

DISCUSSION.

A limited number of studies evaluating the prevalence of symptoms of prostatism in community-based populations have been performed [1, 2, 3, 4, 5]. The percentages of men with moderate and severe symptoms as defined by the respective authors in these studies seem to indicate that the prevalence of moderate to severe symptoms is below 30% before the age of 55 and rises thereafter. Geographical differences in symptom frequency among community-based samples of men have been reported [7, 15]. No study, including the present study, has correlated symptoms with the presence of urodynamically measured outflow resistance. This is the aim of the ongoing non-community-based International Continence Society-BPH study.
Other important properties of the group of "symptoms of prostatism" have been identified:

1. The results of a detailed questionnaire of symptom frequency (IPSS) which showed that only 12% of the men is free of symptoms (score of 0) contrasts with the value of 18% of men who gave a positive answer to the global question whether they had any voiding complaints. Apparently, the majority of men tolerates a certain level of symptom frequency without "complaint" (**table 2**). This confirms the observations made by Jensen et al. [16] and indicates that symptom scores may capture many men who would otherwise not complain of lower urinary tract problems. The validity of the use of symptom questionnaires to screen men for BPH without taking other parameters into account is therefore at least debatable.
2). Diokno et al. found that the symptoms of prostatism can show considerable fluctuations over time in individual patients [17].
3). Some studies [18, 19], seem to indicate that these symptoms may not be specific for men or for clinical BPH.
4). The descriptive term "prostatism" may be misleading because there is evidence that these symptoms may be a manifestation of ageing rather than of a disease like BPH [18]. The results of the present study do not support this idea because there is a better (but still poor) correlation between the IPSS and anatomical and physiological measures for BPH than between the IPSS and age.
5). The present evaluation showed poor correlations between the total symptom score and prostate volume and between the symptom score and physiological measurements such as flow rate and post void residual urine volume (**table 4**). This disturbing finding reflects the difficulty of reaching consensus about a clinical case definition of BPH. A similar lack of correlation was reported by Barry et al. in a non-community based group of men in the BPH treatment outcomes pilot study (BTOPS) [20]. The poor correlation between symptoms of prostatism and post void residual urine volume or peak flow rate could theoretically be related to measurement problems or poor test-retest reliability of the parameters peak flow rate [21] and post void residual urine volume [22]. Alternatively, either these parameters [20] or the symptom

score might be invalid measures of BPH. The lack of correlation between the symptom score and other physiological measures for BPH may also be related to the methods used during the validation process of the AUA symptom index: "only patients who the investigators believed clearly had symptomatic BPH were included in the validation process, but no standard diagnostic evaluation was imposed, since BPH is most commonly defined on clinical grounds" [6]. This indicates that patient selection may not have been based to a sufficient extent on the most important cornerstones in the diagnosis of BPH i.e. the combination of symptoms, prostatic enlargement and some evidence of bladder outflow obstruction [23].

The men in our study could be seen only once since it was a side-study of the randomized pilot study of the value of screening or no screening for carcinoma of the prostate. Therefore it was not possible to repeat flow rate measurements if the voided volume was below a certain value. Thus, the flow rate data indicate the results and correlations obtained in a setting where men can be seen once as would be the case in population studies of the prevalence of BPH and related symptoms. The flow rate values would probably have been somewhat higher if we could have repeated measurements in selected patients. Most probably the value range of this parameter would not have been much wider but only a shift of the value range would have occurred with a limited impact on the correlations.Indeed, in the study conducted by Garraway et al. [11] in which men had to void at least 150 ml for the flow rates to be accepted, the correlation between symptoms and flow rate was equally low (r=-0.20) as the correlation found in our study (r=-0.18).

Only the symptoms "weak stream" and "hesitancy" have been shown to be associated with urodynamically proven outflow obstruction in one report only [24]. The poor correlation between symptoms of prostatism and prostate volume and physiological measures of BPH is well known [25,26,27,28]. Some authors [25,28] conclude from this lack of correlation that objective demonstration of infravesical obstruction is mandatory before surgery for symptoms of lower urinary tract dysfunction.

6). Pathological BPH is an almost universal risk and the dominant determinant of BPH is age [29]. If BPH is a disease with a high prevalence in the community [11] and if symptom scores capture the essence of this disease, it is reasonable to postulate that there should be a positive correlation between the symptom score and age. However, this correlation is poor (r=0.09; p=0.04) and the prevalence of men suffering severely from one particular symptom is higher in the age interval 55 to 59 years than in the interval 60 to 64 years for all symptoms except urgency. Furthermore, the percentage of men with severe symptoms (IPSS >19) remains surprisingly constant at about 6%, which confirms the findings of a French survey [5]. It is difficult to explain these unexpected and counterintuitive findings, but men may first become used to a low level of symptom severity and report an increase only after the discomfort has become even more pronounced. Alternatively, one might explain these findings by assuming a possible bias being introduced by young men with symptoms preferentially agreeing to participate in this study. However, a significantly different self-selection process in younger men is not a likely explanation as the percentage of men between 55 to 59 years for whom the presence of voiding complaints was a reason to participate was lower than for the older age groups (Table 3).

Another factor that would attenuate the relationship between age and symptom severity is the increasing proportion of men per advancing 5 year age-group who were excluded from the evaluation because of a previous prostate operation (**Table 1**). If, however, the correlation

coefficient is recalculated by adding the excluded percentages of men per age group while assuming an IPSS of 21.3 for every excluded man (a score of 21.3 is the average of patients treated operatively for BPH in our department; unpublished data), the correlation coefficient becomes 0.16 ($p<0.001$). If an extreme correction is done by adding the excluded percentages of men per age group in such a fashion that the IPSS is assumed to be 0 in the youngest and 35 in the oldest age group with intermediate values for the age groups between the extremes, the correlation coefficient is 0.18 ($p<0.001$). Thus, despite these corrections the correlation remains poor. The lack of a good correlation with age may also be related to the method of validation of the AUA symptom index i.e. the fact that controls were on average about 25 years younger than the men with symptomatic BPH [6].

Inasmuch as patients present to their urologists because of symptoms, some form of scoring system is needed when studying the prevalence of BPH in the community. Because of the lack of correlation between symptoms and other measures for BPH, symptom scores should not be used to preselect men for further studies in the determination of the prevalence of clinical BPH as has been done by some investigators [11]. It is necessary to combine the presence of symptoms with other measures such as increased prostate volume and abnormal values of physiological measures such as flow rate or even pressure-flow studies because no predictions about the value of a certain parameter can be made by knowing one of the other parameter values. The interpretation of the parameter values in a clinical setting should take the lack of correlation and the variability of the parameter values into account.

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CHAPTER VI

Benign Prostatic Hyperplasia: appropriate case definition and estimation of its prevalence in the community?

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ABSTRACT.

There is no consensus about a case definition of benign prostatic hyperplasia (BPH). In the present study, BPH prevalence rates were determined using various case definitions based on a combination of clinical parameters used to describe the properties of BPH: symptoms of prostatism, prostate volume increase, and bladder outflow obstruction. The aim of this study in a community-based population of 502 men (55 to 74 years of age) without prostate cancer was to determine the relative impact on prevalence rates of the inclusion of these different parameters (and of different cut-off values for these parameters) in a case definition of BPH.

There is agreement that age is the dominant determinant of BPH. However, of 28 different case definitions that were formulated, only 8 gave a statistically significant increase in the prevalence of BPH with age. The highest overall prevalence of 19% (95% CI: 15-23%) occurred using the definition that combines a prostate volume > 30 cm^3 and an International Prostate Symptom Score (IPSS) > 7. The lowest prevalence rate of 4.3% (95% CI: 2-6%) occurred using the definition that combines a prostate volume > 30 cm^3, an IPSS > 7, a maximum flow rate < 10 ml/s, and the presence of a post void residual urine volume of more than 50 ml. Thus, prevalence rates depend very much on the parameters used in a case definition. Follow-up will establish which men will eventually request a work-up and treatment for BPH and will help determine the best clinical definition of BPH.

INTRODUCTION.

Transurethral resection of the prostate for benign prostatic hyperplasia (BPH) is one of the most common surgical procedures performed in men over the age of 65 [1,2]. However, prostatectomy rates are poor indicators of the prevalence of the disease because of biases related to thresholds of referral, availability of health facilities, and differing decision algorithms among surgeons [1]. The classic clinical picture of BPH has been described as a combination of three properties: an increased prostate volume, the presence of symptoms of "prostatism" and evidence of bladder outflow obstruction [3]. However, there is no consensus about a clinical case definition of BPH, primarily because there is neither agreement about the parameters that should be used to describe the aforementioned properties of BPH, nor about the normal range of values for these parameters. There is also a lack of strong correlations between these parameters. It is therefore necessary to address the three properties of BPH separately before they can be considered in relation to each other in attempts to estimate BPH prevalence in the community.
The present study attempted to define the syndrome of BPH in various ways based on relevant parameters used in daily clinical practice:the validated International Prostate Symptom Score (IPSS) [4], prostate volume, and parameters used to screen for bladder outflow obstruction, i.e., urinary flow rate and post void residual urine volume. No preselection is made on the basis of symptoms, prostate volume and/or flow rate.

MATERIAL AND METHODS.

Study design:

The community-based data on BPH presented in this paper were collected as part of a randomized pilot study designed to evaluate the value of screening for prostate cancer.
The municipal authorities of the city of Rotterdam, created a database containing the addresses of all men aged 55 through 74 years residing in 4 areas of the city. A total of 1186 men accepted the invitation to participate in the study and were stratified into four five-year age groups between 55 and 74 years. The response rates for the four age groups varied between 33 and 36.3%, resulting in a community-based population with a slight overrepresentation of men aged between 60 to 64 years and a slight underrepresentation of men aged 55 to 59 years (Table 1).

Table 1.

Frequency distribution of men in 4 age-groups between 55-74 years of age in the general community population and in the population of study participants.

Age (yrs.)	Total population	Participants
55-59	25.8%	20.9%
60-64	27.9%	32.0%
65-69	25.6%	26.1%
70-74	20.7%	21.0%
Total	100%	100%

Serum prostate specific antigen (PSA; Hybritech-assay) was used as a pre-screening tool. If the PSA value was above 10 ng/ml, a work-up was advised because of the high probability for prostate cancer [5]. These men were excluded from randomization into the study (N=30; 15 of these men were ultimately diagnosed with prostate cancer).
The remaining 1156 men were randomly assigned to a screening or a no-screening group. The 554 men assigned to the screening group were further examined by digital rectal examination (DRE) and transrectal ultrasound of the prostate (TRUS). Prostate biopsies were taken if DRE and / or TRUS were abnormal. The men in whom biopsies were positive for prostatic cancer (N=10), those who had undergone a previous operation of the lower urinary tract (N=39) and the men who refused the transrectal ultrasound examination (N=3) were excluded from the evaluation of the prevalence of BPH. Thus, a community-based population was established comprising 502 men in whom prostate cancer had been excluded with reasonable certainty and who had not previously undergone a prostate operation.
This study of the prevalence of BPH was one of several sub-studies planned from the screen versus no-screen pilot study. The parameters studied included uroflowmetry and the determination of the post void residual urine volume by transabdominal ultrasound, performed in 494 and 326 consecutive men, respectively.

Procedures:

Symptoms:

The symptom questionnaire used is the validated American Urological Association (AUA) index [6] which has been adopted by the World Health Organization as the International Prostate Symptom Score (IPSS) after addition of one disease-specific quality of life question (scale 0-6) [4]. This numerical symptom scoring system grades the following symptoms on a discrete scale of 0 (symptom never present) to 5 (symptom always present): incomplete emptying, increased frequency, intermittency, urgency, weak stream, hesitancy, and nocturia. The disease-specific quality of life question was phrased as follows: "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?". The response scale ranged from 0 (delighted) to 6 (terrible). Based on correlations between the symptom index and bother scores three subclasses of men were created according to total score results [6]: those with minor (IPSS 0-7), moderate (IPSS 8-19) and severe (IPSS 20-35) symptoms.
An analysis of the symptom scores in this community-based sample of men showed a weak correlation between age and total IPSS ($r=0.09$; $p=0.04$) [7]. Overall, 70% of the men had no or minor symptoms, 24% were moderately symptomatic, and 6% were severely symptomatic. There was only a small variation among age groups in the percentage of men with severe symptoms (range 5.3 to 6.5%).

Prostate volume:

TRUS was performed with a 7 MHz Bruel and Kjaer multiplane sector scanning probe. The planimetric technique of volume measurement was used [8]. The reliability of this method has been shown in a previous study [9]. Because the specific gravity of prostatic tissue is approximately 1 [10], the prostatic volume in cubic centimetres as determined by the ultrasound method was directly compared to prostate weight in grams when comparisons were made with other studies reporting prostate weights. An analysis of prostate volume in this community-based sample of men showed a weak correlation between total prostate volume and age ($r=0.26$; $p<0.001$) [11].

Almost all men (95%) between 55 and 74 years have a prostate volume of more than 20 cm^3. There is a statistically significant trend for an increase in the percentage of men with a volume of more than 30 cm^3 per 5-year age interval ($p < 0.001$), as well as in the percentage of men with volumes above 40 ($p < 0.001$) and above 50 cm^3 ($p < 0.001$).

Urodynamic parameters:
Uroflowmetry (ml/sec) was done using a Dantec Urodyn 1000 flow meter; the maximum flow rate (Q_{max}) and the accompanying voided volume were recorded.
The post void residual urine volume (ml) was measured by transabdominal ultrasound using an Aloka machine with a 3.5 MHz handheld probe. Volume was calculated using the formula: /6 x (width) x (height) x (depth) [12].
An analysis of the urodynamic parameters showed that of 494 consecutive men who were asked to void in the flow meter, 62 (13%) were unable to do so at that particular moment [7]. The initial bladder volume was 100 ml or more in 83% of those men who voided. In the prevalence estimations of clinical BPH, those men who could not void were categorized as having a flow rate below the chosen cut-off value (either 10 or 15 ml/sec).
On average, 76% of the men had a maximum flow rate of less than 15ml/sec and 43% had a maximum flow rate of less than 10ml/sec. The correlation between maximum flow rate and age was not significant ($r = -0.08$; $p = 0.08$).
Overall, 17% of the men in whom a uroflowmetry was performed had a residual urine volume of more than 50 ml. There was a statistically significant trend ($p = 0.004$) for an increase in this percentage with age, from 12% for men between 55 to 64 years, via 18% between 65 to 69 years to 30% between 70 to 74 years. Overall, the post void residual urine volume was poorly correlated with age ($r=0.12$; $p=0.03$).

Criteria on which prevalence rates can be based.

The following criteria were formulated for several case definitions of clinical BPH, combining two or more parameters and employing various "normal" (cut-off) values for these parameters:

(1) The men should be at least moderately symptomatic. Men who are bothered to a greater extent, i.e., those with an IPSS greater than 7 are more likely to benefit symptomatically from an intervention [6]. Two IPSS cut-off values have been used: greater than 7 (at least moderately symptomatic) or greater than 19 (severely symptomatic).

(2) The prostate volume as measured by transrectal ultrasound should be increased. The analysis of prostate volumes in the present community population has shown that volumes measured by transrectal ultrasound in living men are 21 to 28% larger than those measured at autopsy, and that 95% of the men between 55 to 74 years have prostate volumes of more than 20 cm^3, [11]. An overestimation of the prevalence is therefore likely if a volume of 20 cm^3 is elected as the cut-off, a value that has been derived from a review of autopsy studies by Berry et al.[13]. Furthermore, there is considerable overlap in size between normal and adenomatous prostates [13, 14]. When estimating the prevalence of clinically significant BPH, the prostate volume cut-off value above which there is a reasonably large chance for histopathological BPH should ideally be known. There is no ideal cut-off value, but a volume of 30 cm^3 as measured by ultrasound is a more acceptable value since it is equivalent to the average prostate

volume (and corrected autopsy-volume) for men around 55 years of age.A volume of 30 cm^3 at that age is associated with histopathologic BPH in about half of the cases [14]. Two cut-off values have been used in this evaluation : 20 and 30 cm^3

(3) Voiding dysfunction determined by objective measures should be present because most physicians expect treatment of BPH to relieve obstruction caused by the enlarged prostate. The only way to objectively determine whether men are urodynamically obstructed is by performing detrusor pressure-uroflow studies [15], which unfortunately are too invasive for use in large population studies. Therefore, the determinations of maximum flow rate and/or post void residual urine volume are generally used as screening tests when bladder outflow obstruction is suspected. The value of the maximum flow rate determination as a meaningful parameter in the definition of clinically relevant BPH is based on the following observations. Firstly, in patients with prostatic symptoms, infravesical obstruction was present in only 7% of men with a flow rate of more than 15 ml/sec [16]. Secondly, a maximum flow rate of less than 10 ml/sec indicates bladder outflow obstruction in 88% of patients, whereas a value between 10 to 15 ml/sec indicates obstruction in only half of the cases [17]. Thirdly, no patient with a peak flow rate within 2 standard deviations of normal (equivalent to about 10 ml/sec at a voided volume of about 100 ml) required surgery during a 5-year follow-up period [18]. In some of the criteria for the estimation of BPH prevalence that were formulated for this study, the maximum flow rate cut-off values were 10 ml/sec or 15 ml/sec.
Birch et al. demonstrated that the volume of post void residual urine may vary considerably when serial ultrasound measurements are done on the same day, but all patients in their study had residuals on all bladder scans [19]. It has also been shown that men with normal prostates have residual urine volumes of less than 12 ml [20]. Bruskewitz et al. have shown that in men with symptoms of prostatism who were selected for transurethral prostatectomy, the median residual urine volume was 55 ml (range 0-900 ml) and that the median residual urine volume had fallen to 10 ml (range 0-150 ml) 3 months postoperatively [21]. Since normal men do not have residual urine [20], the mere presence of post void residual urine (more than 50 ml) was considered to be a meaningful parameter in the estimation of BPH prevalence in the present study.

(4) The dominant determinant of BPH occurrence is age [22]. It was therefore postulated that the increase per 5-year age-group of the percentage of men who satisfy a certain criterion should show a statistically significant trend to be accepted as a possibly valid criterion.

Statistical analysis:

Spearman correlation coefficients (r) were used to evaluate the relations between age, IPSS, total prostate volume, post void residual urine volume and maximum flow rate. The Chi-square test for trend was used to assess whether percentages increased or decreased in relation to an ordered classification, i.e., age-groups. The level of statistical significance was set at p=0.05 (two-tailed).

RESULTS.

The estimation of prevalence rates was based on 28 different criteria as shown in table 2.

Table 2:

Summary of 28 criteria examined for a significant increase with age in the percentage of men who satisfied each criterion. These criteria were applied to 494 men except for the criteria including post void residual urine volume (PVR) which were applied to 326 men. The p-values are for trend of increase with age of the percentage of men who satisfy the criterion. An asterisk (*) indicates statistical significance.

Average % = average percentage of men between the ages of 55 and 74 years who satisfied the criterion; VolT = total prostate volume; IPSS = International Prostate Symptom Score;Qmax = maximum flow rate; QoL = disease-specific quality of life score.

Criterion (Case definition)	Average % (range)		P-value
VolT>20cm3+IPSS>7+Qmax<15ml/s	25	(20-32.5)	0.14
VolT>20cm3+IPSS>7+Qmax<15ml/s+QoL>2	13	(11.3-19.3)	0.42
VolT>20cm3+IPSS>7+Qmax<15ml/s+PVR>50ml	7	(2-13.3)	0.02*
VolT>20cm3+IPSS>7+Qmax<15ml/s+PVR>50ml+QoL>2	5	(2-10)	0.22
VolT>20cm3+IPSS>19+Qmax<15ml/s	6	(4.5-6.7)	0.47
VolT>20cm3+IPSS>19+Qmax<15ml/s+QoL>2	5	(3-6.7)	0.37
VolT>20cm3+IPSS>19+Qmax<15ml/s+PVR>50ml	2.5	(1-4.4)	0.20
VolT>20cm3+IPSS>19+Qmax<15ml/s+PVR>50ml+QoL>2	2	(1-3.3)	0.32
VolT>30cm3+IPSS>7	20	(10-27.7)	0.003*
VolT>30cm3+IPSS>7+QoL>2	11	(6.7-16.9)	0.04*
VolT>30cm3+IPSS>7+PVR>50ml	5	(2-10)	0.02*
VolT>30cm3+IPSS>7+PVR>50ml+QoL>2	3	(2-6.7)	0.23
VolT>30cm3+IPSS>7+Qmax<15ml/s	18	(9.2-26.5)	0.004*
VolT>30cm3+IPSS>7+Qmax<15ml/s+QoL>2	10	(6.7-15.7)	0.07
VolT>30cm3+IPSS>7+Qmax<15ml/s+PVR>50ml	5	(2-10)	0.02*
VolT>30cm3+IPSS>7+Qmax<15ml/s+PVR>50ml+QoL>2	3	(2-6.7)	0.23
VolT>30cm3+IPSS>19+Qmax<15ml/s	4	(2.5-4.8)	0.34
VolT>30cm3+IPSS>19+Qmax<15ml/s+QoL>2	3	(2.5-4.8)	0.49
VolT>30cm3+IPSS>19+Qmax<15ml/s+PVR>50ml	2	(0-4.4)	0.06
VolT>30cm3+IPSS>19+Qmax<15ml/s+PVR>50ml+QoL>2	2	(0-3.3)	0.09
VolT>30cm3+IPSS>7+Qmax<10ml/s	13	(5.8-16.9)	0.03*
VolT>30cm3+IPSS>7+Qmax<10ml/s+QoL>2	8	(5-10.8)	0.13
VolT>30cm3+IPSS>7+Qmax<10ml/s+PVR>50ml	3	(1.3-8.3)	0.03*
VolT>30cm3+IPSS>7+Qmax<10ml/s+PVR>50ml+QoL>2	2	(1.1-5)	0.25
VolT>30cm3+IPSS>19+Qmax<10ml/s	3	(0-5)	0.14
VolT>30cm3+IPSS>19+Qmax<10ml/s+QoL>2	2	(0-3.3)	0.14
VolT>30cm3+IPSS>19+Qmax<10ml/s+PVR>50ml	3	(0-5)	0.14
VolT>30cm3+IPSS>19+Qmax<10ml/s+PVR>50ml+QoL>2	2	(0-3.3)	0.14

These criteria represent combinations of an increased total prostate volume (> 20 or > 30 cm^3) and increased IPSS (> 7 or >19), with or without a decreased maximum flow rate (< 10 ml/sec or < 15 ml/sec) and with or without the presence of post void residual urine (> 50 ml). These combinations were also tested with inclusion of an additional parameter i.e. the presence of a score of 3 or more on the disease specific quality of life question (i.e. QoL > 2), which indicates that the men scored their feelings about their urinary condition between "about equally satisfied and dissatisfied" and "terrible".

The increase in the prevalence of clinical BPH per 5-year age-group based on the various criteria showed a statistically significant trend only for the 8 criteria summarized in table 3. Overall prevalence rates of clinical BPH for the whole population of men between 55 and 74 years of age based on these 8 different criteria are shown in **fig. 1**. The highest overall prevalence [19% (95% CI: 15-23%)] was found for criterion B, which combines a prostate volume of more than 30 cm^3 and an IPSS of greater than 7. The lowest prevalence rate [4.3% (95% CI: 2-6%)] was found for criterion H, which combines a prostate volume of more than 30 cm^3, an IPSS of greater than 7, a maximum flow rate of less than 10 ml/s, and the presence of a post void residual urine volume of more than 50 ml.

All criteria that incorporate the presence of a post void residual urine volume of more than 50 ml resulted in low overall prevalence rates.

Figure 1.

Overall prevalence rates of clinical BPH in a community-based population of men aged 55 to 74 years based on different case definitions (criteria).Straight lines connect the character for a certain criterion with the parameters and accompanying cut-off values necessary to satisfy that particular criterion. Error bars indicate 95% confidence intervals. A case definition based on criterion G, for example, means a combination of an International Prostate Symptom Score of greater than 7, a prostate volume of more than 30 cm^3 and a post void residual urine volume of more than 50 ml.

Q_{max} = maximum flow rate; QoI = disease-specific quality of life score.

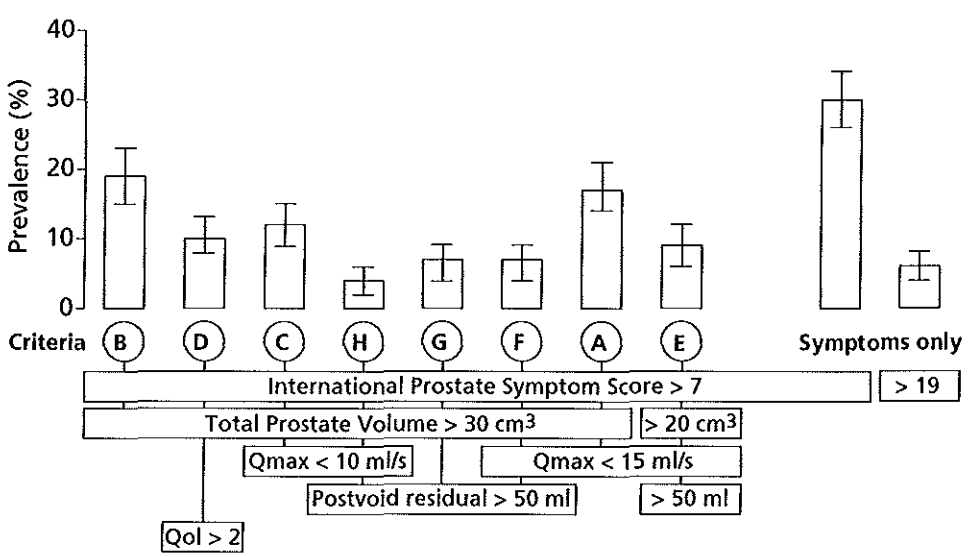

Table 3.

Percentages (with 95% confidence limits in parentheses) of men in age-group intervals with clinical BPH, defined according to 8 criteria that showed a statistically significant trend to increase with age. P-values refer to tests for trend.

VolT = total prostate volume (cm3); Qmax = maximum flow rate (ml/sec); PVR = post void residual urine volume (ml); IPSS = International Prostate Symptom Score; QoL = disease-specific quality of life score.

N	494	494	494	494
Criterion	A	B	C	D
Age (N)	VolT>30 and IPSS>7 and Qmax<15	VolT>30 and IPSS>7	VolT>30 and IPSS>7 and Qmax<10	VolT>30 and IPSS>7 and QoL>2
55-59 (120)	9(5-16)%	10(5-17)%	6(2-12)%	7(3-13)%
60-64 (159)	20(14-27)%	22(16-29)%	16(10-22)%	11(6-17)%
65-69 (132)	19(13-27)%	22(15-31)%	14(9-22)%	10(5-17)%
70-74 (83)	27(17-37)%	28(18-39)%	17(10-27)%	17(10-27)%
P-value	0.004	0.003	0.03	0.04

Table continued

N	326	326	326	326
Criterion	E	F	G	H
Age (N)	VolT>20 and IPSS>7 and Qmax<15 and PVR>50	VolT>30 and IPSS>7 and Qmax<15 and PVR>50	VolT>30 and IPSS>7 and PVR>50	VolT>30 and IPSS>7 and Qmax<10 and PVR>50
55-59 (76)	5(1-13)%	3(0.3-9)%	3(0.3-9)%	1(0.03-7)%
60-64 (100)	2(0.2-7)%	2(0.2-7)%	2(0.2-7)%	2(0.2-7)%
65-69 (90)	9(4-17)%	7(2-14)%	7(2-14)%	3(1-9)%
70-74 (60)	13(6-25)%	10(4-21)%	10(4-21)%	8(3-18)%
P-value	0.02	0.02	0.02	0.03

DISCUSSION.

Symptoms of prostatism should be present to justify a diagnosis of clinical BPH. However, the individual symptoms are not specific for BPH and are not even limited to the male population [23]. The prevalence of symptoms, although interesting by itself [24], is an inappropriate indicator for the prevalence of clinical BPH. Parameters that are indicators of the other properties of BPH and of the severity of the disease, such as prostate volume, maximum flow rate and post void residual urine volume, should be measured in all men without preselection and then be considered simultaneously with symptoms because there is only a poor correlation among these parameters [25].
A high prevalence of BPH has been reported in a survey carried out in a Scottish community [26]. In this survey, a complete work-up, including prostate volume measurement by transrectal ultrasound, was done only in selected participants (31%) who scored above a certain cut-off value on a prostatism symptom score and/or had a urinary flow rate below 15 ml/sec. The men who satisfied one of these two criteria and who were subsequently found to have a prostate volume of more than 20 cm^3 were classified as having BPH. In the present population, most men between 55 and 74 years of age (95%) had a prostate volume of more than 20 cm^3, [11] .This is in agreement with the findings in the study by Garraway et al. [26], which showed that 94% of the men above 60 years had a volume of more than 20 cm^3. Therefore, if 20 cm^3 is elected as the cut-off value above which ultrasound measured volumes are presumed to be abnormal, men would exclusively and inappropriately be classified as BPH patients on the basis of symptoms if the study were designed in the aforementioned fashion. For reasons outlined in the material and methods section of this paper, 30 cm^3 was used as an additional cut-off value in the present evaluation.
The determinations of maximum flow rate and /or the post void residual urine volume are generally used as screening tests in men with suspected bladder outflow obstruction. However, maximum flow rate is a notoriously variable parameter. The fact that a man voids with a poor flow with an adequate voided volume at one point in time does not imply that flow will not be higher at another point in time [27]. In the present attempts at estimation of the prevalence of BPH, maximum flow rate is not used as an ***and/or*** criterion in combination with the symptom score. To qualify for the diagnosis of BPH in some of the formulated criteria, men were required to have sufficient symptoms ***and*** a low maximum flow rate to ensure that those men who had no symptoms and who happened to have voided poorly on one occasion were not misclassified as clinical BPH cases.
An increase in the prevalence of clinical BPH per 5-year age-group based on various criteria showed a statistically significant trend only for the 8 criteria summarized in **table 3**. These criteria all resulted in prevalence rates much lower than those reported by Garraway et al. [24]. This is probably a result of the preselection of men in the latter study, which makes the presence of at least moderate symptoms the main determinant of the case definition in that study.
A limitation of the present study lies in the fact that men between 40 and 55 years is not studied. However, in the Netherlands, 96% of all patients hospitalized with the diagnosis of BPH are above the age of 55 years [2], indicating that clinical BPH is not a big health problem in the younger age group.
The data summarized in **table 3** indicate some additional important aspects. Adding maximum flow rate to the parameters of prostate volume and symptoms only slightly changes the prevalence rates if 15 ml/sec is chosen as the cut-off value (compare criterion A to B), but moderately

decreases the prevalence rates if 10 ml/sec is chosen as the cut-off value (compare criterion C to B). Choosing a cut-off value of 10 ml/sec increases the likelihood that patients qualifying for that criterion are urodynamically obstructed [17]. Thus, the parameter maximum flow rate has limited impact on the BPH prevalence rates and may, therefore, be a less important parameter in the case definition of BPH. Adding the presence of post void residual urine to the case definition drastically reduces the prevalence rates (compare criterion A to F, B to G and C to H). Although the presence of residual urine is sometimes used as a selection criterion for surgery, severe obstruction may be present without residual urine [28]. Inclusion of post void residual urine volume may lead to a case definition that is too strict.
A decrease in prevalence rates is also observed with the addition of the quality of life score (compare criterion B to D). This parameter was added to better estimate the percentage of individuals who might benefit from an intervention, although the relationship between this score and the likelihood that a man will actually undergo a prostatectomy has yet to be established in a prospective rescreening study.

Conclusions:

(1). It is likely that a prevalence estimation based on a preselection of men by symptoms and / or flow rate or the use of a prostate volume cut-off value of 20 cm^3 will overestimate the prevalence of BPH.

(2). The "true" prevalence of clinical BPH can presently not be determined because of a lack of consensus about a case definition for clinical BPH.This study has attempted to define clinical BPH on the basis of parameters used in daily clinical practice.Based on the approach followed, prevalence rates do not seem to be higher than about 10% and 25-30% in 55 to 59 year and 70 to 74 year age groups, respectively.These data are "open-ended" because detailed information on who will actually request a work-up and treatment for BPH is still not available.Follow-up by rescreening will eventually provide this information and help determine the best clinical definition of BPH.It is presently unwise to accept particular rates before a clear connection has been established between these rates and the actual need for treatment.

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PART B.

PATHOPHYSIOLOGICAL ASPECTS OF BENIGN PROSTATIC HYPERPLASIA.

CHAPTER VII

TREATMENT OF BENIGN PROSTATIC HYPERPLASIA BY ANDROGEN DEPRIVATION: MODERATE DECREASE IN PROSTATE VOLUME BUT NO SIGNIFICANT CHANGE IN URETHRAL RESISTANCE.

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ABSTRACT.

The effect of medical androgen deprivation in the treatment of benign prostatic hyperplasia has been studied in 12 patients. Six patients received the luteinizing hormone-releasing hormone agonist buserelin and 6 others received the antiandrogen cyproterone acetate. The treatment resulted in an average decrease in prostatic size of 29 per cent after 12 weeks as measured by ultrasonography. This decrease led to an increase in maximum urinary flow rate, a reduction in residual urine volume and a decrease in daytime voiding frequency. However, it caused no decrease in urethral resistance but only an increase in bladder contraction strength. After discontinuation of the treatment the prostates showed regrowth to the initial size within 6 to 36 weeks. The urodynamic changes were reversed as well. Although statistically significant, the urodynamic changes were minimal from a clinical viewpoint and did not lead to an unobstructed state after 12 weeks of treatment. For this reason the clinical indication for use of medical androgen deprivation in benign prostatic hyperplasia patients will remain limited for the time being.

INTRODUCTION.

The enlarged prostate in benign prostatic hyperplasia consists of epithelial and stromal elements. Increased numbers of stromal elements have been described by Bartsch and associates as the most prominent morphological difference between normal prostatic tissue and benign prostatic hyperplasia [1]. Shrinkage of the prostatic epithelium after castration has been reported by Huggins and Stevens in 1940 in 3 patients with benign prostatic hyperplasia treated by orchiectomy, who subsequently underwent prostatectomy [2]. Similar observations were reported by Wendell and associates [3]. Some evidence in the literature suggests that the pathogenesis of benign prostatic hyperplasia depends on an intact testicular function. Benign prostatic hyperplasia does not occur in eunuchs, although it has been described on 1 occasion in an early castrated patient by Scott [4]. Presently, it is unclear whether androgens, oestrogens directly secreted by the testicle or originating from peripheral aromatization of androgens, other growth factors or a combination of any of these induce prostatic growth in men. The strongest evidence for at least some testicular dependence of benign prostatic hyperplasia is based on the fact that prostatic volume decreases after castration. Schröder and associates found an average volume decrease of 31 per cent (range 19 to 55 per cent) within 2 to 3 months in 5 patients with benign prostatic hyperplasia (4 treated by castration and 1 by a luteinizing hormone-releasing hormone agonist)[5]. These findings are in agreement with the results of Peters and Walsh, who found an average decrease of 28 per cent (range 15 to 48 per cent) within 4 months using chemical castration by the luteinizing hormone-releasing hormone agonist nafarelin [6]. Tunn and associates reported an average volume decrease of 26 per cent as well as an increase of plasma testosterone in 7 patients responding to the aromatase-inhibitor testolactone, suggesting a possible role of oestrogens in the pathogenesis of benign prostatic hyperplasia [7]. These studies all reported a relief of obstructive symptoms documented either by a decrease in residual urine or an improved flow rate. We believe that maximum flow rate alone is an inadequate indicator of obstruction or of the success of therapy in clinical trials in which medical treatments of benign prostatic hyperplasia are tested, since it can classify objectively only about half of the cases as obstructive or non-obstructive. Furthermore, residual urine is a sign of an abnormality of bladder function rather than the direct result of urethral obstruction [8]. These observations encouraged us to design a protocol for medical treatment of benign prostatic hyperplasia patients in which prostate size was followed by transrectal ultrasonometry and an objective assessment of obstruction due to benign prostatic hyperplasia was made by extensive videourodynamic examinations at entry and during follow-up.

MATERIAL AND METHODS.

Study design.

A prospective study was done to compare the biochemical effects of cyproterone acetate and the luteinizing hormone-releasing hormone agonist buserelin on benign prostatic hyperplasia tissue. Patients with benign prostatic hyperplasia were treated by one of these drugs before transurethral resection of the prostate (TURP). The study protocol was approved by the ethical committee of our university hospital. Patients participated after signing an informed consent form. As part of this study, patients who were candidates for TURP but who were opposed to an operation were offered the opportunity to determine whether a possible reduction in prostatic volume, achieved

by androgen deprivation, would result in an improvement of the outflow obstruction. To be eligible for this study, patients had to present with obstructive and/or irritative voiding symptoms, complaints typical of benign prostatic hyperplasia. There had to be an enlarged prostate on rectal examination and transrectal ultrasound, with no signs of malignancy. Most importantly, there had to be urodynamic evidence of an obstructive pressure-flow plot [8,9] together with radiographic narrowing of the proximal urethra on an intake videourodynamic examination. Patients with urodynamic evidence of abnormal voiding due to causes other than benign prostatic hyperplasia and urodynamically non obstructed patients were excluded from this study. Other exclusion criteria were the use of drugs with an action on the bladder or prostate and the presence of endocrine abnormalities. Eligible patients were randomly assigned to 1 of 2 possible treatment regimens. Group 1 (6 patients) was treated with the anti-androgen cyproterone acetate (100 mg orally twice daily). Group 2 received the luteinizing hormone-releasing hormone agonist buserelin (0.4 mg 3 times a day intranasally). The treatment period was 12 weeks. Patients consented to be treated for at least 6 weeks and were free thereafter to leave the study and be treated by conventional means if no changes were noted in prostatic volume and/or symptoms. Buserelin patients were pre-treated until serum testosterone had decreased to the castration level. The treatment period in this group was considered to start as soon as the castration level was reached. The cyproterone acetate patients were treated for 12 weeks counted from the start of treatment. After 12 weeks the treatment was stopped in all patients. Patient compliance was evaluated at each visit by determining the serum testosterone level in all patients and the serum level of cyproterone acetate in those receiving the drug. The patients recorded voiding frequency in a diary throughout the study, starting 2 weeks before the start of treatment.

Urodynamic studies.

Videourodynamic studies were done at entry, 6 and 12 weeks after the start of treatment and 12 weeks after discontinuation of treatment. In the urodynamic studies the methods, definitions and units used were in accordance with the standards recommended by the International Continence Society [10]. The use of urethral resistance factors, which are discussed in the appendix, is an exception to this rule.

Before each urodynamic examination a free flow study was done and thereafter the amount of residual urine was measured. The urodynamic examination involved 2 bladder fillings at a medium rate with room temperature contrast fluid. The bladder was catheterized with two 5F catheters: 1 was used for filling and 1 for pressure recording. During filling the pressure and the volume in the bladder, and the pressure in the rectum were measured. During micturition the pressures in the bladder and rectum, flow rate, voided volume and residual urine were measured with external pressure transducers and a Dantec flowmeter. Throughout the study pelvic floor electromyography was recorded by stick-on electrodes and was used to indicate whether the patients were relaxing the pelvic floor muscles during voiding. We combined filling and voiding with short periods of fluoroscopy. The x-ray picture was recorded on videotape simultaneously with the pressure, flow and electromyography curves for later review.

The detrusor pressure (P_{det}) was plotted against the flow rate (Q) on an X-Y recorder.Computer analysis was used to determine the strength of the voiding detrusor contraction. The contraction strength at maximal flow was represented by the variable W_{max} as described previously [11]. A new urethral resistance factor called URA was calculated using an empirically determined formula (see appendix).

At the end of the micturition studies the filling catheter was removed and the remaining catheter was used for measurement of the resting urethral pressure profile by a perfusion method [12]. The length and height of the prostatic plateau region were noted [13]. For the analysis of the urodynamic data we used for each session the values for the different parameters determined in the voiding with the higher maximum flow rate.

Prostate volume.

Prostate size was determined at 2 to 3-week intervals by transrectal ultrasonometry. Measurements of the prostate volume were made by adding the surface areas of a series of transverse prostatic scans with a separation of 1 cm. The technique and equipment used in this study have been described previously [14].

Statistical analysis.

For the statistical analysis of the results nonparametric tests were used. Friedman's analysis of variance was used to give an impression of the over-all degree of difference between the measurements at 0, 6, 12 and 24 weeks (that is prostatic volume, the various urodynamic parameters and the micturition frequency). Wilcoxon's matched-pairs signed-ranks test was used to determine the significance of differences between 2 series of measurements of a particular parameter at 2 different times. Spearman's rank correlation coefficient was used to determine the association between prostatic size and urethral resistance variables at the entry examination. The same test was used to determine the significance of associations between changes in 2 different urodynamic parameters and between changes of prostatic volume and a single urodynamic parameter. This implies that for the statistical analysis of differences in urodynamic parameters at 2 different times only patients for whom matched pairs of urodynamic data at both of these times were available could be incorporated. Since 8 patients completed all the urodynamic studies up to 12 weeks only the data for these 8 patients were used for the analysis of differences between 0 and 12 weeks, and 6 and 12 weeks. Since 11 patients completed the urodynamic studies up to 6 weeks the analysis of differences between 0 and 6 weeks incorporated these 11 patients. However, since there were no statistically significant differences in the latter analysis only the data for the 8 patients who completed the studies up to 12 weeks are incorporated in table 1.

Table 1.

Prostatic volume as a percentage of initial volume (defined as 100 per cent) in patients with benign prostatic hyperplasia before (0 weeks) and during (6 and 12 weeks) androgen deprivation therapy, and 12 weeks after discontinuation of treatment (at 24 weeks).

Week	Mean % Volume (range)	No.pts.
0	100	12
6	76.5 (47-100)*	11
12	70.8 (47-100)	10
24	97.0 (60-113)**	7

* P<0.005 compared to week 0 (11 patients), ** p<0.01 compared to week 12 (7 patients).

For the analysis of the differences in prostatic volume between 0 and 6 weeks, 6 and 12 weeks, 0 and 12 weeks and 12 and 24 weeks the data of 11, 10, 10 and 7 patients respectively, were used for the same reason. It should be noted that 10 patients underwent the prostatic ultrasound study at 12 weeks but that 2 of them dropped out of the study before the corresponding urodynamic study was done, which explains the difference in the patient numbers between urodynamic studies and prostatic ultrasound studies at 12 weeks.

RESULTS.

Of the 18 patients studied urodynamically 6 were not entered in the protocol on the basis of the urodynamic findings. Of the remaining 12 patients, with an average age of 66 years (range 55 to 86 years) and an average prostatic volume of 41 ml (range 15 to 83 ml), 6 were treated with cyproterone acetate, while 6 received the luteinizing hormone-releasing hormone agonist buserelin.

Buserelin group.

Before treatment the levels of serum testosterone in these patients ranged from 9 to 14.3 nmol/l, with a mean of 12.4 nmol/l (normal intact male 20 nmol/l, range 10-50; after castration less than 2 nmol/l). The pre-treatment period (that is the time needed for the serum testosterone level to decrease to the castration range) lasted 2 to 4 weeks in all but 1 patient, who never reached the castration range even after 2 months of treatment and who dropped out of the study. The buserelin excretion value in the urine was low (2.51 ng/ml, creatinine 2.63 µg/gm). The cause of this low excretion value was not determined but poor compliance may be a possible explanation. The use of a depot preparation would have prevented this type of failure. The remaining 5 buserelin patients were compliant, with testosterone values ranging from 0.7 to 2.9 nmol/l. Of these patients 2 dropped out of the study after 11 and 12 weeks of treatment, respectively: 1 did not have a decrease in prostate size and 1 did not believe he was improving despite a decrease in prostatic volume.

Cyproterone acetate group.

Before treatment the levels of serum testosterone in these patients ranged from 9.9 to 25.7 nmol/l (mean 19 nmol/l). All 6 cyproterone acetate-treated patients were compliant, with serum levels of cyproterone acetate ranging from 0.71 to 3.35 nmol/l. The serum testosterone values during treatment ranged from 1.7 to 10.8 nmol/l. The lower levels reflect the fact that the anti androgen cyproterone acetate has some anti gonadotropic effects. Two cyproterone acetate-treated patients dropped out after 9 and 12 weeks of treatment, respectively: 1 because of a cerebrovascular accident and 1 because he had continued the medication after the 12-week treatment period.

Prostatic volume.

The prostatic volumes at 0, 6, 12 and 24 weeks were evaluable in 12, 11, 10 and 7 patients, respectively. The initial prostatic volume ranged from 15 to 83 ml. in cyproterone acetate-treated patients and from 15 to 50 ml. in those who received buserelin (average 45 and 36 ml., respectively). The percentage volume changes for the 5 evaluable buserelin-treated patients are shown in **figure 1.**

Figure 1.:

Effects of buserelin treatment and its discontinuation on prostatic volume in 5 patients.(tur.=transurethral resection of the prostate).

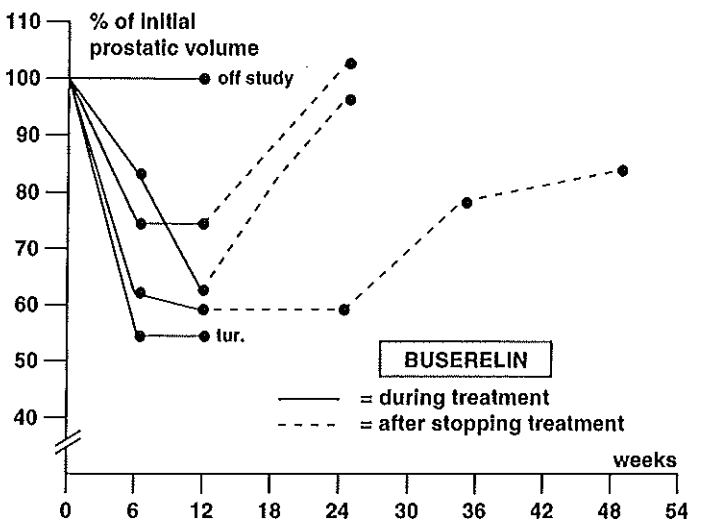
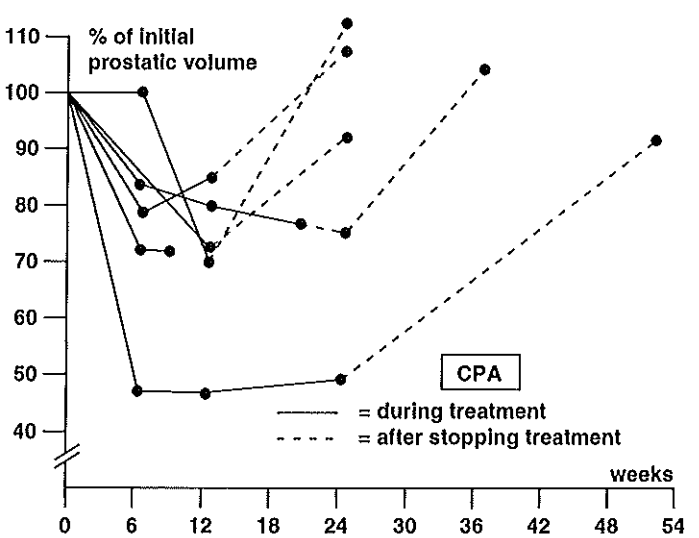


Figure 2.:

Effects of cyproterone acetate (CPA) treatment and its discontinuation on prostatic volume in 6 patients.



The percentage volume changes for the 6 cyproterone acetate-treated patients are shown in figure 2. All patients showed a decrease in prostatic volume, mainly in the first 6 weeks of treatment. One patient showed no decrease in the first 6 weeks but a steep decrease between 6 and 12 weeks of treatment. Two patients experienced a further decrease between 6 and 12 weeks, while 1 showed a slight increase during that period. Interestingly, 2 patients continued to use cyproterone acetate after 12 weeks: 1 did so in agreement with the investigator and he dropped out of the study, while 1 only confessed to having continued the medication for 8 weeks when it became clear that the prostatic volume had continued to decrease slightly after "discontinuation" of the medication (this patient was considered to be evaluable at 24 weeks). After discontinuation of the treatment the prostatic size increased to near its initial value in all patients who were followed.
The overall volume changes for the total group of buserelin and cyproterone acetate-treated patients are shown in table 1.

An average decrease of 29.2 per cent after 12 weeks of treatment was achieved. The average decrease of 23.5 per cent in the first 6 weeks of treatment was statistically significant ($p<0.005$). The further decrease between 6 and 12 weeks (5.7 per cent average) was not significant. After discontinuation of the treatment a mean increase of 26.2 per cent ($p<0.01$) was seen between 12 and 24 weeks. The prostatic volumes increased again to near the initial values within 6 to 36 weeks.

Urodynamic parameters.

The number of patients urodynamically evaluable at 0, 6, 12 and 24 weeks were 12, 11, 8 and 7, respectively. The urodynamic data of the 8 patients evaluable after 12 weeks of treatment and the data of the 7 patients evaluable at 24 weeks are shown in table 2.To determine the effects of treatment and discontinuation of treatment, overall differences between the 4 urodynamic examinations (that is at intake, after 6 and 12 weeks and 12 weeks after discontinuation of treatment) for the values of the parameters studied were tested statistically in the 7 patients who had undergone all 4 examinations according to the protocol. Significant differences were found for the residual urine after the free flow measurement ($p<0.05$, 7 patients). Correspondingly, Wilcoxon's matched-pairs signed-ranks test showed a significant decrease in residual urine between 0 and 12 weeks of treatment ($p<0.05$, 8 patients). Although the over-all differences were not statistically significant, detrusor pressure, detrusor contraction strength and maximum flow rate tended to be highest and the urethral resistance factor to be lowest at 12 weeks. The maximum flow rate at 12 weeks was significantly higher than at entry (Wilcoxon, $p<0.025$, 8 patients) and the increase in detrusor contraction strength between 6 and 12 weeks also was statistically significant (Wilcoxon, $p<0.025$), 8 patients). When $P_{det.Qmax}$ is plotted in the Abrams-Griffiths nomogram (figure 3), it becomes clear that only one patient has moved from the obstructed area to the unobstructed area; all others remain in the clearly obstructed area. No significant correlations were found between the changes in urethral resistance (urethral resistance factor) and percentage changes in prostate size occurring between 0 and 12 weeks ($r=-0.64$, $p=0.05$, 8 patients).

The daytime and night-time voiding frequencies of the 8 patients evaluable after 12 weeks of treatment and of the 7 patients evaluable at 24 weeks are shown in table 3. The daytime micturition frequency showed over-all significant differences among 0, 6, 12 and 24 weeks (Friedman's analysis of variance, $p<0.05$, 8 patients) and decreased significantly between 0 and 12 weeks (Wilcoxon,

$p<0.025$, 8 patients). From a clinical viewpoint, however, a decrease in daytime frequency from an average of 8.3 to 7 times can hardly be considered of importance. The same can be said for the statistically significant changes in the urodynamic parameters (table 2).

Table 2.
Results of detrusor pressure at maximum flow rate, maximum flow rate, detrusor contraction strength (Wmax), urethral resistance factor (URA), prostatic plateau pressure and length, and residual urine at 0, 6, 12 and 24 weeks.Values are means with ranges in parentheses.

	week 0	week 6	week 12	week 24
No.patients.	8	8	8	7
Residual urine after free flow (ml.)	51(10-146)	43(10-100)	35(2-100)*	52(5-140)
Maximum flow rate in pressure/flow study (ml/s)	6.2(3.5-11)	6.7(4-13.5)	7.9(5-16.5)**	6.5(3-11)
Detrusor pressure at max. flow rate (cmH_2O)	78(53-95)	75(48-100)	81(55-120)	73(38-100)
Urethral resistance factor URA (cmH_2O)	47(30-66)	47(17-82)	49(15-75)	49(20-73)
Maximum detrusor contraction strength W_{max} ($\mu W/mm^2$)	9.6(6.7-13.3)	9.7(5.9-14.2)	10.6(5.8-13.7)***	9.5(5.7-12.8)
Prostatic plateau pressure (cmH_2O)	21(8-44)	22(9-50)	23(14-44)	21(10-46)
Prostatic plateau length (mm)	11(7-19)	11(5-15)	11(7-15)	12(8-16)

* Significantly lower than week 0 ($p<0.05$), ** Significantly higher than week 0 ($p<0.025$), *** Significantly higher than week 0 ($p<0.025$)

Figure 3.
Effect of 12 weeks of androgen deprivation on pressure/flow parameters. Values for detrusor pressure at maximum flow rate are plotted in Abrams-Griffiths nomogram. Closed circles indicate pretreatment measurements and open squares indicate post-treatment measurements

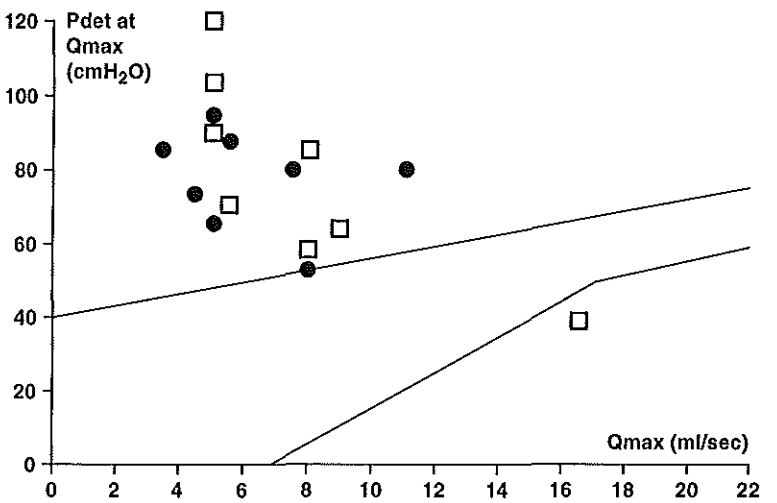


Table 3.
Daytime and night-time voiding frequency in patients with benign prostatic hyperplasia before (0 weeks) and during (6 and 12 weeks) androgen deprivation therapy, and 12 weeks after discontinuation of treatment (at 24 weeks). Values are means with ranges in parentheses.

Week	No.pts.	No. daytime voidings	No. night-time voidings
0	8	8.3 (6.0-11.5)	1.9 (0.5-4.5)
6	8	8.1 (4.5-10.5)	2.2 (0.0-5.0)
12	8	7.0 (4.5-10.5)*	1.9 (0.5-5.0)
24	7	7.4 (7.4-10.5)	1.7 (0.5-4.0)

*$p<0.025$ compared to week 0.

Side effects.

Hot flushes were experienced by the 2 of 6 patients using cyproterone acetate and by all 6 patients using buserelin. In 1 buserelin-treated patient this was an additional reason for dropping out of the study. A cyproterone acetate-treated patient dropped out at 9 weeks after a cerebrovascular accident. Whether the treatment contributed to this complication remains obscure. Fortunately, this patient recovered completely. At entry 5 patients (3 in the cyproterone acetate and 2 in the buserelin groups) were impotent and 7 claimed to be potent (3 in the cyproterone acetate and 4 in the buserelin groups). All patients were impotent during the treatment except for 1 cyproterone

acetate-treated patient who was compliant, with cyproterone acetate serum levels ranging from 1.85 to 2.57μmol/l. After discontinuation of the treatment all patients who were potent at entry regained potency except for 1 buserelin-treated patient who still is impotent after stopping the treatment and who, subsequently, underwent transurethral resection of the prostate.

DISCUSSION.

In this study an average decrease in prostate size of 29.2 per cent (range 0 to 47 per cent) was found in 10 benign prostatic hyperplasia patients after 12 weeks of treatment by androgen deprivation. These results are in agreement with those of others who documented changes in prostate size by transrectal ultrasonography [5,6]. The fact that an increase in stromal elements has been described as being the most prominent morphological difference between normal prostatic tissue and benign prostatic hyperplasia [1] makes it attractive to speculate that the incompleteness and wide range of shrinkage (0-55 per cent in the studies cited) are due to differing relative volumes of the epithelial fraction within the individual glands. This has been confirmed preliminarily on prostatic biopsy specimen by Peters and Walsh [6]. The study by Tunn and associates, who reported a 26 per cent volume decrease and an increase in serum testosterone in 7 patients who responded to aromatase inhibition, suggests that suppression of circulating oestrogens may be another factor of importance in achieving a decrease in prostatic volume in benign prostatic hyperplasia [7]. Unfortunately, oestrogen levels were not measured either in their study or in ours. Gabrilove and associates showed a decrease in serum oestradiol levels in 3 benign prostatic hyperplasia patients treated with the luteinizing hormone-releasing hormone agonist leuprolide [15]. From our data and the data available from the literature it can be concluded that an average volume decrease of about 30 per cent (with a wide range of 0 to 55 per cent) probably mainly representing the epithelial fraction, can be achieved by androgen deprivation within 6 to 12 weeks.

Our study demonstrates that the volume decreases achieved by androgen deprivation are not maintained after discontinuation of treatment and that regrowth of the prostate to near the initial volume occurs within 6 to 36 weeks. Our urodynamic data show that urethral resistance is correlated positively with the initial prostate size in the selected group of patients who were urodynamically obstructed. However, androgen deprivation did not lead to a clear-cut change in urethral resistance but it did lead to an increase in the strength of the detrusor contraction. As a result of these changes the maximum flow rate improved, and the residual urine volume and daytime voiding frequency decreased. Although these changes are statistically significant, they are not of great importance from a clinical viewpoint, that is they did not result in an unobstructed state. However, it is noteworthy that urodynamic changes, although minimal, do occur. The best urodynamic results were not seen until after 12 weeks of treatment. Thus, the urodynamic response appears to be delayed compared to the decrease in prostate size, which occurred mainly during the first 6 weeks of treatment.

The value of prolonged androgen suppression and prostatic volume reduction beyond 12 weeks was not the subject of this study. The urodynamic improvement seen at 12 weeks was reversed again at 24 weeks (that is 12 weeks after stopping treatment) in combination with regrowth of the prostate. The fact that the urodynamic response was delayed poses the question whether the urodynamic parameters would have improved further after a longer treatment period even if the

prostatic volume did not decrease any further. However, we believe that the side effects of impotence and hot flushes preclude a treatment period lasting longer than 3 months.
Although a "placebo effect" cannot be entirely ruled out as the cause of the changes that we have observed, the delay in urodynamic response suggests that it is a real rather than a placebo effect. Reece Smith and associates in a double-blind trial comparing the effect of permixon (a drug with an antiandrogenic effect) to that of placebo in benign prostatic hyperplasia patients, found a significant improvement in flow rate and symptoms in both groups but no significant difference between the results of treatment in either group [16]. However, a placebo-controlled study of the drugs used in our study does not seem to be justified, since the effects on the urodynamic parameters were only marginal.
Based on our results and those of our previous study [5] it is evident that androgen withdrawal has a pronounced effect on benign prostatic hyperplasia volume, which is associated with a statistically significant but clinically marginal urodynamic improvement. All of our current patients had an intermediate symptomatology. In the previous study it was shown that all patients in chronic urinary retention were able to void and remove the indwelling catheters. Perhaps then, in patients with a more advanced stage of benign prostatic hyperplasia (chronic retention) the urodynamic effect of a volume reduction of 30 per cent is sufficient to allow voiding. Furthermore, the possible effectiveness of androgen withdrawal at an early stage of benign prostatic hyperplasia has not been evaluated in this study. It remains possible that androgen withdrawal or suppression has a symptomatic effect in early benign prostatic hyperplasia.
The side effects of impotence and hot flushes certainly will continue to limit the development of conservative management of benign prostatic hyperplasia. It remains to be seen whether new drugs that exploit different mechanisms, such as 5-alpha-reductase or aromatase inhibition, will change the scene.
At this moment we would recommend androgen suppression in all situations when patients must await an operation for any reason, when patients are and will remain inoperable or when potency is a secondary consideration. A luteinizing hormone-releasing hormone agonist seems to be less suited to bridge a waiting period because of the delay in reaching the castration level of testosterone.

Appendix.

Changes in urethral resistance are difficult to assess. The resistance factors in common use (for example P_{det}/Q^2) are based on theoretical assumptions of doubtful validity [10]. For this reason the value of the resistance factor changes whenever the flow rate changes (for example at different bladder volumes) even if there is no real change in urethral resistance. To overcome this difficulty partially, we have constructed a new resistance factor that is based empirically on the average pressure-flow relations measured in 292 voidings of a separate group of adults with and without urethral obstruction. Thus, changes in the urethral resistance factor represent changes in urethral resistance for an average adult patient. Changes of detrusor detrusor pressure and flow rate for which the urethral resistance factor remains constant imply that (for the average patient) there has been no real change of urethral resistance. Further details have been reported elsewhere [17]. We have named the urethral resistance factor: URA.

URA can be calculated from the empirical formula:

$$URA=[(1+2aQ^2P_{det})^{1/2}-1]/aQ^2$$

where Q is the voiding flow rate and P_{det} is the corresponding detrusor pressure. If Q is expressed in ml. per second and P_{det} in cm. water, then the constant a has the value of $7.6x10^{-4}$ and the units of the urethral resistance factor are cm.water.In our study we have used the value of the urethral resistance factor at peak flow.

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CHAPTER VIII

Treatment of benign prostatic hyperplasia by laser coagulation (TULIP): Negligible prostate volume reduction but clear decrease in urethral resistance.

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ABSTRACT.

This prospective study was undertaken to evaluate the effects of transurethral ultrasound-guided laser-induced prostatectomy (TULIP) on urodynamic, symptomatic and prostate volume parameters as well as serum prostate-specific antigen.

The TULIP procedure was performed in 33 patients with benign prostatic hyperplasia with a mean age of 66 years. Patients were evaluated by pressure-flow studies, prostate volume measurement by transrectal ultrasound and the American Urological Association (AUA) symptom score.

At 3 month follow-up, laser prostatectomy has resulted in an increased maximum flow rate from 6.6 ± 0.5 to 11.2 ± 0.6 ml/s and in an objectively proven relief of the urodynamic obstruction, as evidenced by a decrease of the average value of the urethral resistance parameter URA and the detrusor pressure at maximum flow rate from 38.3 ± 2.7 to 21.3 ± 1.3 cmH_2O and from 62.7 ± 4 to 38.9 ± 2.1 cmH_2O, respectively. Symptomatic improvement is evident from a decrease in the AUA symptom score from 20.4 at baseline to 8.8 at 6-month follow-up. Although the total symptom score did not change significantly between 6 months and 1 year follow-up, the score of the symptom "weak stream" was significantly higher again at 12 months follow-up.

The TULIP procedure is a urodynamically and symptomatically effective treatment. Conclusions about the durability of this treatment modality should be made with reservations.

INTRODUCTION.

Transurethral Neodynium:yttrium-aluminum-garnet (Nd:YAG) laser treatment is one of the alternatives to transurethral resection of the prostate that is currently being investigated for the treatment of benign prostatic hyperplasia. Several methods of laser energy delivery to prostatic tissue are available [1]. Non-contact side-firing laser fibers operate by the creation of deep coagulation necrosis of the prostatic tissue without direct tissue contact. Contact fibers can vaporize tissue at a sufficiently high power when in direct contact with the tissue. Although most side-firing fibers are operated under direct vision, transurethral ultrasound-guided laser induced prostatectomy (TULIP) is a technology that utilizes the side-firing principle under ultrasound guidance. Via the transurethral route, the prostate is irradiated in a systematic way by a Nd:YAG laser source.
This study was initiated to determine objectively the effects of this treatment modality on urodynamic (urethral resistance) parameters, symptom score, prostate volume and serum PSA. Data on symptomatic changes and changes in uroflowmetry values have been reported previously for the TULIP procedure [2] and for visual laser ablation of the prostate (VLAP) [3, 4]. This study addresses changes in urethral resistance parameters after laser treatment for benign prostatic hyperplasia.

MATERIAL AND METHODS.

The procedure:

The TULIP system consists of an ultrasound imager and a 20F transurethral probe that incorporates a side-firing laser window positioned between two halves of a split ultrasound transducer. The TULIP probe is enclosed in a sleeve that incorporates a balloon at its distal end. The balloon, which is filled and pressurized with sterile water, creates a constant stand-off from the tissue, stabilizes the system in the prostatic urethra and decreases blood flow in the tissue. The 2 atmospheres of balloon pressurization are not associated with a dilatation effect [5]. The part of the probe that contains the laser window and the ultrasound transducer can be moved in a longitudinal and rotational fashion in the working window, which is created by the pressurized balloon. The TULIP system was coupled to a 60 W Nd:YAG laser set a 40 W. The procedure has been described in detail by McCullough et al. [1]. In the present series 48F balloons were used in all but 2 patients. Laser passes were initiated with a 5 second dwelling time at the bladder neck followed by a pull rate of 1 mm per second. Laser passes were terminated when the thickness of the prostatic tissue became 1 cm on the ultrasound imager. An average of 8 to 10 passes in different positions were made per patient. After the procedure, cystoscopy was performed to check for blanching of the prostatic urethra and a suprapubic catheter was inserted.

Study parameters:

Prostate volume was measured by transrectal ultrasound with a 7 MHz Bruel and Kjaer multiplane sector scanning probe. The planimetric technique of volume measurement was used at baseline and 3 months post-treatment [6].
Serum PSA levels (Hybritech-Tandem) were measured at baseline and 24 hrs, 48 hours, 1 week, and 3 months postoperatively. Prostate biopsies were performed in all men with PSA >10 ng/ml and in all men who had hypoechogenic lesions on transrectal ultrasound.

No prostate cancers were detected in the men included in this study.
The AUA symptom index [7] was determined at baseline and 3, 6 and 12 months post-treatment.
The post void residual urine volume (ml) was measured by transabdominal ultrasound using an Aloka machine with a 3.5 MHz handheld probe using the formula: /6x(width)x(height)x(depth) [8]. Measurements were done at baseline and 3, 6 and 12 months post-treatment.
Flow rates at 6 and 12 months are not reported because most patients did not produce voided volumes in excess of 100 ml, whereas voided volumes varied widely on different occasions, which would make comparisons not very relevant. Only the flow rates obtained during the controlled situation of the urodynamic tests at baseline and at 3 months follow-up are considered.
At baseline and 3 months post-treatment urodynamic studies, including pressure-flow studies, were done: the parameters URA (a group-specific urethral resistance factor) [9], $P_{det.Qmax}$, Q_{max}, W_{max} [10] (a bladder contractility parameter) were determined.
The values for $P_{det.Qmax}$ were plotted in the Abrams-Griffiths nomogram [11].
The protocol allows for repeat urodynamic studies after the 3-month period if during further follow-up the symptom index showed a significant deterioration (increase of 7 or more points i.e. an average increase of at least 1 point per symptom) together with an increase or stabilization of the residual urine volume above 50 ml.

Patients:

The 33 patients had an average age of 66 years (range, 50 to 79 years). The average prostate volume was 56 cm^3 (range, 20 to 118 cm^3). The average preoperative symptom score as measured by the AUA-7 index was 21.3 (range, 5 to 35). Two patients were in retention before the treatment. All patients had a 5-day course of prophylactic antibiotics. A minimum follow-up of 3 months is available in all patients. Twenty-six and 17 patients were followed for 6 and 12 months, respectively.

Statistical analysis:

Wilcoxon's matched pairs signed rank test was used to determine the significance of differences between two series of measurements of a particular parameter at two different times. The level of significance was set at $p<0.05$.

RESULTS

The average amount of energy (±SE) delivered to the prostate was 13,272 ± 936 Joule.
Patients were discharged after an average of 3.4 (range, 2 to 10) days. The first micturition per urethra occurred after an average of 2.7 (range, 1 to 29) days. The suprapubic catheter was removed after an average of 19 (range, 1 to 139) days when the residual urine was less than one third of the initial bladder volume on at least two consecutive occasions.

Prostate-Specific Antigen.

The effect of laser treatment of the prostate on the serum PSA value is shown in Table 1. There is on average a 14-fold increase in serum PSA after 24 hours. By the 3-month follow-up, the serum PSA has on average dropped below the baseline value.

Table 1.

Changes in serum prostate specific antigen values in relation to the TULIP procedure. Values are means ± standard error with ranges in parentheses.

	PSA (ng/ml)
Preoperative.	4.5 ± 0.9 (0.8 - 27.3)
24 hrs postop.	61.9 ± 18.7 (1.6 - 354)
48 hrs postop.	28.9 ± 6.8 (1.4 - 136)
1 week postop.	10.2 ± 1.9 (1.0 - 33.8)
3 months postop.	2.9 ± 0.5 (0.4 - 10.3)

Prostate volume.

The effects of laser treatment on prostate volume are summarized in Table 2. The average prostate volume as measured by transrectal ultrasound did not change significantly after the procedure. A clear conical defect in the prostatic urethra was seen in only 8 men after the procedure.

Table 2.

Effects of TULIP procedure on urodynamic (N=30), symptomatic (N=32) and prostate volume parameters (N=33) at three months follow-up. Values are means with ranges in parentheses.

Parameter	Baseline	3 mo.follow-up	p-value
AUA-7 index	21.3 (5-35)	10.7 (2-23)	0.0001
Prostate vol.(cm^3)	56 (20-118)	51 (15-125)	n.s.
$P_{det.Qmax}$(cmH_2O)	63 (26-110)	39 (18-58)	0.0001
Max.flow (ml/s)	6.6 (3.7-15)	11.2 (4.4-20.4)	0.0001
Resid.urine (ml)	87 (0-330)	58 (0-400)	n.s.
URA (cmH_2O)	38 (17-78)	21 (11-35)	0.0001
Wmax (W/m^2)	9.8 (3.4-16.6)	8.6 (4.3-14.6)	0.04

Urodynamic data.

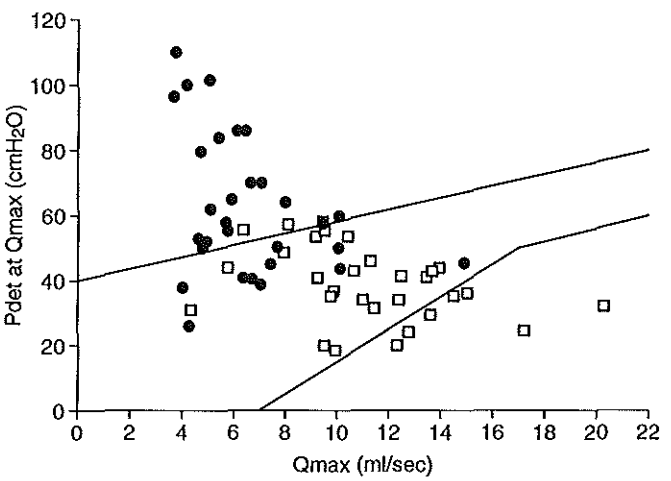
Comparative urodynamic data including pressure-flow studies (Table 2) are available for 30 patients. For the other 3 patients, baseline and follow-up residual urine volumes are available: both patients who were in retention and the one patient who refused invasive testing at 3 months had an excellent symptomatic result and voided well with residual urine volumes of 0, 60 and 74 ml, respectively.

The obstruction parameters $P_{det.Qmax}$ and URA decreased significantly. On average the URA value is in the non-obstructed range at the 3-month urodynamic follow-up. The bladder contraction strength parameter W_{max} showed a small but significant decrease. The flow rate increased significantly. However, the residual urine volume did not change significantly. If, however, the residual urine volumes of the 2 patients who were in retention preoperatively and the one

patient who did not undergo invasive urodynamic testing at 3 month are included, there is a significant (p=0.02) decrease of the average (± SE) residual urine volume from 163±71 ml to 57±18 ml.

Figure 1.

Effect of TULIP procedure on pressure-flow parameters.Values for detrusor pressure at maximum flow rate are plotted in Abrams-Griffiths nomogram.Closed circles indicate pre-treatment measurements and open squares indicate post-treatment measurements.



When $P_{det.Qmax}$ is plotted in the Abrams-Griffiths Nomogram (Fig. 1), it becomes clear that 12 and 4 patients, respectively, move from the obstructed area to the equivocal area and from the obstructed to the non-obstructive area. Three patients move from the equivocal to the non-obstructed area. Four and 7 patients, respectively, remain in the obstructed and in the equivocal areas. Preoperatively 20 patients were in the obstructive and 10 in the equivocal range, whereas at 3-months urodynamic follow-up, 4 men remained in the obstructive area and 19 and 7 were in the equivocal and non-obstructive area, respectively.

The average (± SE) residual urine volumes at 6 months and 12 months were 34±12 ml and 35±12 ml, respectively; these values were not significantly different from the values at 3-month follow-up.

Symptoms.

Baseline and 3-month symptom score data were available for 32 patients (Table 2; one patient did not complete a symptom score preoperatively). There was no correlation between the percentage change in urethral resistance (URA) and the percentage change in the total symptom score (r=0.13; p=0.537) at 3-month follow-up.

The baseline, 3- and 6-month follow-up symptom data of the 26 patients who have completed a minimum follow-up of 6 months are summarized in Table 3. Laser treatment of the prostate results in a significant improvement of the individual symptoms and the total score on the AUA-7 index. It takes between 3 and 6 months for the symptom "urgency" to improve significantly.

Table 3.

Effects of TULIP procedure on individual symptoms and total AUA symptom score at 3 and 6 months follow-up. Values are means with ranges in parentheses. All changes in scores are statistically significant ($p<0.05$) when compared to baseline, except those marked with an asterisk (*).

Symptoms	Baseline	Follow-up (3 mo;N=26)	Follow-up (6 mo;N=26)
1.Emptying	3.1 (0-5)	1.4 (0-5)	1.2 (0-5)
2.Frequency	3.4 (0-5)	2.3 (0-5)	1.7 (0-5)
3.Intermittency	2.8 (0-5)	0.8 (0-4)	1.0 (0-5)
4.Urgency	2.6 (0-5)	2.2 (0-5)*	1.5 (0-5)
5.Weak stream	4.2 (2-5)	1.3 (0-5)	1.3 (0-5)
6.Hesitancy	1.5 (0-5)	0.3 (0-2)	0.4 (0-4)
7.Nocturia.	2.7 (1-5)	2.0 (0-5)	1.8 (0-4)
AUA-7 index	20.4 (5-35)	10.3 (2-23)	8.8 (1-26)

This reflects the severe irritative symptoms which are sometimes encountered in the first weeks after the procedure.

In 17 patients the 12-month follow-up has been reached. The total score and the scores for the individual symptoms were not significantly different from the 6-month data, except for the symptom "weak stream" which showed an increase from 0.9 to 1.6 ($p=0.03$).

Repeat urodynamics after 3 months and retreatment.

At 6 months the symptom index had increased again significantly in 1 patient, but the residual urine volume in this patient was 0 ml as opposed to 80 ml preoperatively. At 12 months, a repeat urodynamic study was done in one patient because of a deteriorating symptom score and an increasing residual urine volume. The urodynamic study showed an increased urethral resistance and a TURP was subsequently performed in this patient. A TURP was performed in 1 additional patient at the 12-month follow-up. This patient developed macroscopic hematuria due to his BPH and underwent a TURP in spite of the fact that the AUA-symptom score remained low.

Complications.

Few complications were seen. The procedure had to be abandoned in one patient who is not included in this series, because of a false passage of the TULIP probe. Water intoxication did not occur in any of the patients. No blood transfusions were necessary. In 1 patient a transurethral catheter had to be inserted for bladder irrigation because of bleeding blocking the thin suprapubic catheter. This catheter was removed again 3 hours later. One patient needed intravenous antibiotics because of septiceamia. Another patient developed drug-fever due to the routinely administered antibiotics. No urethral strictures have been found during follow-up. No patient has complained of incontinence.

DISCUSSION.

There is still a paucity of articles dealing with results of laser treatment of the prostate. Kabalin [3] has compared the results of TURP and VLAP in 12 and 13 patients, respectively, and found comparable improvements in symptom score and maximum flow rate at 3 and 6 months follow-up. A 10-fold increase in serum PSA was noted after laser treatment. In the present series a 14-fold increase was found on average. Norris et al. [4] reported an average increase in flowrate from 7.6 to 12 ml/s after visual laser ablation of the prostate. McCullough et al. [2] have reported on the results at 6 months follow-up in 63 patients treated with the TULIP procedure. In these men the modified Boyarsky symptom score [12] decreased from 18.8±5 to 6.1±4.4 and the maximum flow rate increased from 6.7±3.2 ml/s to 11.9±4.7 ml/s. These results are comparable to the results of the present series.

No objective data on changes in urethral resistance and pressure-flow parameters in relation to laser prostatectomy are available in the literature. In the present study, the average (±SE) value of the parameter URA showed a decrease from 38.3±2.7 to 21.3±1.3 cmH_2O which represents an average change from the clearly obstructed range to the unobstructed range. These improvements are also apparent when the preoperative and postoperative values for $P_{det.Qmax}$ are plotted in the Abrams-Griffiths nomogram (**Fig. 1**). These results indicate that laser treatment of the prostate is clearly effective from a urodynamic point of view. The magnitude of the average change in the value of the urethral resistance parameter is comparable to the improvement seen in a group of 29 TURP patients as reported by Rollema and van Mastrigt [13], who found an average change from 41 to 16 cmH_2O for the parameter URA.

Symptomatically there is a clear effect as well. The average (±SE) AUA-symptom score had decreased from 21.3±1.4 to 10.7±1.0 at 3 months follow-up. This change is comparable to the change found by Barry et al [7] in a group of 27 TURP patients who showed a decrease from 17.6 to 7.1 at 4 weeks post-TURP. A further decrease to 8.8 at 6 months follow-up which is found in the present series, is mainly due to an improvement of frequency and urgency which reflects the late improvement of the sometimes severe irritative symptoms in the early postoperative period. Seventeen patients have been followed for 12 months or longer and the scores for the individual symptoms did not change significantly between 6 and 12 months except for the score of the symptom "weak stream" which increased from 0.9 to 1.6 on average ($p=0.03$).

The results of this series show that a significant decrease in prostate volume as measured by transrectal ultrasound is not necessary to achieve a clear urodynamic and symptomatic improvement. The minimal changes in prostate volume may not accurately reflect the effect on the prostate because there is a 14-fold increase in serum PSA 24 hours after the treatment, which indicates that considerable tissue damage has taken place. Furthermore, the average serum PSA at 3-month follow-up has fallen below the baseline value, which may indicate that tissue loss has taken place. The TULIP procedure is an effective treatment for benign prostatic hyperplasia. The long-term results have to be awaited. The fact that the score of at least one symptom, that is, "weak stream" shows deterioration at 12-month follow-up indicates that further studies of the durability of the effect of laser treatment of the prostate are certainly necessary.

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CHAPTER IX

Reasons for the weak correlation between prostate volume and urethral resistance parameters in patients with prostatism.

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ABSTRACT.

In an attempt to increase our understanding of the clinical syndrome of benign prostatic hyperplasia (BPH) an analysis was made of the association between prostate volume as measured by transrectal ultrasound and several reported urodynamically determined urethral resistance parameters. Two types of obstruction can be recognized on the basis of urodynamic data: a compressive type characterized by a high urethral opening pressure and a prolonged isovolumetric contraction phase before urine flow can start and a constrictive type characterized by a normal opening pressure and an increased slope of the urethral resistance relation. A combination of both types is often seen in BPH.

In our study, parameters that selectively quantify compression correlate weakly to moderately with prostate volume, whereas parameters that mainly quantify constriction do not correlate at all with prostate volume. Parameters that combine a measure for compression and constriction correlate less well with prostate volume than parameters that mainly quantify compression. The variation in prostate volume was found to determine the variation in urethral resistance by 15 % or less depending on the parameter used, which implies that the different pathophysiological mechanisms that can increase urethral resistance in the complex process of clinical BPH are mainly determined by factors other than the volume of the prostate. Thus, despite the lack of correlation between prostate volume and urethral resistance, pressure-flow studies and the determination of urethral resistance parameters provide a valuable contribution to the understanding of the pathophysiology of the voiding dysfunction in individual men with symptoms of prostatism.

INTRODUCTION.

The clinical syndrome of benign prostatic hyperplasia (BPH) has been characterized by a combination of 3 properties: the presence of symptoms of "prostatism", increased prostate volume and the presence of bladder outflow obstruction [1]. The relationship among these properties is complex and only partially understood. Many patients, especially those with predominantly stromal hyperplasia, have small prostate volumes [2] and up to 34% of the patients with clinical BPH who are treated by transurethral resection of the prostate (TURP) may be unobstructed urodynamically [3]. Therefore, it is clear that a considerable number of those men who presently undergo transurethral resection of the prostate because of clinical BPH do not exhibit the combination of the aforementioned 3 properties. A reason for this is the fact that there is no general agreement about a clinical case definition of BPH due to the lack of a strong correlation among the symptoms with which a patient presents to a urologist, the presence of BPH in a histopathological sense, prostate volume and the presence of urodynamically proved bladder outflow obstruction.

Patients with bothersome symptoms of prostatism seek treatment because they would like to be relieved of these symptoms. Therefore, relief of symptoms is undoubtedly the best indicator for a successful treatment from the patient perspective. However, symptoms of prostatism are non-specific, seem to be equally severe in age-matched groups of males and females [4], may at least to some extent be related to ageing [4] and have been shown to fluctuate considerably with time [5]. This fluctuation is also evident in the placebo arms of 2 different randomised drug trials studying an alpha-blocker and a 5-alpha reductase inhibitor with a follow-up of 4 weeks and 1 year respectively [6,7]. Although symptom scores decreased significantly in the placebo groups in both studies, there was no significant change in urethral resistance parameters showing the reproducibility of pressure-flow studies. Furthermore, up to 30% of patients with prostatism followed for 5 years without being treated have shown symptomatic improvement [8]. McGuire stated that symptoms of prostatism may be due to BPH, but that BPH and these symptoms are not synonymous with bladder outflow obstruction. Furthermore, he stated that BPH cannot solely be defined by its response to a treatment, when the rate of spontaneous improvement is high enough to account for considerable improvement without treatment [9].

Future research should provide a better understanding of the origin of the symptoms that have traditionally been called the symptoms of prostatism. Until that time, the study of objective anatomical and physiological parameters related to BPH can be expected to provide the clearest insight into the natural history and pathophysiology of BPH. Because most urologists expect a prostatectomy to relieve bladder outflow obstruction by the removal of a certain volume of obstructive prostatic tissue, the relationship between prostate volume and bladder outflow obstruction needs further clarification to increase our understanding of the pathophysiology of this disease.

MATERIAL AND METHODS.

We studied 67 consecutive patients with a mean age of 66 (range 37 - 84) years, who consented to participate in various treatment trials and who underwent detailed urodynamic studies because of the participation in these trials. These patients were selected on the basis of symptoms of prostatism and a flow rate of less than 15ml/sec.

Symptoms of prostatism.

All patients complained of a weak stream with varying degrees of hesitancy, intermittency, urge-frequency, nocturia, post-void dribbling and/or a feeling of incomplete emptying. In most men symptoms were not scored according to one of the well known scoring systems but, after its introduction, the AUA-7 index [10] was determined in the last one third of the patients for an average score of 19 (range 5 - 30). Patients with a proved or suspected neurogenic cause of the voiding dysfunction and those with prostatic or bladder cancer, or urethral strictures were excluded.

Prostate volume.

Transrectal ultrasound was performed using a 7 MHz multiplane sector scanning probe (Bruel and Kjaer).The planimetric technique of prostate volume measurement was used [11].

Urodynamics.

In all patients urodynamic studies were done including two pressure-flow studies. The methods, definitions and units used were in accordance with the standards recommended by the International Continence Society [12]. The use of urethral resistance parameters is an exception to this rule. The urodynamic examination involved 2 bladder fillings at a medium rate with fluid at room temperature. The bladder was emptied by catheterization. Thereafter, two 5F catheters were introduced: one was used for filling and one for pressure recording. During filling the pressure and volume in the bladder, and the pressure in the rectum were measured. During micturition the pressures in the bladder and rectum, flow rate and voided volume were measured with external pressure transducers and a Dantec flowmeter. The residual urine at the end of the examination was determined by catheterization or calculation. Throughout the study the pelvic floor EMG was recorded by stick-on electrodes and was used to indicate whether the patients were relaxing the pelvic floor muscles during voiding. From the two filling/voiding studies in each patient,the pressure-flow study with the highest maximum flow rate was used for the analysis. Pressure and flow rate signals were digitally stored with a specially developed computer program at a sample rate of 10Hz.

Parameters studied.

After filtering the data using a low pass digital Butterworth filter with a cut-off frequency of 1 Hz, pressure-flow plots were constructed from the stored detrusor pressure and flow rate signals. A flow delay time correction of 0.8s was applied. A computer algorithm selected those points with a flow rate above 0.25 ml/s that fell within a 10 cm H_2O band of the lowest monotonically increasing part of the pressure-flow plot. Through these selected points the passive urethral resistance relation [13] ($P_{muo}+c.Q^2$) and an orthogonal polynomial [14] ($A+B.[Q-ß]$) were fitted. In these formulas P_{muo} [13] is an estimate of the minimal urethral opening pressure; c [15] is an estimate of the curvature of the passive urethral resistance relation (PURR); A is an estimate of the average height and B is an estimate of the average slope of the lowest part of the pressure-flow plot. ß is the average of the flow rate values that correspond to the data points that constitute the lowest part of the pressure flow plot and roughly equals $Q_{max}/2$.
Several other indexes for bladder outflow obstruction that yield values on a continuous scale were determined as well:

- Qmax: the maximum flow rate. Because of its wide use, the maximum flow rate is included

in this study as an objectively determined urodynamic parameter; a poor flow rate may however be caused by detrusor failure and not by increased urethral resistance.

- $P_{det.Qmax}$: detrusor pressure at maximum flow.

- R_{min}: the "minimal resistance" [16], represented by the formula $P_{det.Qmax}/Q_{max}^2$. The value of this factor changes whenever the flow rate changes (for example at different bladder volumes) even if there is no real change in urethral resistance [17].

- URA: a group specific urethral resistance factor that is based on a statistical approximation of the average pressure-flow relations measured in a large number of patients. This parameter can be calculated for any micturition in which the maximum flow rate and the corresponding detrusor pressure are known [18].

- OBI: a parameter calculated as the weighed sum of the average height (A) and the average slope (B) of the lowest part of the pressure flow plot, by means of the formula OBI=A+2.4.B. The weighing factor 2.4 was obtained by Fisher's linear discriminant method [19].

Statistical analysis.

Using a statistical software package, descriptive statistics, the Spearman rank correlation coefficient (r) and the coefficient of determination (r^2) were determined to describe the association between prostate size and the various urodynamic parameters. The level of statistical significance was set at $p<0.05$ (one-tailed).

RESULTS.

Descriptive statistics with respect to patient age, prostate volume and urodynamic parameters are summarized in **table 1**. Results of urodynamic studies before and after transurethral resection of the prostate have shown that a decrease in urethral resistance hardly ever occurs below a certain preoperative cut-off value. Such a cut-off value can, therefore, be chosen to separate patients with and without obstruction preoperatively.
The rather low value of 20cm H_20 has been suggested as a cut-off point below which a patient is clearly considered not to have obstruction for P_{muo} and patients with values between 20 and 30cm H_2O have been considered to have mild obstruction [13]. For URA a cut-off value of 29cm H_2O has been suggested [2]. However, it should be realized that values of 28 and 32cm H_2O, for example, represent only small differences in urethral resistance so that these cut-off points should be used cautiously.
To make statements about the relative contribution of prostate volume to urethral resistance in patients with prostatism, the study population should include a sufficient number of men with a normal and increased prostate volume and a sufficient number with and without obstruction. The average values of the parameters P_{muo} and URA for the patients included in this evaluation were in the obstructed range if cut-off values of 20 and 29cm H_2O are used for P_{muo} and URA respectively (table 1).

Table 1.

Descriptive statistics of the patients showing mean values and ranges for the different urodynamic parameters, which were used in the correlation studies with prostate volume.

Parameter (unit)	mean	(range)
Age (yrs.)	66	(37-84)
Prostate volume (cm^3)	46	(8-132)
Q_{max} (ml/s.)	6.6	(1.5-12.6)
$P_{det.Qmax}$ (cmH_2O)	61	(25-127)
R_{min}.($cmH_2O.s^2/ml^2$)	2.4	(0.2-26.1)
P_{muo} (cmH_2O)	40	(11-78)
c ($cmH_2O.s^2/ml^2$)	0.85	(0.52-7.84)
URA (cmH_2O)	38	(15-77)
A (cmH_2O)	48	(15-87)
B (cmH_2O/ml/s)	4.7	(0.6-17.7)
OBI (dimensionless)	60	(17-107)

If a cut-off value of 29cm H_2O would have been chosen for both URA and P_{muo}, these parameters agreed that 13 of the 67 men (19 %) did not have obstruction. When using a rather low cut-off value that is 20cm H_2O for both parameters, they agreed that 59 men did and 2 clearly did not have obstruction. Two patients had obstruction according to P_{muo} but not according to URA, whereas 4 patients had obstruction according to URA but not according to P_{muo}. If the parameter URA with its cut-off value of 29cm H_2O is used as the only classifier, then 20 of 67 patients (30 %) are classified as urodynamically unobstructed cases. In this population of men who were selected for treatment on the basis of symptoms of prostatism and a maximum flow rate below 15 ml/sec, up to 30%, therefore, did not have urodynamic evidence of obstruction. This percentage corresponds to data of Abrams et al. who found that 36 percent of 318 patients with symptoms suggestive of outflow obstruction were urodynamically unobstructed [20] and to data of Rollema and van Mastrigt [3], who found that up to 34 % of cases with clinical BPH who are treated by transurethral resection of the prostate (TURP) may be unobstructed urodynamically.

The range of prostate volumes in our patients is wider than the range found in a community-based sample of men 55 to 74 years old [21]. Of our patients, 12 percent had a prostate volume of less than 20 cm^3,compared to only 5 percent of the men in the community-based sample. Furthermore, 67 percent of our men had a prostate volume greater than 30 cm^3 while this was the case in 60 percent of the community-based men.

The coefficients of correlation between the different parameters and prostate volume are summarized in table 2. The coefficients of determination show that the variation in the values of the parameters used to characterize bladder outflow obstruction can be attributed to the variation in prostatic volume by only 15% or less depending on the parameter selected. In descending order, the best (but still moderate) correlations between prostate volume and the parameters studied are found for A (r=0.39; p=0.001) (see Fig. 1), P_{muo} (r=0.38; p=0.001), OBI (r=0.31; p=0.006) and $P_{det.Qmax}$ (r=0.30; p=0.006). The parameters A, P_{muo}, $P_{det.Qmax}$ and URA correlate

better with prostate volume than B and C which both show a statistically non-significant correlation with prostate volume. The parameter OBI which combines A and B, correlates less well with prostate volume than A alone. Q_{max} and R_{min} both show a statistically non-significant correlation with prostate volume.

Table 2:

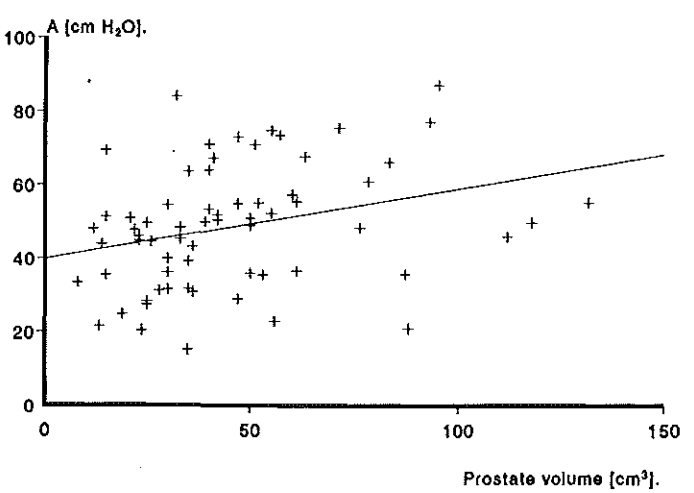
Correlation between prostate volume and various parameters that characterize bladder outflow obstruction represented by Spearman correlation coefficients (r) and coefficients of determination (r^2).

Parameter	r	r^2	p-value
Qmax	-0.05	0.003	0.33*
$P_{det.Qmax}$	0.30	0.09	0.006
R_{min}	0.18	0.03	0.07*
P_{muo}	0.38	0.14	0.001
c	0.08	0.006	0.26*
URA	0.24	0.06	0.027
A	0.39	0.15	0.001
B	0.04	0.002	0.37*
OBI	0.31	0.10	0.006

* Not statistically significant.

Figure 1.

Scattergram with regression line shows the correlation between the urethral resistance parameter A and prostate volume (r=0.39; p=0.001). The parameter A is an estimate of the average height of the lowest part of the pressure-flow plot.



DISCUSSION.

The properties of parameters to characterize urethral resistance are the subject of ongoing discussions. From a physical viewpoint it is clear that pressure-flow studies or parameters derived from them, are a more appropriate indicator of urethral resistance than uroflowmetry alone. Despite this, the urological community has been reluctant to accept the inclusion of more sophisticated urodynamics in the diagnostic evaluation of patients with symptoms of prostatism. Some of the reasons for this reluctance are that, urodynamic studies are invasive, there is a poor correlation between symptom severity or prostate size and simple urodynamic parameters such as maximum flow rate and post void residual urine volume [22], and that the preoperative severity of urodynamically determined bladder outflow obstruction seems to be a moderate predictor of outcome as measured by subjective symptoms and flow rate [23]. Also, many patients without urodynamic evidence of obstruction seem to do well symptomatically after prostatectomy [23]. A correlation between symptoms and urodynamically proved outflow obstruction has been shown in one study only, and only for the symptoms "weak stream" and "hesitancy" [24]. Finally, the correlation between prostate volume and urodynamically determined urethral resistance is believed to be weak.

Our study was performed to clarify the latter point, that is the relationship between prostate volume and urethral resistance in patients with symptoms of prostatism.

The non-correlation among prostate volume, and the parameters Q_{max} and R_{min} in the present evaluation is in agreement with the fact that pressure-flow studies or parameters derived from them are a more appropriate indicator of urethral resistance than uroflowmetry alone or a parameter that is biased by changes in uroflow such as R_{min}. These results are at variance with those of other investigators who noted a strong correlation ($r=0.8$; $p<0.001$) between prostate volume and the parameter R_{min} [25]. However, the patients in the latter study were highly select, since only men with voiding pressures of greater than 100cm H_2O and with flow rates of less than 15 ml/sec were included. Tan et al. [26] have reported a weak correlation between P_{muo} and prostatic volume ($r=0.27$; $p=0.003$) in 118 BPH patients with the same average age as our men. Details about the prostatic volumes of those patients were not given.

In our study the coefficient of determination was 0.15 at best (for the parameter A), which indicates that the variation in urethral resistance is determined by the variation in prostate volume by only 15% or less. Therefore, it can be concluded that most of the urethral resistance is determined by factors other than prostate volume alone. Since the correlation between prostate volume and urethral resistance is relatively poor, the size of the prostate should not be an important consideration when determining the necessity for therapy. The choice of the treatment modality, however, depends more on prostate volume.

Two types of obstruction can be recognized on the basis of urodynamic data: a compressive type characterized by a high urethral opening pressure and a prolonged isovolumetric contraction phase before flow can start and a constrictive type characterized by a normal opening pressure and an increased slope of the PURR [13]. In most BPH patients the compressive obstruction is accompanied by a certain degree of constrictive obstruction. In the parameter URA the constrictive and compressive elements are combined in one parameter based on a statistical approximation of the average pressure-flow relations measured in a large number of patients [18]. Selective quantifiers for compression, that is the parameters A and P_{muo}, correlate better with prostate volume than the quantifiers for constriction, that is B and C which both show a statistically non-significant

correlation with prostate volume. The parameters OBI, $P_{det.Qmax}$ and URA which combine the compressive and constrictive factor, correlate less well with volume than A and P_{muo}.
The weak to moderate correlation between prostate volume and various parameters describing bladder outflow obstruction does not disqualify these parameters and make them less useful in the characterization of voiding dysfunction due to BPH. From a pathophysiological viewpoint both factors are important in the characterization of the voiding dysfunction and, therefore, a parameter combining both may describe the global dysfunction more accurately.
The histological properties of the gland may at least in part determine the type of obstruction. Not all prostates treated by TURP show the same histological abnormalities. Dorflinger et al [2] showed that among 81 patients, predominantly stromal hyperplasia, predominantly glandular hyperplasia and mixed hyperplasia were present in 48, 28 and 23%, respectively. Although symptomatically there were no differences in outcome, the men with predominantly stromal hyperplasia had smaller resected weights and a significantly lower maximum flow rate 3 months postoperatively. They concluded that the stromal group may have incomplete relief of obstruction with standard TURP ,which conserves the surgical capsule, and they may be prone to suffer early recurrence of symptoms. This finding indicates that some treatment options may have a more pronounced effect on one of both aspects of bladder outflow obstruction. Alpha-blocker treatment has a relaxing effect on smooth muscle cells and, therefore, can theoretically influence the elasticity of the prostatic urethra. Urodynamic effects of alpha-blocker treatment can be expected to be more clear when a parameter that emphasizes or includes the factor constriction is used. The parameters URA and OBI were able to show small but significant effects of treatment with the alpha-blocker doxazosin at a dose of 2 and 4 mg [19]. A study of the urodynamic effects of transurethral microwave thermotherapy (TUMT) has shown no decrease of P_{muo}. However, a decrease in the curvature of the PURR (lower value of c) was noted with this treatment modality and it was postulated that urethral elasticity changes with TUMT [27].
In conclusion, the correlation between prostate volume and parameters for bladder outflow obstruction is at best only moderate, which does not imply that these parameters are of limited value. Some parameters are better suited to study one of the two elements of obstruction, that is either compression or constriction. A particular treatment modality may have more pronounced effects on one of these two elements. Furthermore, the different pathophysiological mechanisms that can increase urethral resistance in the complex process of clinical BPH are mainly determined by factors other than the volume of the prostate. Thus, despite the lack of correlation between prostate volume and urethral resistance, pressure-flow studies and the determination of urethral resistance parameters provide a valuable contribution to the understanding of the pathophysiology of voiding dysfunction in men with symptoms of prostatism.

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CHAPTER X

DEPENDENCE OF MALE VOIDING EFFICIENCY ON AGE, BLADDER CONTRACTILITY AND URETHRAL RESISTANCE.

-Development of a voiding efficiency nomogram-

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ABSTRACT.

The influence of age, urethral resistance and bladder contractility on voiding efficiency was studied in males. In 138 men with a mean age of 60 (range 18-86) years, pressure-flow studies were done. From these, the urethral resistance parameter URA was calculated and the maximum bladder contraction strength was determined using the contractility parameter W_{max}. If premature fading of the bladder contraction occurred, this was quantified by a bladder contraction strength decay factor (W80-W20). Voiding efficiency was expressed by the parameter % PVR that is the post void residual urine volume as a percentage of the initial bladder volume.

Multiple regression analysis showed that voiding efficiency depended significantly on: URA, W_{max} and W80-W20, in this order. Patient age was not an independent factor. W_{max} and W80-W20 were not correlated; therefore, maximum bladder contraction strength and its decay seem to constitute different properties of bladder contractile function. A voiding efficiency nomogram is proposed, making use of the values for W_{max} and URA in individual patients. Such a nomogram may have predictive value for the occurrence of acute retention and has to be tested prospectively.

INTRODUCTION.

The most important determinant of benign prostatic hyperplasia (BPH) occurrence is age [1]. The clinical syndrome of BPH has been characterised as a combination of 3 properties: symptoms of "prostatism", increased prostate volume and voiding dysfunction which is best described as bladder outflow obstruction [2]. The relationship among these properties is complex and only partially understood. Voiding (dys)function is determined by neurogenic factors, the contractile properties of the bladder and the urethral resistance [3]. The interaction of these basic properties can be observed during a urodynamic study. As yet,no efforts have been made to quantitatively relate voiding efficiency to urodynamic parameters representing these properties. Such a quantitative relation might, among other things, be predictive of the occurrence of acute retention in individual patients. As a first step towards this goal, the influence of age, the urethral resistance parameter URA [4] and the bladder contraction strength variable W [5] on voiding efficiency were studied in men.

MATERIAL AND METHODS.

138 consecutive men with a mean age of 60 (range 18-86) years, with various obstructive and irritative voiding symptoms were studied urodynamically. Patients with (suspected) neurogenic voiding disorders, malignancies of the urinary tract, diabetes mellitus or patients who had previously undergone operations of the lower urinary tract were excluded.
The methods, definitions and units used in the urodynamic studies were in accordance with the standards recommended by the International Continence Society [6]. The use of urethral resistance and bladder contraction strength parameters are exceptions to this rule. The urodynamic examination involved 2 consecutive bladder filling and pressure-flow studies. The bladder was catheterised with two 5F catheters: one of which was used for medium rate bladder filling with room temperature contrast fluid, and one was used for pressure recording. The pressures in the bladder and rectum and flow rate were measured with external pressure transducers and a Dantec flowmeter. The residual urine volume at the end of the pressure-flow studies was determined by catheterization unless x-ray screening showed that there was no remaining contrast fluid in the bladder; in the latter situation the residual urine volume was considered to be zero. The rectal pressure was subtracted from the intravesical pressure to derive the detrusor pressure. Throughout the study the pelvic floor EMG was recorded by stick-on electrodes and used to indicate whether the patients were relaxing the pelvic floor muscles during voiding. In some patients there were considerable differences between the two pressure-flow studies. To establish uniform data processing the pressure-flow study with the highest maximum flow rate was used for further analysis in all patients. Since bladder contractility is not likely to change between two measurements, the measurement with the highest flow rate represents the measurement with the lowest urethral resistance, that is the most relaxed micturition.
Detrusor pressure and flow rate signals were sampled at a 10Hz sampling rate and stored on computer disk. The signals were filtered off-line by means of a digital low pass Butterworth filter with a cut-off frequency of 0.5 Hz. Pressure-flow plots were constructed from the filtered detrusor pressure and flow rate signals. A flow delay time correction of 0.8 s was applied.
Urethral resistance was quantified using the parameter URA: a group specific urethral resistance

factor which is based on a statistical approximation of the average urethral resistance relation in a large number of patients. This parameter can be determined for any micturition in which the maximum flow rate and the corresponding detrusor pressure are known; a quadratic urethral resistance relation is then drawn through this point and its intersection with the pressure axis of the pressure-flow plot determines the value of URA [4].

Bladder contraction strength was quantified using the contractility variable W [5]. This variable expresses the strength of a detrusor contraction in terms of a combination of the detrusor pressure, the flow rate and the bladder volume. This variable can be considered to approximate the mechanical power developed by the contracting bladder and has the dimension of power per bladder wall surface area. W was plotted as a function of the decreasing volume in the bladder throughout micturition. From the bladder contraction strength variable the following parameters were calculated (Fig.1): W_{max}, the maximum value of W during micturition; $rV(W_{max})$, the relative volume or the percentage of the voided volume at which this maximum of W occurred, and W80-W20, the value of W at a relative volume of 80% minus its value at a relative volume of 20%.

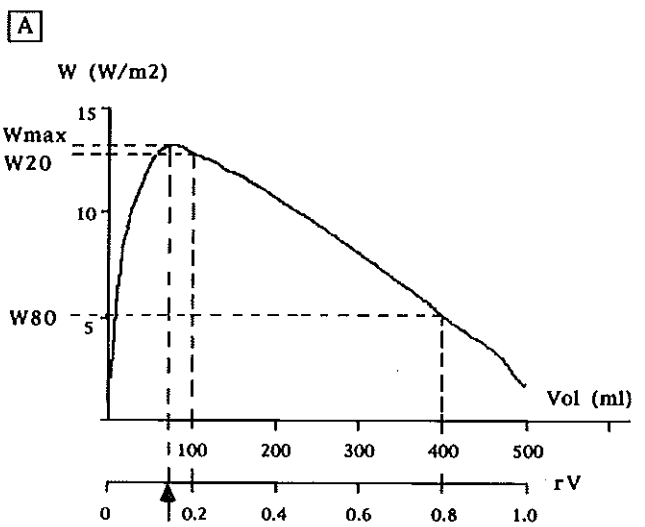
The parameters W80-W20 and $rV(W_{max})$ were used as quantitative measures of the decay of bladder contraction strength when a contraction faded away prematurely (see Fig.1). The parameter W80-W20 has been shown to perform best in the discrimination of patients with normal and fading contractions [7] and has been named bladder contraction strength decay factor. A positive value of this parameter indicates that the contraction fades away prematurely.
Voiding efficiency was expressed in terms of % PVR which is the residual urine volume expressed as a percentage of the initial premicturition bladder volume. A value of 50 ml is often used as the limit above which the residual urine volume is called significant in prostatism [8]. Others have stated that the residual urine volume is pathologically high if it is more than 10 percent of the bladder capacity [9].
In this study we have assumed that a % PVR of more than 10 percent is significant. The group of men with % PVR of more than 10 percent (N=84) included all men with a PVR of more than 50 ml and 7 men with a PVR of less than or equal to 50 ml.

Statistical analysis.

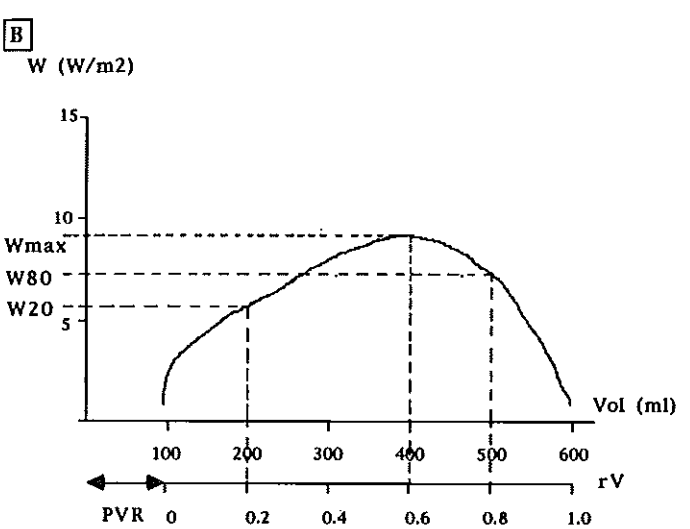
Mann-Whitney's U test was used to compare parameter values between sub-groups of patients. Correlations between parameters were calculated using Spearman's rank correlation coefficient (r). The level of statistical significance was set at $p<0.05$ (one-tailed).
Multiple regression analysis was used to examine whether the parameters age, W_{max}, W80-W20 and URA were independent factors determining voiding efficiency expressed in terms of the post void residual urine volume as a percentage of the initial premicturition bladder volume (% PVR).

Figure 1.:

Schematic examples of the variable W (approximation of power per detrusor muscle surface area) as a function of bladder volume (Vol) and parameters used to quantify the shape of this function. The graphs trace voiding from right to left starting at the initial bladder volume and ending when micturition ceases with or without residual urine. Bladder volume is also expressed on a relative scale (rV); rV=1 indicates the initial bladder volume at the start of micturition and rV=0 indicates the bladder volume when micturition has ceased. PVR indicates post void residual urine volume.



A.
Normal micturition:
W increases with decreasing bladder volume and voiding ends without residual urine. W80 (W at rV=0.8) is lower than W20 resulting in a negative value for W80-W20. The arrow indicates rV(W_{max}).



B.
Prematurely fading bladder contraction:
W decreases towards the end of micturition leaving 100 ml of residual urine. W80 is higher than W20 resulting in a positive value for W80-W20.

RESULTS.

Table 1.

Urodynamic characteristics of the study population (N=138).

	mean	median	range
Age (years)	60.3	65	(18-86)
Q_{max} (ml/s)	8.7	7.5	(1.5-27.3)
$P_{det.Qmax}$ (cmH_2O)	55	50	(9-143)
URA (cmH_2O)	32.5	28.7	(7.8-98.8)
W_{max} (W/m^2)	9.7	9	(1.7-20.9)
Residual urine (ml)	151	90	(0-800)
% PVR (%)	28	23	(0-90)

Table 1 summarises the urodynamic characteristics of the patient population: 47 percent (65 of 138) of the men were obstructed on the basis of a discriminating value of URA (more than or equal to 30 cmH_2O)[10]. Half of the men had an age above or below 65 years respectively.

Table.2

Urodynamic characteristics of men with (%PVR more than 10 percent) and without (% PVR less than or equal to 10 percent) a significant amount of residual urine. Values are means ± standard error. P-values indicate that the groups are different for all listed parameters, except for W_{max}.

	PVR 10% (N=54)	PVR > 10% (N=84)	p-value
Age (yrs)	55.5±2.3	63.5±1.3	0.008
URA (cmH_2O)	24.8±1.3	37.4±1.9	0.004
W_{max} (W/m^2)	10.4±0.5	9.3±0.4	n.s.
$rV(W_{max})$ (ml)	0.31±0.04	0.77±0.03	<0.001
W80-W20 (W/m^2)	-1.0±0.3	1.5±0.3	<0.001

Table 2 compares the parameters for urethral resistance and bladder contractility between the group of men with (% PVR > 10 percent) and without (% PVR 10 per cent) a significant amount of residual urine. Men with a significant amount of residual urine were significantly older and on average had a fading bladder contraction. These men also had a significantly higher urethral resistance but their maximum bladder contraction strength did not differ from the value found in men without a significant residual urine volume; by inference, men without a significant residual urine volume, on average, had better flow rates.

The correlation coefficients among patient age, parameters describing bladder contractile function (W_{max} and W80-W20), urethral resistance (URA) and residual urine volume as a percentage of

the initial bladder volume (% PVR) are summarised in table 3. Maximum bladder contraction strength and the bladder contraction strength decay factor were not correlated and seem to constitute two different properties of bladder contractile function. The parameter % PVR seemed to be related more strongly to the bladder contraction strength decay factor W80-W20 (r=0.40; p<0.001) than to the maximum bladder contraction strength (r=0.22; p=0.01) during micturition (Table 3).

Table 3.

Correlation coefficients among age, parameters describing bladder contractile function (W_{max} and W80-W20), urethral resistance (URA) and residual urine volume as a percentage of the initial bladder volume (%PVR)

	Age (yrs.)	W_{max} (W/m^2)	W80-W20 (W/m^2)	URA (cmH_2O)
W_{max} (W/m^2)	-0.23 (p<0.001)			
W80-W20 (W/m^2)	0.20 (p=0.02)	0.15 (n.s.)		
URA (cmH_2O)	0.23 (p<0.001)	0.31 (p<0.001)	0.51 (p<0.001)	
%PVR	0.29 (p<0.001)	0.22 (p=0.01)	0.40 (p<0.001)	0.46 (p<0.001)

However, W80-W20 strongly depended on URA (r=0.51; p<0.001). Therefore, a multiple regression analysis is a more appropriate way to determine which parameters are the best predictors of %PVR.

Table 4.

Multiple regression analysis with %PVR as the dependent and age, URA, W_{max} and W80-W20 as the independent variables.

Variable	Coefficient	Standard error	T-value	Probability	Partial F
INTERCEPT	0.229				
Age (yrs)	0.001	0.001	0.772	0.442	0.6
URA (cmH_2O)	0.008	0.001	5.359	0.000	29
W_{max} (W/m^2)	-0.028	0.006	4.979	0.000	25
W80-W20 (W/m^2)	0.021	0.008	2.595	0.0105	7

Such an analysis (table 4) with % PVR as the dependent variable showed that URA, W_{max} and W80-W20 were the significant independent variables in the regression equation. Patient age was not an independent factor. Thus, based on the correlations in table 3 and the multiple regression analysis, the urodynamic factors which determined the voiding efficiency (% PVR) were: the urethral resistance parameter URA and the parameters W_{max} and W80-W20. Based on these considerations W_{max}-URA (Fig. 2), [W80-W20]-URA (Fig. 3) and W_{max}-[W80-W20] scattergrams were constructed.

Figure 2.
Scattergram of maximum bladder contraction strength (W_{max}) and urethral resistance (URA), which can be used as a voiding efficiency nomogram. Open circles indicate men with a percentage of residual urine which is less than or equal to 10 percent of the initial bladder volume and closed circles indicate men with a percentage of residual urine which is more than 10 percent of the initial bladder volume. Area C indicates empty area where no voidings have been recorded. Voiding is physically impossible in this area (see text). Area B only contains data points of men with a % PVR which is less than or equal to 10 percent of the initial bladder volume.

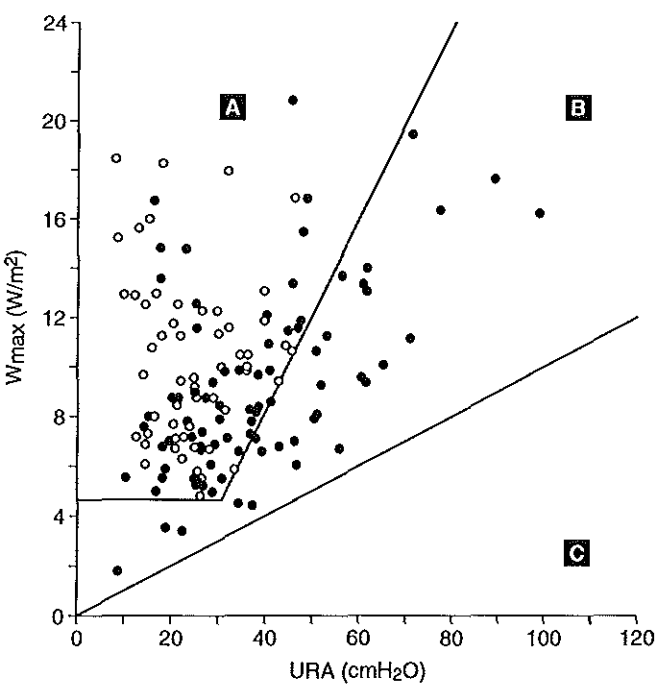
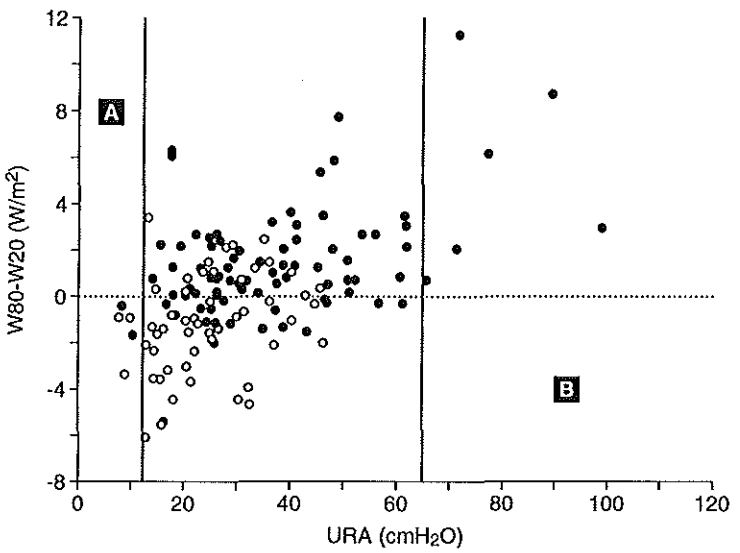


Figure 3.
Scattergram of the bladder contraction strength decay factor (W80-W20) and the urethral resistance factor (URA). Open circles indicate men with a % PVR of less than or equal to 10 percent of the initial bladder volume and closed circles indicate men with a % PVR of more than 10 percent of the initial bladder volume. Area A does not contain data points; it represents an area where no prematurely fading contractions occur. Area B is also empty;it indicates that above a certain value of URA, bladder contractions have faded prematurely.



In the W_{max}-URA scattergram an empty area (area C; Fig. 2) appeared. This area can be explained theoretically. If there is no urine flow, the value of W_{max} (in W/m2) equals approximately one tenth of the detrusor pressure (in cm H_2O)[6]. Under the same circumstances, URA is equivalent to the minimum urethral opening pressure. Inasmuch as voiding cannot occur when the isometric detrusor pressure is lower than the minimum urethral opening pressure, voiding is impossible if the numerical value of Wmax is less than one tenth of the numerical value of URA. Based on these considerations, a line separating area B and C was drawn in Fig. 2; below this line voiding is physically impossible. In reality, URA slightly underestimates the minimal urethral opening pressure which means that the line would move even closer to the data points in area B. Looking at the data in this way shows that voiding was impossible if a certain minimum value of W_{max} could not be reached. This necessary minimum value is higher when the urethral resistance is higher. Another pair of lines was drawn to border the data points of those men who voided with a residual urine of less than 10 percent of the initial bladder volume. In this way, three areas (A, B and C) were identified in Fig. 2. Area B i.e. the area between the drawn lines did not contain data points of men with residual urine volumes of less than 10 percent of the initial bladder volume. In fact, about half (14 of 29) of the men in area B had residual urine volumes of more

than 70 percent of the initial bladder volume and 14 of 16 men (88 percent) with a %PVR of more than 70 percent in this series resided in area B. In area A there was an overlap of men with and without a % PVR of more than 10 percent.
A W_{max}-[W80-W20] scattergram (not shown) was also studied; using such a scattergram in the same way as the W_{max}-URA scattergram it was not possible to separate patients with % PVR of more than 70 percent from patients with % PVR of more than 10 percent as well as in the W_{max}-URA scattergram. An area equivalent to area B in Fig. 2 contained only 8 of the 16 (50 percent) men with a % PVR of more than 70 percent and only 8 of the 24 (33 percent) men in this area B had a % PVR of more than 70 percent.
Figure 3 shows the [W80-W20]-URA scattergram. The empty area A in this scattergram indicates that fading bladder contractions did not occur in men with a low urethral resistance (URA below $\pm 12 cmH_2O$). This is in agreement with the relatively strong correlation between URA and W80-W20 ($r=0.51$). The empty area B indicates that in this evaluation all patients with a high value for the urethral resistance parameter URA (more than about 65 cmH_2O) had a prematurely fading bladder contraction. It is also obvious that the vast majority of patients with a % PVR of more than 10 percent had prematurely fading bladder contractions and that 36 of 55 patients (65 percent) with a non-fading contraction had a % PVR of less than or equal to 10 percent. Patients with a % PVR of more than 70 percent were not clustered in a clearly defined area as was the case in the W_{max}-URA scattergram.
The W_{max}-URA plot with its division in the areas A, B and C is proposed as a voiding efficiency nomogram.

DISCUSSION

The relationship between voiding efficiency and patient age, bladder contractility and urethral resistance, has been poorly explored in the literature. Equally rare are studies that correlate structural changes in the detrusor muscle with urodynamic findings. In a qualitative electron microscopic study of bladder biopsy specimen from 6 males who were 72 to 96 years old, El Badawi et al. [11] have shown that urodynamically proven outflow obstruction was structurally related to myohypertrophy with or without superimposed degeneration of muscle cells and axons. Degeneration was associated with impaired detrusor contractility. In a group of 13 patients (including only 2 men) the same authors [12] established that ageing was associated with the occurrence of the so-called dense band pattern in the perimeter of muscle cells. This may affect exchange and storage of ions, with a negative effect on the excitation-contraction coupling mechanism.
In a large group of men and women of mixed pathology, van Mastrigt [13] found that in women W_{max} correlated better (negatively) with age than in men. It was also noted that the maximum or normal contractility values for females decreased almost linearly with age whereas this trend was less marked in males. It was postulated that this difference between men and women was caused by bladder compensation as a response to outflow obstruction. In our study, bladder contraction strength was positively correlated with urethral resistance which seems to support the view that bladder compensation is a possible explanation for the difference between the sexes. However, the data presented here are cross-sectional. Whether compensation is truly an important factor can only be determined in a longitudinal study. The positive correlation between bladder

contraction strength and urethral resistance may alternatively be due to selection bias: men who are in retention, i.e men who would most probably exhibit a relatively high urethral resistance combined with a relatively low bladder contraction strength, can not be studied by pressure-flow analysis.
In the present study, voiding efficiency was based on residual urine volume measurements after pressure-flow studies. These residuals may not always be comparable to residuals measured after a free uroflowmetry in the same patient. However, a study of the quantitative relation between voiding efficiency and pressure-flow parameters is most valid when all data originate from the same voiding. Residuals measured after free uroflowmetry can not be directly related to bladder contraction strength and urethral resistance parameters. In our study 39 percent of the patients voided with a clinically insignificant residual urine volume; this shows that a large proportion of the men did not exhibit a voiding efficiency worse than what could have been achieved at a free uroflowmetry. It is prudent, however, to state that a patient classified as a case of borderline voiding efficiency in the W_{max}-URA nomogram may be a patient in whom the voiding efficiency may have been underestimated to some degree.
Maximum bladder contraction strength was negatively and weakly correlated with age ($r=-0.23$; $p<0.001$). The % PVR was positively correlated with age; however, multiple regression analysis showed that age was not a significant independent factor in the determination of voiding efficiency expressed in terms of % PVR. Therefore, % PVR increases with age because URA, W_{max} and W80-W20 change with age. The factors on which voiding efficiency depended were, in descending order of significance: urethral resistance (URA), maximum bladder contraction strength (W_{max}) and the bladder contraction strength decay factor (W80-W20).Maximum bladder contraction strength and the bladder contraction strength decay factor were not correlated and seem to constitute different properties of bladder contractile function. This is in agreement with findings that a bladder contraction which is fading away prematurely preoperatively, is usually restored to normal after a TURP, whereas a low maximum bladder contraction strength is not [7].
These findings can be explained on the basis of results obtained in animal experimental work. Levin et al [14] described the biphasic nature of bladder contraction: an initial phasic contractile response which determines the pressure response, is followed by a plateau phase which determines the ability to empty. The initial phasic response appears to be related to the intracellular ATP concentration whereas the ability to sustain a contraction may be linked to active mitochondrial respiration. Outlet obstruction has been shown to cause a marked increase in anaerobic metabolism in the rabbit bladder [15]. Malkowicz et al. [16] have shown in the whole rabbit bladder model of obstruction that the ability of the bladder to empty is impaired to a greater degree than its ability to generate pressure.
The occurrence of an acute retention is clinically unpredictable [17] and relatively rare [18]. Spiro et al. [19] have shown that prostates removed from patients with acute retention differ histologically from prostates of patients without acute retention. Vascular infarctions were noted in 85% of patients with, but only in 3% of patients without an acute retention. An infarction of the prostate probably occurs rather suddenly, but its aetiology is unknown [20]. The proposed W_{max}-URA voiding efficiency nomogram may be a first step towards a better prediction of acute retention. In its present form the nomogram is divided in 3 areas. Area C represents the area where voiding is physically impossible. Intuitively, patients who are closer to the borderline between area B and C would seem to be more at risk for a total retention. A sudden small increase in urethral resistance could occur in the case of a prostatic infarction with its secondary edema. This could suffice to let

a patient cross over between area B and C, and result in an acute retention provided that W_{max} would remain constant. Bladder contraction strength changes (W_{max}) have been reported in men, but these changes occurred in the course of weeks and months [21]. On the other hand, no significant changes in W_{max} were reported following TURP [7]. It is therefore unlikely that W_{max} can increase instantaneously in order to compensate for a sudden increase in urethral resistance. The voiding efficiency nomogram has to be validated in a prospective longitudinal study in which patients presenting with mild to moderate symptoms of prostatism would have to undergo a baseline pressure-flow analysis before being entered in a watchful waiting protocol.

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CHAPTER XI.

SUMMARY.

SAMENVATTING.

SUMMARY.

The different theories of the etiology of histopathological BPH are outlined in this chapter 1. Despite many years of research, the pathogenesis of histopathological BPH has remained obscure. Three major (groups of) theories have evolved over the years, each emphasizing a possible causative mechanism. The first is based on hormonal mechanisms. The second is named the stem cell theory and the third group of theories relates to altered stromal-epithelial interactions. The only two factors that are definitely known to be of importance in the onset of BPH are the presence of testes and advancing age. Direct proof is lacking regarding a definite association between BPH and any or all of the mechanistic theories postulated thus far. Histopathological BPH is not equivalent to the clinical syndrome, but apparently is the first step on the path to symptomatic BPH.

Chapter 2 reviews the facts about the natural history and prevalence of benign prostatic hyperplasia and its properties (i.e. symptoms of prostatism, prostatic enlargement and bladder outflow obstruction). It is difficult to interpret the available information on the prevalence of BPH, since there is no generally accepted case definition of the clinical syndrome. Despite this limitation it is clear that BPH is very prevalent. To determine the true impact on health care facilities it is necessary to develop a better case definition to make a better estimate of the number of men that truly needs therapeutic intervention. As a first step towards this goal, the normal values of several parameters associated with BPH must be determined in community-based samples of men. The following 4 chapters are devoted to these epidemiological aspects of BPH.

Chapter 3 describes parameters of prostate volume and shape in a community-based population of 502 men 55 to 74 years old. Of all men in this age range, 95% had a total prostate volume of more than $20cm^3$. The percentage increase per year of the central hypoechoic volume (3.5%) was higher than that of the total prostatic volume (2%). The average total prostate volumes as measured by transrectal ultrasound were 21 to 28% higher than reported average volumes measured at autopsy in men in the same age range. Therefore, reference values for prostate volume as determined by transrectal ultrasound should not be based on the results of autopsy studies.

Chapter 4 is an account of the correlation between both serum prostate specific antigen levels (PSA) and prostate specific antigen density (PSAD) and age, prostate volume parameters, body mass index and the International Prostate Symptom Score (IPSS) in a community-based population of men 55 to 74 years old, excluding men with a serum PSA level of greater than 10 ng/ml, those with biopsy proven prostate cancer and those who had previously undergone a prostate operation. PSA and PSAD did not correlate with the body mass index. Weak correlations were found between PSA and age, PSAD and age and between PSA and the total prostate volume. PSA did not correlate independently with age after adjustment for volume. The finding that PSAD correlates with age is partly explained by the incomplete volume adjustment of PSAD, which is proved by a positive correlation between PSAD and prostate volume.
In the main target age range for prostate cancer screening there is a poor basis for the use of age-specific reference values or volume adjustment for PSA levels as a way to increase the clinical usefulness of this serum marker.

The prevalence of symptoms of prostatism in the community and the correlations between these symptoms and age, prostate volume, flow rate and residual urine volume are the subjects of chapter 5. Overall, 6 % and 24 % of the men were severely and moderately symptomatic, respectively. There was a weak correlation between the International Prostate Symptom Score (IPSS) and anatomical and physiological measures of BPH such as prostate volume parameters, peak flow rate and post void residual urine volume, and a very weak correlation between the IPSS and age. Since no predictions about the value of a certain parameter can be made by knowing one of the other parameter values, it is concluded that symptom scores should not be used as a preselection criterion in the determination of the prevalence of clinical BPH without taking other measures into account. The interpretation of the parameter values in a clinical setting should take the lack of correlation and the variability of the parameter values into account.

In chapter 6 prevalence rates of BPH in the community were determined using various different case definitions. These definitions were based on a combination of clinical parameters that are employed to describe the properties of BPH. These properties are: symptoms of prostatism, prostatic enlargement and bladder outflow obstruction. In this chapter, the relative impact on prevalence rates of the inclusion of these different parameters (and of different cut-off values for these parameters) in a case definition of BPH, is determined.
There is agreement that age is the dominant determinant of BPH, but of 28 different case definitions that were formulated, only 8 gave a statistically significant increase of the prevalence with age. The highest overall prevalence of 19% is found for the definition that combines a prostate volume of more than 30 cm^3 and an IPSS of greater than 7. The lowest overall prevalence rate of 4.3% is found for the definition that combines a prostate volume of more than 30 cm^3 and an IPSS of greater than 7 and a maximum flow rate of less than 10 ml/s and the presence of a post void residual urine volume of more than 50 ml. Thus, prevalence rates depend very much on the parameters used in a case definition. Follow-up will establish which men will eventually request a work-up and treatment for BPH and will help determine the best clinical definition of BPH.

The following four chapters are devoted to pathophysiological aspects of BPH.
Chapters 7 and 8 are accounts of the effects of androgen deprivation and transurethral laser treatment of the prostate in patients with BPH.
Medical androgen deprivation led to an average decrease in prostatic size of 29% after 12 weeks. However, this decrease did not result in a clinically significant decrease in urethral resistance. After discontinuation of the treatment the prostates showed regrowth to the initial size within 6 to 36 weeks.
After 3 month of follow-up, transurethral ultrasound-guided laser-induced prostatectomy (TULIP) had resulted in an objectively proven decrease in urethral resistance and in symptomatic improvement. However, there was no significant change in prostate volume.
It appears that the removal of small strategically placed amounts of prostatic tissue, is more effective urodynamically than a global decrease in prostatic volume of up to 30%.

Chapter 9 is an account of an analysis of the association between prostate volume and several reported urodynamically determined urethral resistance parameters. Two types of obstruction can be recognized on the basis of urodynamic data: a compressive type and a constrictive type. A

combination of both types is often seen in BPH. In this chapter it is shown that parameters that selectively quantify compression correlated weakly to moderately with prostate volume, whereas parameters that mainly quantify constriction did not correlate at all with prostate volume. Parameters that combined a measure for compression and constriction correlated less well with prostate volume than parameters that mainly quantify compression. The variation in prostate volume was found to determine the variation in urethral resistance by 15 % or less, depending on the parameter used, which implies that the different pathophysiological mechanisms that can increase urethral resistance in the complex process of clinical BPH are mainly determined by factors other than the volume of the prostate. Thus, despite the lack of correlation between prostate volume and urethral resistance, pressure-flow studies provide a valuable contribution to the understanding of the pathophysiology of the voiding dysfunction in individual men with symptoms of prostatism.

Chapter 10 reports on the influence of age, urethral resistance and bladder contractility on voiding efficiency in males. Voiding efficiency, as expressed by the parameter % PVR (that is the post void residual urine volume as a percentage of the initial bladder volume), depended significantly on the urethral resistance parameter URA, the contractility parameter W_{max} and the bladder contraction strength decay factor W80-W20, in this order. Patient age was not an independent factor. W_{max} and W80-W20 were not correlated; therefore, maximum bladder contraction strength and its decay seem to constitute different properties of bladder contractile function. A voiding efficiency nomogram is proposed, making use of the values for W_{max} and URA in individual patients. Such a nomogram may have predictive value for the occurrence of acute retention and has to be tested prospectively.

SAMENVATTING.

De verschillende theorieën over de etiologie van goedaardige prostaatvergroting (BPH) passeren in hoofdstuk 1 de revue. Ondanks vele jaren van onderzoek is de pathogenese van BPH nog steeds een duistere zaak. Drie (groepen van) theorieën, die ieder de nadruk leggen op een mogelijk oorzakelijk mechanisme, zijn in de loop der jaren ontwikkeld. De eerste is gebaseerd op hormonale mechanismen, de tweede wordt stamcel-theorie genoemd en de derde gaat uit van veranderde interacties tussen het stroma en het klierepitheel van de prostaat.
De enige twee factoren waarvan buiten enige twijfel vaststaat dat ze van belang zijn bij het ontstaan van BPH, zijn de aanwezigheid van testikels en een gevorderde leeftijd. Een direct bewijs voor een verband tussen BPH en één of alle genoemde theorieën ontbreekt nog steeds. Histopathologische BPH staat niet gelijk aan het klinische syndroom, maar is wel de eerste stap op de weg naar symptomatische klinische BPH.

Hoofdstuk 2 geeft een overzicht van de feiten met betrekking tot de natuurlijke historie en het voorkomen (de prevalentie) van benigne prostaathyperplasie en van de 3 kenmerken van benigne prostaathyperplasie, te weten de symptomen ofwel "prostatisme"-klachten, het toegenomen prostaatvolume en de subvesicale obstructie van de mictie. Deze informatie is soms moeilijk te interpreteren omdat er geen overeenstemming bestaat over een definitie van klinische BPH. Ondanks deze beperkingen is het duidelijk dat het hier om een zeer vaak voorkomend probleem gaat. Om de werkelijke betekenis van dit probleem voor de gezondheidszorg goed te kunnen inschatten is het allereerst nodig een goede definitie van klinische BPH te ontwikkelen om vervolgens een betere schatting te kunnen maken van het aantal mannen dat een behandeling nodig heeft. Een eerste stap op weg naar dit doel is het, in de algemene bevolking, bepalen van normaalwaardes voor de verschillende parameters die in verband worden gebracht met BPH. De volgende vier hoofdstukken zijn aan deze epidemiologische aspecten gewijd.

Hoofdstuk 3 beschrijft waarden van parameters voor prostaatvolume en vorm in de algemene bevolking; de gegevens zijn verkregen bij een groep van 502 mannen tussen de 55 en 74 jaar. Bij 95% van de mannen werd een prostaatvolume van meer dan 20 cm^3 gevonden. De procentuele toeneming per jaar van het volume van het centrale hypo-echoïsche deel van de prostaat, waar BPH met name ontstaat, bedroeg 3.5%. De procentuele toeneming per jaar van het totale prostaatvolume bedroeg 2%. Het gemiddelde, met transrectale echografie gemeten, totale prostaatvolume was 21 tot 28% groter dan de gemiddelde volumina die bij obductie gemeten zijn bij mannen van vergelijkbare leeftijd. Wanneer prostaatvolumina bepaald worden met behulp van transrectale echografie gelden dus andere referentiewaardes dan de waardes die afgeleid zijn uit obductiegegevens.

Hoofdstuk 4 beschrijft de prevalentie van prostatismeklachten in de bevolking en de correlatie tussen deze symptomen en leeftijd, prostaatvolume, urinedebiet en urineresidue. Globaal, hadden respectievelijk 6% en 24% van de mannen tussen de 55 en 74 jaar ernstige en matige symptomen. De correlatie tussen de Internationale prostaat symptoomscore (IPSS) en anatomische en fysiologische maten voor BPH zoals prostaatvolumeparameters, het maximale urinedebiet en het volume van het urineresidue, was zwak. De correlatie tussen IPSS en leeftijd was zeer zwak. Aangezien de waarde van een bepaalde parameter geen enkele voorspelling toelaat omtrent de

waarde van andere parameters, wordt geconcludeerd dat symptoomscores niet op zichzelf als voorselectiecriterium gebruikt mogen worden bij de bepaling van de prevalentie van klinische BPH. Bij de klinische interpretatie moet rekening worden gehouden met de variabiliteit van de waardes van de verschillende parameters en het gebrek aan correlatie tussen de waardes van de verschillende parameters.

Hoofdstuk 5 beschrijft zowel de correlatie tussen serumwaarden voor het prostaatspecifieke antigeen (PSA) als de correlatie tussen waarden voor de prostaatspecifieke antigeen densiteit (PSAD) en de leeftijd, prostaatvolume parameters, body mass index en de IPSS. De studie is uitgevoerd in een groep mannen uit de algemene bevolking tussen de 55 en 74 jaar. Mannen met een serum PSA-waarde boven 10 ng/ml, degenen waarbij door middel van een biopsie prostaatkanker was aangetoond en mannen die eerder reeds aan de prostaat geopereerd waren, werden van de evaluatie uitgesloten.PSA en PSAD correleerden niet met de body mass index. Zwakke correlaties werden gevonden tussen PSA en leeftijd, PSAD en leeftijd en tussen PSA en het totale prostaatvolume. PSA correleerde niet meer met de leeftijd na correctie voor prostaatvolume. De positieve correlatie tussen PSAD en prostaatvolume bewijst dat het gebruik van de PSAD geen complete correctie voor prostaatvolume inhoudt; dit verklaart ten dele waarom PSAD correleert met de leeftijd.
In de belangrijkste doelgroep voor screening op prostaatkanker bestaat geen goede basis voor het gebruik van leeftijdsspecifieke referentiewaardes voor PSA en voor volumecorrectie van PSA waardes, als methode om de klinische bruikbaarheid van deze serummerkstof te vergroten.

In hoofdstuk 6 worden, gebruikmakend van verschillende definities van het begrip "klinische BPH", prevalentiepercentages voor BPH bepaald. Deze definities zijn gebaseerd op combinaties van parameters die gebruikt worden om de kenmerken van klinische BPH te beschrijven. Deze kenmerken zijn: prostatismeklachten, prostaatvergroting en subvesicale obstructie van de mictie. In een definitie van het begrip klinische BPH kunnen verschillende parameters (en verschillende grenswaarden voor deze parameters) betrokken worden. In dit hoofdstuk wordt het relatieve effect van de inclusie van deze parameters op de prevalentiepercentages bepaald.
Er bestaat overeenstemming over het feit dat leeftijd de belangrijkste determinant van BPH is. Echter, van 28 verschillende geformuleerde definities van klinische BPH gaven er slechts 8 een statistisch significante prevalentiestijging met de leeftijd te zien. De hoogste prevalentie van 19% wordt gevonden bij gebruik van de definitie die een prostaatvolume van meer dan 30 cm^3 combineert met een Internationale prostaat symptoomscore (IPSS) van meer dan 7. De laagste prevalentie van 4.3% wordt gevonden bij gebruik van de definitie die een combinatie inhoudt van een prostaatvolume van meer dan 30 cm^3, IPSS van meer dan 7, een maximaal urinedebiet van minder dan 10 ml/s en de aanwezigheid van een urineresidue van meer dan 50 ml. Dus, prevalentiepercentages hangen sterk of van de wijze waarop verschillende parameters betrokken worden bij een definitie van klinische BPH. Vervolgonderzoek zal uitwijzen welke mannen uiteindelijk vragen om een verdere diagnostiek en behandeling van BPH. Deze informatie is belangrijk voor de selectie van de beste definitie van klinische BPH.

De volgende vier hoofdstukken zijn gewijd aan pathofysiologische aspecten van BPH.
In de hoofdstukken 7 en 8 worden de resultaten besproken van de behandeling van patienten met BPH met respectievelijk medicamenteuze androgeendeprivatie en transurethrale lasercoagulatie van de prostaat.

Medicamenteuze androgeendeprivatie leidde tot een gemiddelde vermindering van het prostaatvolume met 29 % in 12 weken. Deze vermindering resulteerde echter niet in een klinisch relevante vermindering van de urethrale weerstand. Na het stoppen van de behandeling herkregen de prostaten binnen 6 tot 36 weken hun oorspronkelijk volume.
Drie maanden na de behandeling met "transurethral ultrasound-guided laser-induced prostatectomy" (TULIP) werd een duidelijke vermindering van de urethrale weerstand en een symptomatische verbetering vastgesteld. Er was echter geen significante verandering van het prostaatvolume aantoonbaar.
Het verwijderen van een kleine strategisch geplaatste hoeveelheid prostaatweefsel is urodynamisch effectiever dan een globale vermindering van het prostaatvolume met een percentage van 30%.

Hoofdstuk 9 geeft een analyse van het verband tussen het prostaatvolume en verschillende gerapporteerde urodynamisch bepaalde urethrale weerstandsparameters. Twee typen obstructie kunnen op basis van urodynamische gegevens worden onderkend: een compressief type en een constrictief type. Een combinatie van beide types wordt vaak gezien bij BPH. Parameters die selectief compressie quantificeerden, correleerden zwak tot matig met het prostaatvolume, terwijl parameters die vooral constrictie quantificeerden in het geheel niet correleerden met het prostaatvolume. Parameters die een gecombineerde maat voor compressie en constrictie vertegenwoordigen correleerden minder goed met het prostaatvolume dan parameters die vooral compressie quantificeerden. De variatie in prostaatvolume bepaalde slechts voor 15 % of minder, afhankelijk van de gebruikte parameter, de variatie in urethrale weerstand. Dit geeft aan dat toeneming van de urethrale weerstand in het complexe proces dat klinische BPH heet, vooral bepaald wordt door andere factoren dan het prostaatvolume. Dus, ondanks het gebrek aan correlatie tussen prostaatvolume en urethrale weerstand leveren "pressure-flow" studies een waardevolle bijdrage aan het begrip van de pathophysiologische achtergrond van de dysfunctionele mictie bij individuele mannen met prostatismeklachten.

In hoofdstuk 10 wordt de invloed van de leeftijd, de urethrale weerstand en de blaascontractiliteit op de efficientie van de mictie bij de man geanalyseerd. De efficientie van de mictie, uitgedrukt in de waarde van de parameter % PVR (dat is het volume van het urineresidue als percentage van de initiële blaasinhoud), is in aflopende volgorde van belangrijkheid afhankelijk van de urethrale weerstandsparameter URA, de blaascontractiliteitsparameter W_{max} en de vervalfactor van de blaascontractiekracht W80-W20. De leeftijd van de patient was geen onafhankelijke factor van belang. W_{max} en W80-W20 waren niet met elkaar gecorreleerd; de maximale blaascontractiekracht en het verval van de contractiekracht lijken daarom verschillende kenmerken van de contractiele functie van de blaas te vertegenwoordigen. De invoering van een mictie-efficientie-nomogram dat gebruik maakt van de waarden voor W_{max} en URA bij individuele patienten, wordt voorgesteld. Een dergelijk nomogram heeft mogelijk voorspellende waarde voor het optreden van een acute retentie en moet prospectief getest worden.

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CURRICULUM VITAE.

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Since 1992 he is a fellow of the European Board of Urology.
He is married to Ina Langhout and has two children (Steven and Iris).