Evaluation

of

Prostatic obstruction

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Abstract

Benign prostatic hyperplasia is a common condition. Little is known about the criteria for selecting patients subjected to prostatic surgery. The aim of the study is to define obstruction Two-hundred fourteen patients underwent a serum prostatic specific antigen (PSA) determination, a rectal exam, a transrectal ultrasound, a uroflow and filled questionaires for symtom score analysis. Patients with peak or mean flow below two standard deviations from the mean from the nomograms described by Siroky should be treated for BPH especially if they also present one of the following: obstructive score (AUA part A) $\geq$ 14 , irritative score (AUA part A) $\geq$12, total objective score (AUA part A) $\geq$ 22 or a urethral resistance $\geq$ 42 cm H_2O. The transrectal ultrasound should be reserved for those with a suspicious rectal exam or with a serum PSA $\geq$ 4 ng./cc.. Six sextants biopsies of the peripheral zone should be done in those with a PSA prostate density $\geq$ .2 ng./cc./gr. to rule out adenocarcinoma.

L'hyperplasie bénigne prostatique est une condition très fréquente. Cependant les critères thérapeutiques sont imprécis. Le but de ce travail est de définir l'obstruction prostatique. Deux cent quatorze patients ont subi un examen rectal, une échographie transrectale prostatique, un dosage sérique de l'antigène spécifique prostatique (APS), ainsi qu'une débitmétrie. Les patients qui présentent un débit maximum ou moyen en-deça de deux déviations standart de la moyenne selon les nomogrammes décrits par Siroky devraient etre traités pour prostatisme en particulier s'ils présentent également l'une des caractéristiques suivantes: un pointage obstructif $\geq$ 14, un pointage irritatif $\geq$12, un pointage total objectif $\geq$ 22 ou une résistance urétrale supérieure à 42 cm H_2O. L'échographie transrectale prostatique devrait etre réservée aux patients présentant un examen rectal suspect ou à ceux présentant un dosage sérique de l'APS égal ou supérieur à 4 ng./cc. On devrait alors pratiquer une biopsie des six quadrants de la zone périphérique chez ceux qui présentent une densité tissulaire prostatique de l'APS égale ou supérieure à .2 ng./cc./gr. afin d'éliminer la présence d'adénocarcinome.

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2-Introduction

Benign prostatic hyperplasia is a common disease among older men. Among men 40 years of age, 5 to 10% have prostatic enlargement, whereas at age 80, the prevalence is as high as 80%. Patients with clinical BPH can present with nocturia (68%), day time frequency , hesitancy (77%), intermittency, terminal dribbling, urgency (67%), impairment of stream (80%), dysuria and sensation of incomplete voiding (111). Little is known about the criteria for selecting patients subjected to prostatic surgery besides the symptoms and the cystoscopic appearance of obstruction. Patient's assessment of urinary flow may be quite misleading, having been shown that 60% of patients with prostatism report symptomatic improvement on placebo therapy alone (91). It has been shown that the symptoms related to prostatic obstruction particularly the irritative syndrome have notoriously been unresponsive to the prostatic surgery. In 50-60% of patients presenting with irritative and obstructive symptoms, persistent dysfunction in their voiding patterns was found in spite of a successful prostatic surgery (open or endoscopic) to alleviate the obstruction(113).

Prostate morphology

The prostate ducts originate from urethra and surround it. It is composed of tubuloalveolar or tubulosaccular glands.. The stromal component encompasses all cellular and extracellular elements outside of the epithelial basal lamina and includes smooth muscle cells , fibroblasts, blood vessels, connective tissue, nerve terminals and lymphatics embedded in extracellular matrix. The prostatic urethra shows a sharp anterior angulation of 35 degree of its posterior wall at about half the distance between the apex of the prostate (ventral surface being the veru montanum where exit the ejaculatory ducts) and its base at bladder neck. This point of angulation divides the urethra into proximal and distal segments of about equal length.

The two major regions of the glandular prostate may be defined as the **peripheral zone and the central zone**, comprising respectively, nearly 75% and 25% of the volume of the glandular prostate. The two zones differ markedly. The central zone surrounds the ejaculatory ducts along their entire course through the prostate. Its duct orifices immediately surrounds the orifices of the ejaculatory ducts on the rounded apex of the veru montanum. Two of the enzymes of seminal fluid, pepsinogen II and tissue plasminogen activator are produced by the epithelial cells of the central zone but not the peripheral zone.The main peripheral zone ducts join the urethra separately from those of the central zone. Their orifices form a double lateral line extending along the posterolateral recesses of the distal urethral segment from the prostate apex to the recesses lateral to the veru montanum.

The **anterior fibromuscular stroma** blends proximally with the detrusor muscle fibers surrounding the urethra at the bladder neck. It is composed mainly of smooth muscle that is continuous proximally with the detrusor fibers of the anterior bladder wall. These fibers sweep distally from the bladder neck and fan out laterally, covering the entire and anterolateral surface of the glandular prostate.

A "cylinder" surrounds the proximal segment of the urethra between the base of the veru montanum and the bladder neck called the **preprostatic sphincter** because its distal border is located proximal to all of the prostatic duct orifices of the central and peripheral zones. Its ring of smooth muscle fibers are tightly compacted into a narrow band around the posterior or dorsal aspect of the urethra. Extending laterally and anteriorly, all but the innermost rings expand, spreading away from the urethra and from each other. Anterior to the urethra they interdigitate with the fibers of the anterior fibromuscular stroma. A functionally distinctive role for the preprostatic sphincter is indicated by the recent observation that it is innervated by noradrenergic nerve fibers (48).

It has been proposed that the unique function of this sphincter is to prevent retrograde flow of semen by contracting during ejaculation This sphincter is consistently ablated at transurethral resection, accounting for the retrograde ejaculation seen postoperatively Probably this sphincter also maintains some degree of resting tone at all times and prevents pooling of urine in the proximal segment of the urethra(49).

About 5% to 10% of the tissue of the glandular prostate remains unaccounted for this description. Nearly all of this tissue is found in the transition zone immediately lateral to the preprostatic sphincter. Its duct empty into the posterolateral recesses of the urethral wall at a single level. This level is situated just proximal to the highest of the peripheral zone duct orifices and immediately distal to the distal border of the preprostatic sphincter. The ducts of the transition zone branch mainly proximally along the long axis of the proximal urethral segment and laterally away from it. The obliquely branching course of its ducts places the mass of the transition zone entirely anterior to the coronal plane of the peripheral zone. The anatomical separation of the transition zone from the peripheral zone is accentuated by its uniquely intimate relationship to the preprostatic sphincter. Its entire medial border is adherent to the external aspect of this sphincter and some of the most medial small ducts and acini of the transition zone actually penetrate the sphincter. In addition, isolated ring fibers of the sphincter penetrate the transition zone stroma. The **transition zone** is the site of origin of benign prostatic hyperplasia.

Benign hyperplasia nodules also develop, to a much lesser extent in the periurethral gland region. Its duct arise from the proximal urethral segment as a double lateral line, representing the further proximal continuation of the peripheral zone and transition zone duct systems, and the periurethral glandular histology resembles that of the two zones. Because these ducts develop in an area completely surrounded by sphincter, their growth is confined to the immediate periurethral tissue.

They exist as tiny, almost microscopic abortive ducts and acini, embedded in the periurethral longitudinal smooth muscle and generally deficient in periacinar smooth muscle stroma.

Neuroanatomy and neurologic control of prostatic function

The autonomic nervous system is customarily divided into sympathetic and parasympathetic components. The sympathetic system produces its effect by liberation of the neurotransmitter norepinephrine from the postganglionic nerve endings, which then acts on adrenergic receptors in the target cells. Acetylcholine is liberated from the postganglionic fibers of the parasympathetic system and acts on muscarinic receptors in the target cells. The neurotransmitter in all the preganglionic synapses, whether parasympathetic or sympathetic, is likewise acetylcholine, which in these sites acts on nicotinic receptors in the postganglionic nerves.

The adrenergic receptors are divided into two main groups, alpha and beta, according to the effects produced on the target cell. In the lower urinary-tract muscle, stimulation of the alpha receptors produces contraction, whereas stimulation of the beta receptors causes relaxation. The alpha receptors are further classified in two subgroups. The alpha-1 receptors are found on the target cell and mediate the effect produced on it. The alpha-2 receptors are found on the postganglionic nerve terminals, where they control the reabsorption of excess norepinephrine into the neurons (figure 1).

Many studies (2,3,4,5,6,7) have demonstrated the following: Raz and associates observed that rat prostate contracts in the presence of norepinephrine (102). The human prostate adenoma and capsule were subsequently shown to contract in the presence of the same neurotransmitter (103).

The prostatic nerves are derived from cell bodies of postganglionic sympathetic nerves.The prostatic nerves via postganglionic sympathetic alpha adrenergic stimulation supply the surrounding smooth muscle and blood vessels (5).The secretory products are then expelled into the draining ducts and propelled through the ductal network under the influence of alpha-adrenergic sympathetic muscular nerves. The **beta adrenergic** receptor content of the prostatic muscle is negligible. The **muscarinic** receptors are not found on the prostatic smooth muscle, but are localized to the glandular tissue. Although parasympathetic postganglionic fibers have been documented, their function remain unclear. Three inhibitory mechanisms within the prostate down-regulate the sympathetic periglandular and periductal muscular contraction: chromaffin cells (containing norepinephrine, epinephrine and dopamine), collateral postganglionic adrenergic fibers and prostaglandin E (PGE). The hyperplastic portion of the prostate is rich in alpha-adrenergic receptors related to the smooth muscle. These are predominantly of the alpha-1 type (5), altough some postsynaptic alpha-2 receptors are present (99). There is evidence that the latter are associated specifically with the blood vessels. The surgical capsule surrounding the hyperplastic prostatic tissue is also rich in alpha receptor, and beta receptors are virtually absent. In this tissue, muscarinic receptors are abundant in the muscle of the anterior part of the capsule but negligible in that of the posterior part.

Hormonal regulation related to prostate function

Pituitary luteinising hormone (LH) is regulated by pulsatile release of LH-releasing hormone (LHRH or GnRH) from the hypothalamus (arcuate and ventromedial nuclei). Subsequently LH stimulates production of testosterone (T) by testicular Leydig cells. This T regulates both LH and LHRH release by negative feedback mechanisms. Only approximately 10% of total prostatic androgens are of adrenal origin. Testosterone can be free or protein-bound to a sex steroid binding globulin (TeBG) (57%), to albumin (40%), to a cortisone-binding globulin (CBG) (less than 1%), and only 2% is free and diffuses into the prostate gland (89). Administration of testosterone decreases TeBG levels in the plasma, while estrogen therapy stimulates TeBG levels. Altough T is the principal hormonal production of the testis, minor amounts of DHT, androstenedione, progesterone and 17-OH progesterone are also secreted by the testis (figure 4). In the prostate, T diffuses into both epithelial and stromal cells and is converted through the enzyme 5 alpha reductase to DHT (which is 90% of the total prostatic androgen). DHT and T bind to the same high affinity androgen receptor protein (R) in the cytoplasm.

DHT has a higher affinity than T and DHT-R complex seems more stable than T-R complex. Binding of the hormone (DHT) to a cytoplasmic form of the receptor is followed by a conformational change of the complex (DHT-R), the so-called "activation" or "transformation"step that leads to liberation by the receptor of a DNA-binding domain with high affinity for selective chromatin sites: these inducible enhancer nucleotide sequences are termed hormone-response elements (34,35) . The hormone receptor complex (DHT-R) binds to specific DNA sites in nucleus, which activates transcription of androgen dependent genes leading to stimulation of protein synthesis and ultimately to cell growth . Conversely, androgen withdrawal from androgen sensitive tissue results in a decrease in protein synthesis with tissue involution and in some cases cell death.

Indeed the enzyme 5-alpha reductase is essential for the development of the prostate gland: humans with 5 alpha reductase deficiency are born with ambiguous genitalia and have small prostates (suggesting other mechanisms that may be operating) or undetectable(41,42).

The prostate metabolizes testosterone (T), to dihydrotestosterone (DHT), to 5 alpha-androstane - 3 alpha,17 beta-diol or 5 alpha-Androstane-3 beta, 17 beta-diol. From studies on rat prostatic explants (55,56), T, 3 beta-diol and 3 alpha diol maintained epithelial cell height and secretory activity whereas hyperplasia of the epithelium was induced only at very high concentration. On the other hand, DHT is less active to maintain secretory activity and height but is more effective in inducing epithelial hyperplasia.

The prostate undergoes an increase in size and develops histologic evidence of stimulated growth during three periods of life: prior to and at birth, during puberty and with advancing of age (benign prostatic hyperplasia).

Prostate embryology

The cloaca gives rise to the rectum and urogenital sinus in the embryo. The pelvic part of the urogenital sinus will give rise to the prostate. The ductal network within the prostate are derived from solid epithelial outgrowths of prostatic buds that emerge from the endodermal urogenital sinus below the developing bladder and grow into the surrounding mesenchyme (loose connective tissue). The first epithelial outgrowths arise from the prostatic urethra around the tenth week of gestation(28,29). Normal human prostatic ductal morphogenesis and growth occur in two separate periods, prenatally and pubertally while pathological growth in benign prostatic hyperplasia is initiated in the fourth decade (30,31). During period of net prostatic growth the rate of cell proliferation exceeds the rate of cell death, while in the normal adult prostate these rates are equal (32, 33).

Endocrine regulation of the fetal prostate

Prostatic development is androgen dependent prenatally and post natally throughout periods of prostatic morphogenesis (36,37). Castration of fetal testes results in inhibition of prostate development in the rat (38). But development of prostate is not completely halted by castration in rats. Androgens remaining after castration may be sufficient to promote partial prostate growth (43). Androgens act upon developing urogenital sinus via specific intracellular androgen receptors (44,45,46) expressed prenatally in the mesenchyme but not in the epithelium (45,46).

Endocrine regulation of the adult prostate

Growth responsiveness to androgen may depend on the balance between both stromal and epithelial cell types within the prostate. Both stromal and epithelial cell types are potential target sites for androgen action. Both contain 5 alpha reductase as well as androgen receptors . Administration of exogenous testosterone to immature males accelerates prostatic growth so that maximal size is attained precociously (39,40). However, once maximal size is attained, further androgen treatment does not elicit further increase in DNA content, suggesting a possible "homeostatic mechanism"(39). Indeed following castration,there is a greater loss of epithelial cell than stromal tissue (47), there is reduction in prostate size, and prostatic DNA content decreases to 80%-85% (in the rat) (48,49) Using a biomorphometric approach, following castration, there is a reduction of 93% in epithelial cells, and a reduction of 27% in stromal cells (50). The regression is however not uniform: the distal tips of epithelial ducts are more affected than the proximal segments of the ducts (51). Administration of testosterone to castrated rats causes an increase mainly in prostatic epithelial activity but also in connective tissue stroma and vasculature (52,53), mostly in distal tips of regenerating ducts (54). This suggest heterogeneity among prostatic cells in their sensitivity and dependence upon androgens.

Estrogens, via the hypothalamus and pituitary, suppress secretion of gonadotropins, reducing testicular androgen production and leading to involution of prostate. Estrogens stimulate fibromuscular tissue (57,58) and induction of squamous metaplasia of prostatic epithelium, reversible in adult rodent (57,58,59,60). In dogs (not in rats however), estrogen synergizes with androgen in prostatic growth (61). Estrogens increase the level of androgen receptors in the prostate (25, 27).

Role of mesenchymal-epithelial interactions in prostatic development and growth.

Receptors for androgens (62,63), estrogens (64,65) and progestins (66,67)have beeen demonstrated in epithelial and stromal cells (66,67,68,69,70,71). Equal levels of 5 alpha reductase activity in prostatic epithelium and stroma have been demonstrated (69,70). DHT stimulates prostate DNA synthesis if administered to animals castrated 4 or 7 days previously,; no response is encountered 24 hours after castration (49,71,72,73).

In intact adults, androgen levels are high while prostatic epithelial cell proliferation is low and new cell forming is in balance with cell death (48,74,75). The amount of mesenchyme present determines the final size organ (from studies of homotypic urogenital mesenchyme (UGM) plus urogenital epithelium (UGE) recombinants) (77). This concept was tested with adult prostatic ducts by experimentally altering the ratio of prostatic epithelium to mesenchyme in tissue recombinants. The following results were obtained: 1500 epithelial cells + bladder mesenchyme maintained the ducts but no growth was observed. However, these epithelial cells + UGM showed tremendous growth (78). These findings demonstrate the importance of mesenchymal-epithelial interactions in regulating epithelial growth within developing and mature hormonally responsive glands.

During prostatic development, providing androgens are present, the mesenchyme induces epithelial ductal morphogenesis and differentiation. UGM can act as permissive or instructive inductor. The mesenchyme is a permissive inductor when the epithelium will express its normal developmental fate i.e. UGM + seminal vesicle epithelium give rise to the seminal vesicle (79). The mesenchyme is an instructive inductor when the epithelium is not irreversibly commited and thus the mesenchyme can induce the epithelium to express an entirely new developmental fate specified by the mesenchyme itself i.e. UGM + epithelium of adult rodent bladder give rise to the prostate rodent (80,81). These epithelial ducts induced by UGM express histological, ultrastructural and functionnal features indicative of prostate: androgen receptors, prostate-specific antigens, androgen dependency for DNA synthesis, prostatic patterns of proteins when analysed by two-dimensional electrophoresis and histochemical profiles indicative of the prostatic phenotype. None of these changes occur if the epithelium is grown by itself (79). Tissue recombinations from 16 days old fetuses urogenital sinus tissue (epithelium + mesenchyme) and vaginal tissues (epithelium + stroma) from 1 to 20 days old mice under androgen stimulation and confirmed a progressive age-dependent decrease in the ability of vaginal stroma to participate in prostatic morphogenesis (82). Tissue recombinants constructed between Tfm mice (no androgen receptors) and wild type UGS (urogenital sinus) were exposed to androgen. Prostatic morphogenesis occurred only in those recombinants constructed with the wild type mesenchyme (83). Thus in the developing prostate, the mesenchyme is the actual target and mediator of androgenic effects upon the epithelium. This formation of prostate involves 3 major processes: ductal morphogenesis, epithelial proliferation, secretory cytodifferentiaton. All these processes are androgen-dependent and must be regulated by the receptor-positive stromal cells (82,83). However there is no proof that the prostatic tissue of these recombinants synthesizes all of the androgen-dependent epithelial secretory proteins characteristic of normal prostate. Similar results are obtained with the adult male rodent (72,83).

Benign prostatic hyperplasia

Between 50 and 70 years of age, the progression of benign prostatic hyperplasia (BPH) may be represented predominantly by an increased number of stromal and mainly glandular nodules, whereas the subsequent growth of each newly formed nodule is generally slow. BPH nodules originate selectively from the transition zone which is a very small region near the cylindrical urethral sphincter above the veru montanum and usually on the outer aspect of that sphincter laterally. Transition zone nodules are, in their early phase, a proliferation of glandular tissue without an expansible border and often with a reduction in the relative amount of stroma. The stroma usually consists of mature smooth muscle like that of the uninvolved transition zone. A second area of strong predilection for BPH nodule formation is the periurethral stroma inside the confines of the preprostatic sphincter. In this location, the distribution of small nodules is relatively uniform along the proximal urethral segment between the bladder neck and the base of the veru montanum. Periurethral nodules occur with nearly equal frequency dorsal, lateral and ventral to the urethral lumen (96).

Between the late years of the seventh decade and the first half of the eight decade, a second phase of evolution occurs, characterized by a rather abrupt and marked increase in the number of prostates having nodules of large mass (the difference between glandular and stromal nodules is accentuated). Marked increase in size is overwhelmingly a complication affecting glandular nodules and consequently is a process that in most men is limited to the transition zone. Prominent epithelial activity with crowded cells having abundant cytoplasm, with larger glandular nodules showing tangent duct branching and high epithelial to stromal ratio is common in the second phase of nodule enlargement.

McNeal has proposed that the pathogenesis of BPH may be due to the reactivation of embryonic inductive activity within stromal cells of BPH nodules (84,85). This putative inductive stroma induces branching in nearby prostatic ducts. It could mean that the shutdown mechanism imposed on the prostate since adolescence is overridden by an imbalance of regulatory factors during aging process.

There is some evidence for androgen dependence of benign prostatic hyperplasia (BPH). Androgens are essential to the prostate since the gland cannot develop, differentiate or maintain size or function in their absence. Prepubertal castration prevents BPH (25, 26, 27). Prostatic levels of DHT and receptors remain normal with aging despite a decrease in plasma testosterone (25,27), a decrease in free testostrone and an increase in sex hormone binding globulin. This permits androgen dependent growth of prostatic tissue. Androgen ablation by castration or medical therapy leads to some degree of prostatic involution. On the other hand, DHT content in hyperplastic prostatic tissue is not higher than that of normal prostate. Prostatic hyperplasia in dogs is accelerated by estrogens, which increase the level of androgen receptors in the prostate (25, 27).

Prostate specific antigen (PSA) is a serine protease (molecular weight of 34000), secreted by the acinar and ductal cells of the prostate, and is not found in other body tissue in the absence of metastatic prostate cancer (125,126).

The normal prostate gland synthesises fibroblast growth factor (FGF) and epidermal growth factor (EGF). The latter is produced under androgenic regulation and secreted under beta-adrenergic and cholinergic control (87). Prostate cells in culture proliferate in response to FGF-like called prostatropin, to insulin, to insulin-like growth factor (IGF-1), to EGF, to a transforming growth factor (TGF alpha type) and to TGF-beta, for which the cells have receptors(85,87,88).

Proto-oncogenes are also involved in growth regulation. Nuclear proto-oncogenes are regarded as "key switches" converting extracellular stimuli into intracellular events. At least two of these, c-fos and c-myc, function as essential intermediaries for a wide range of peptide growth factors and have been implicated in androgenic and estrogenic control of cellular proliferation (87,88).

Thus it seems that the androgenic response in stroma is directed toward growth, whereas that in the epithelial cells is restricted to secretory functions. During prostatic development, the mesenchyme is the actual target and mediator of androgenic effects upon epithelium. Estrogens play an important role also in this androgenic response by increasing the level of DHT receptor at the cellular level, by stimulating fibromuscular tissue and synergising with androgen in prostatic growth (at least in the dog). Prostatic growth factors, under androgenic and autonomic stimulation, seem to be also involve also in prostate growth. This role is however for the moment obscure.

3- Methodology

The aim of the study will be:

1. to identify the correlation between the symptomatology, the urodynamic parameters (uroflow, post voiding residual and pressure-flow studies), serum PSA and prostate volume.
2. to find precise parameters to confirm the presence of prostatic obstruction.
3. determine which patient should be observed. A proper definition of obstruction by non invasive means is essential in every day urological practice for the selection of patients regarding any form of therapy.

This study is based on detailed history, physical exam and urological evaluation. Prior to the physical exam (rectal exam), a complete questionnaire, a serum PSA and a urianalysis is done on every patient.

Patients and Methods

Symptom scoring

Most prostatectomies are performed to alleviate symptoms. Because BPH does not correlate well with symptoms, a common concern with many studies is the degree of symptoms actually related to BPH.

Patients are investigated in a **prospective** fashion. A complete detailed history is taken. The symptoms of each patient are put on the symptom severity table described by the AUA symptom Index for BPH (92). This index is designed to provide elements desirable in any protocol for controlled clinical testing of a drug and to determine whether the drug is safe and effective in relieving obstruction signs and symptoms of BPH(3). This symptom index score is filled by the patient. Other Symptom severity tables have even been done to quantify the symptomatology of a given patient. Thus a Boyarsky score will be also filled by the physician (90). The first one, the *AUA Symptom Index for BPH* is divided in three parts and is filled by the patient where:

The *AUA Symptom Index for BPH part A* describes the urinary symtoms (objective symptoms), *AUA Symptom Index for BPH part B* describes the problems due to symptoms (subjective symtoms), and the *AUA Symptom Index for BPH part C* defines the quality of life due to urinary symptoms. Each section can be divided into irritative symptoms and obstructive symptoms. Note that "*" preceding some questions corresponds to questions in AUA Index **not** found in Boyarski questionnaire. On the other hand, note that "@" preceding some questions corresponds to questions in Boyarsky scoring system not found in the AUA Symtom Index score. Here is a brief description and scoring (depending on the severity of the symtomatology) of the two questionnaires used for this study.

AUA Symptom Index part A (0-35))

(irritative (0-15)

-how often to urinate within 2 hours
-how difficult to postpone urination
-nocturia

AUA Symptom Index part A

- obstructive (0-20)

-sensation of not emptying bladder
-stopped and started several times when urinating
-weak urinary stream
*-push/strain to begin urination

**AUA Symptom Index for part B (0-28)*

(how much of a problem have been to the patient)

irritative (0-12)

*-frequent urination
*-getting up at night
*-need to urinate with little warning

*** AUA Symptom Index part B***

(how much of a problem have been to the patient)

obstructive (0-16)

* -sensation of not emptying bladder
*-stop and start when urinating
*-impaired size and force of urinary stream
*-push or strain to begin urination

* *AUA Symptom Index part C (0-19)*

Over the past month

* -how much physical discomfort
* -how did you worry about your health
*-how bothersome overall
*-how would you feel about spending the rest of your life with such symptoms
*-how much of the time has urinary problems kept you from doing the things you used to do.

Boyarsky (0 27)

irritative (0-9)

-nocturia
-daytime frequency
-urgency

(obstructive) *(0-18)*

@-hesitancy
-intermittency
-terminal dribbling
@-dysuria
-sensation of incomplete emptying.
-impairment of stream

Physical examination

This includes an abdominal, genital and rectal examination. Any suspected prostatic nodule is followed by appropriate investigation (prostate biopsy) to rule out malignancy. Patients with previous open or transurethral prostatectomy will be excluded from the study.

Prostatic imaging

An extensive attempt to evaluate the prostatic size is often unecessary since it has no bearing in the therapeutic intervention for symptomatic BPH. However, for the purpose of our study, to be able to quantify a certain relation between prostatic volume, symptomatology and uroflow, the prostate size is measured. Transrectal ultrasound is increasingly available and provides the best cross-sectionnal anatomic depiction of the prostate gland (93,94). A high degree of correlation was obtained for the measurement of 71 cadaveric benign prostate glands =0.982) using per-rectal ultrasonography (107).

The ultrasound imaging characteristics of the prostate depends on its major histopathologic composition. BPH is microadenomatous in structure, usually in the transition zone.This produces mid-range amplitude echoes which are coarser than in the normal gland. Associated calcification, if any, has a characteristic distribution around the adenomas. Stromal nodules have a different structure (amorphous) and develops inside the periurethral muscle. They produce low ultrasonic echoes (93).

I will also describe the transition zone volume (compared to the total prostate volume on ultrasound) in the following way.

well developed transition zone: i.e. >75% of total gland on ultrasound .

moderately developed transition zone i.e. 50% to 75% of total gland on ultrasound.

poorly developed transition zone i.e. <50% of total gland surface on ultrasound.

Method

A "Bruel and Kjaer" transrectal ultrasound equipment model 1846 scanner equipped with a type 8551 biplanar 7.0 MHz probe (Bruel and Kjaer Instruments, Inc., Marlborough., Mass.) was used. A standart examination was performed to determine any abnormality as well as the size of the gland. A transrectal ultrasound with special reference to the prostatic size was a requirement. The two perpendicular maximal dimensions of the prostate in the axial scan and the lenght of the gland in the sagittal scan. The prostatic volume was estimated using the prolated ellipse V= L X W X D X 3.42 /6 ml. The prostate and seminal vesicle were carefully examined to rule out any abnormality suggestive of a tumor. A biopsy was done of any unsuspected image compatible with prostate cancer such as an irregular capsule, an asymetric and hypoechoic mass in the parenchyma or any lesion that could possibly suggest a tumor (97). The early detection of prostate cancer being an important issue in this population (121), transrectal ultrasound guided random biopsies were performed in patients presenting with a serum PSA higher than the maximum predicted PSA (obtained from prostate volume in cc. X 0.25 ng./cc.) (118)

and those patients presenting absolute serum PSA value above 10 ng. (118, 120, 122,123,124,127). The PSA/prostate volume index (PSA density) was also calculated in every patient to verify its accurracy in differentiating benign from malignant prostate disease as suggested by some authors (119,128,129). The post voiding residual urine was measured using the depth and height of the bladder on sagittal view and using the formulae (112):

5.3 (height X depth of bladder on sagittal view) - 21

(with a mean error of 16% and a 95% confidence limits +/- 31 cc. for bladder volumes between 5 and 175 cc.) Any residual urine above 25% of average total bladder capacity (above 150cc.) (suggested by ultrasound measurements) was quantified by suprapubic ultrasound (bladder scan) or by urethral catheterization for more precise assessment.

Urodynamics

In many instances, infravesical obstruction may be difficult to assess by clinical parameters alone. Thus objective means to evaluate prostatic obstruction and treatment outcome must be used.

Bladder outlet obstruction is defined as a low uroflow in the presence of a detrusor contraction of adequate force, duration and speed. The simple urinary flow rate has not been accepted widely as an estimate of outflow resistance, primarily because of difficulties in its interpretation (91). The sensitivity of reduced flow for diagnosing obstruction is 100% but the specificity is reduced because the prevalence of poor detrusor function in patients with BPH is 25% (99). However it is the least invasive urodynamic mean to objectivate an obstruction or an atonic bladder (failure to empty).

Uroflow due to its simplicity is used by most trials as one of the objective parameters of response. We propose to evaluate its validity to predict outcomes as compared to more elaborate measurements of outflow resistance.This entails continuous monitoring of detrusor pressure and flow during voiding. Combined uroflowmetry and external sphincter electromyography studies have not been found to be useful in patients with prostatic hyperplasia (108). The value of stop-flow test which is the measurement of the increase in isometric pressure during a stop test was found to be limited (109).

Method

Patient were asked to void into a Dantec uroflowmeter (minimum accepted voided volume being 150cc. when possible). The maximum flow and the average flow were measured. The post voided residual was measured by transrectal ultrasonography as mentioned previously or by catheterisation as needed. All patients presenting a postvoided residual above 150cc. and patients demonstrating a discrepancy between symptom scores and uroflow results were submitted to pressure-flow studies.

These patients undergoing pressure-flow studies, in the sitting position, were first submitted to a cystometrogram: using a 12 F infusion catheter and a 8fr. curved-tip catheter for intravesical pressure monitoring, the bladder was infused with isotonic saline at body temperature at an infusion rate of 30cc/min. Simultaneously, a rectal probe measured the intraabdominal pressure throughout the study. The detrusor pressure was obtained by substracting the intraabdominal pressure from the recorded intravesical pressure. .

The 12fr. catheter was removed at full bladder capacity. The 8 fr. curved -tip catheter was left in place. A simultaneous cystometrogram and uroflow were done. The rectal catheter is left in place. Measurement of post void residual was done.

These results were recorded on the "Dantec - Menuet" urodynamic equipment. The following datas were obtained for each patient and subjected to analysis of variance: the urethral opening pressure (being the detrusor pressure needed to open the urethral lumen to permit flow), the detrusor pressure at maximum flow rate, the detrusor power at maximum flow (max. flow. X detrusor pressure at max. flow.), the maximum and average flow rates, and the urethral resistance.

-The urethral resistance (100) was obtained with the following formula:

$$[(1+ 15.8X\ 10^{-4} \times \text{Max. Flow}^{2} \times \text{Pdet. at max. flow})^{1/2} - 1]/ (7.6 \times 10^{-4} \times \text{max. flow}^{2})$$ expressed in cm H_2O.

Statistics and parameters studied

Following this work up the following datas were studied individually and compared using **linear regression analysis, correlation analysis, t-student and non parametric wilcoxon rank sum tests:**

-symtom scores will be compared,
-age vs PSA and prostate volume,
-serum PSA vs prostate volume,
-residual volume vs obstructive and irritative symptoms,
-prostate transverse measurements vs. irritative and obstructive scores,
-prostate sagittal measurement vs. irritative and obstructive scores,
-Poorly , moderate and well developed transition zone vs. symptom scores,
-standart deviation of peak and mean flow found on the nomograms of Siroky, Olsson and Krane (114, 115),
-standardized peak and mean flow (**"st. peak" and "st. mean flows"**) at a volume of 300cc. from nomograms of Siroky,Olsson and Krane (114, 115) obtained in the following way:

1. Obtain the standart deviation of peak and mean flow from nomograms for average and maximum flow rates (114) based on the measured peak and mean flow of each patient and the total initial urine voided (measured residual urine and voided volume): it has been shown that "the variation of flow rate in an individual depends primarily on the initial vesical volume, not on the voided volume" (114). The same results has been obtained by an entirely theoretical consideration of emptying rate versus bladder volume (116). Thus in" the presence of significant urinary residual, consideration of the voided volume alone may result in a gross overestimate of voiding ability" (114).

2. Flow rates values being a standart normal distribution (114), the Z score will be used to calculate the standardized peak and mean flow at a volume of 300cc.. When the distribution of a variable ias approximately normal, observations are often standardized by substracting the mean and dividing by the standart deviation. This operation is called the Z score (130).
Z= (X - mean)/measured standard deviation (117) where

standardized peak flow = (standard deviation peak flow X 6) + 26.

where 26 = average peak flow at 300 cc. on nomograms

standardized mean flow= (standard deviation mean flow X 4) +22 .

where 22 = average mean flow rate at 300cc on nomograms

- "St. peak" and "st.mean flow" rates vs. irritative and obstructive symtom scores (AUA symtom Index score part A+B+C and Boyarsky).
- Poorly , moderate and well developed transition zone vs. " st. peak " and "st. mean flow",

-age vs. "st. peak flow" and "st. mean flow", and when needed (for those patients presenting with post void residual above 25% of bladder capacity or a discrepancy between peak flows and symptom scores):
-detrusor pressure at maximum flow vs. symptom scores
-detrusor power at maximum flow vs symptom scores
-the urethral opening pressure vs. symptom scores and mean flows + peak flows,
-The urethral resistance (100) vs. symptom scores and mean flows + peak flows:

A correlation between PSA density, absolute PSA value and the occurrence of prostate cancer will be also evaluated.

4-RESULTS

Two hundreds and forteen patients were evaluated between December and May 1992. All patients with urinary tract infections or with previous prostatectomy were excluded from this study. The mean age was 64.21 ± 7.95 **(st. deviation)**. The average symtom scores (mean +- SEM) were:

AUA part A
irritative:6.77+-.3 (range 0-15)
obstructive: 7.4 +-.3 (range 0-20)
total: 14 1 +- 0.5 (range 0-35)
AUA part B
irritative: 4 5 +- 0.2 (range 0-12)
obstructive: 4 8 +- 0.3 (range 0-16)
total: 9.3 +-0.5 (range 0-28)
AUA part C:
7.45 +- 0.3 (range 0-20)
Boyarski
irritative: 3.9+- 0.14 (range 0-9)
obstructive: 4.4 +- 0.2 (range 0-9)
total: 8.3 +- 0.3 (range 0-27)

The average peak and mean flows were 13.77+-0.6 and 7.03 +-0.3 (SEM). The serum PSA was below 4 ng./cc. in 152 patients, between 4 and 10 ng./cc. in 44 patients and over 10 ng./cc. in 13 patients. The average post voiding residuals (minimum voided volume of 150 cc.) was 82.67 ± 9.27 cc. **(SEM)**. The digital rectal exam was suspicious in 13 patients and the ultrasound pictures were suspicious in 13 cases. Twenty-two patients underwent pressure-flow studies. Twelve patients underwent biopsies of the transition zone for morphometric analysis and twenty-three patients underwent biopsies of the peripheral zone for suspicious lesion on digital rectal exam and/or on ultrasound . Biopsies of the peripheral zone were also done in patients presenting elevated PSA to rule out the presence of prostatic adenocarcinoma.

Correlation analysis and simple regression analysis were done to compare irritative and obstructive scores of both questionnaires. These two questionnaires are comparable regarding the objective symptomatology. There is a statistical significant relationship between the AUA scores part A (objective symptoms), part B (problems due to symtoms) and part C (quality of life affected by symptoms). Thus, there is a strong relationship betwen the objective symptoms and the subjective findings in BPH patients **(Table 1A and 1B)**. On the other hand, there is no statistical significant relationship between objective irritative and obstructive symptoms.

A statistically significant relationship was found between the obstructive objective symtom scores (AUA part A +Boyarski) and peak and mean flows for voided volume above 50cc., 100cc. and 150 cc. **(tables 2,3,5,6,8,9)**. . A significant correlation was discovered between AUA total symptom score part A + total Boyarski score and peak flows for voided volume above 50, 100 and 150 cc.. Such association was not found in the case of objective symtom scores and mean flows **(tables 2,3,5,6,8,9)**. No relationship was demonstrated between symptom scores and bladder residuals (4,7,10) No statistical significant correlation was found between the subjective symtoms (problems due to symptoms-AUA part B) and flows. No relationship was found between the quality of life due to urinary symtoms (AUA part C) vs. peak and mean flow and vs. bladder residuals **(tables 2 to 9)**.

The average irritative and obstructive objective and subjective symptom scores were compared at given standard deviation of the average peak and mean flows based on the nomograms described by Siroky (114,115). There is a statistical significant difference in the average irritative, obstructive and total objective and subjective symptom scores for those presenting a peak flow equal or below -3 standard deviation from the mean and the others (tables 11 to 20). For this group of patients, the quality of life is significantly altered.

The same findings are observed for patients at -2 standart deviation (peak flow). However, in this latter group, the irritative objective symptoms are not statistically different from those presenting a peak flow above -2 standard deviation (tables 11 to 20).

The same comparisons were made for mean flows (tables 21 to 30). No statistically significant difference were found in any groups regarding the irritative symptoms. A statistically significant difference in the obstructive and total objective and subjective symptoms was observed in patients below -2 standard deviation and those above.

No statistical significant correlation was found between symtom scores and serum PSA (table 32) nor between these scores and prostate volume (table 33) nor between flows and prostate volume (table 55).

Nevertheless, there is a strong evidence that the **transition zone is the site of obstruction:** there was a significant difference in the post void residual in those with poorly developed and well developed transition zone (table 36). There was also a statistical difference in the three groups regarding peak and mean flows (table 37). However, no significant difference were found in symptoms between patients with well developed, moderately developed and poorly developed transition zone (tables 34 and 35).

One hundred fifty two patients had a serum PSA below 4 ng./cc. No patients with a serum PSA below 4 ng./cc. and a normal digital rectal exam had a suspicious lesion on transrectal ultrasound. Forty-four (21%) patients had a PSA between 4 and 10 ng./cc.. Thirteen patients (6%) had a PSA above 10 ng./cc. Twenty-three (11%) patients underwent biopsies of the peripheral zone of which thirteen (5.5%) patients had a positive rectal exam and thirteen (5.5%) patients had a suspicious transrectal ultrasound. Nine (4.2%) patients had an abnormal rectal exam and a suspicious lesion on transrectal ultrasound.

The biopsies were all negative in three patients with a serum PSA below 4 ng./cc. and what seemed to be a suspicious lesion on digital rectal exam (of which two transrectal ultrasounds were suggestive of tumor). Four out of eight patients with serum PSA below 10 ng./cc., had positive biopsies of their suspicious lesion seen on transrectal ultrasound (gleason score: 5.5±1) (positive predictive value of 50%) . Three out of ten patients who underwent a biopsy of a suspicious lesion felt by digital rectal examination had positive biopsies (gleason score: 5.67±1.15) (positive predictive value of 30%). It is important to note that all these patients with an abnormal rectal exam or a positive ultrasound with biopsies confirming the presence of adenocarcinoma had a serum PSA **between 4 and 10 ng./cc.**

In patients presenting an absolute serum PSA above or equal to **10 ng./cc.** with a suspicious lesion on ultrasound, three out of five biopsies were positive (positive predictive value of 60%). In those patients with an absolute PSA value equal or above **10 ng./cc.** and an abnormal rectal exam, all three patients had positive biopsies (each of them had also a positive ultrasound) (positive predictive value of 100%). The sensitivity and specificity of the digital rectal exam, the transrectal ultrasound and the combination of both were comparable (table 31): the sensitivity was 66.6% and the specificity between 71% and 81%.

Regarding the random prostate biopsies performed, three out of nine (positive predictive value of 33.3%) patients with a serum PSA between 4 and 10 ng./cc. had positive findings (adenocarcinoma) (gleason score: 4.5±1). No random biopsies were performed in those with a serum PSA below 4. The positive predictive value was higher in patients with a serum PSA equal or higher to 10 ng./cc.: the value was 55.5% (5 out of 9 patients with a gleason score of 5.75±.95). Four out of eight patients who had a suspicious lesion on transrectal ultrasound had both positive biopsies of the lesion and positive random biopsies (gleason score: 5.4±.89), suggesting a multifocal disease. All four patients with an abnormal digital rectal exam (had also positive ultrasound) had both positive biopsies of the lesion and positive random biopsies (gleason score: 5.5 ± 1).

Even if the predictive value of digital rectal exam and transrectal ultrasound seem to increase with increasing absolute serum PSA value, the **PSA tissue density** seems to be more important than the absolute PSA value in predicting cancer in the case of 6 quadrants peripheral zone random biopsies (table 38) and in the cases of biopsies of suspicious lesion seen on transrectal ultrasound (table 39).

Twenty-two patients underwent pressure-flow studies mainly because of a discrepancy between symtom scores and uroflow results, or in the case of significant post void residuals observed. These patients were midly to moderately symptomatic, but presented low peak flows, significant urethral resistance and significant post void residual volumes (table 51). The urethral resistance is the most useful urodynamic parameter, besides a peak and mean flow, to document an obstruction. A high urethral resistance is accompanied by significant irritative symptom scores (tables 40 to 46), low peak and mean flows (tables 47 to 50) and high post void residual (table 51). A statistical significant relationship was found between the urethral opening pressure and bladder residuals (table 52).

Biopsies of the transition zone were done in 13 patients (total of four biopsies per patient).. Prostatic intraepithelial neoplasia was found in one patient. No adenocarcinoma was found. Mixed stromal and glandular cells were seen in five patients, a predominance of stromal cells was found in four patients and a predominance of glandular cells was found in four patients. A correlation analysis demonstrated a relationship between the ratio of stromal cells vs. epithelial cells and irritative symptoms (positive association) and mean flows (negative association) (table 53). Stromal cell predominant prostate gland patients had less irritative symtoms than epithelial predominant cell prostate gland patients whereas the latter group had smaller mean flows than the former one (table 54).

V-Discussion and conclusion

Patients, with voided volume equal or above 50 cc., with peak or mean flow below two standard deviations from the mean from the nomograms described by Siroky (114,115), or patients with peak flow equal or below 12 cc./sec. (which is the maximum peak flow observed at -2 sd on nomograms), or patients with mean flows equal or below 8 cc./sec. (which is the maximum mean flow observed at -2 sd on nomograms) with minimal voided volume ≥ 150 cc., should be treated for BPH especially if they also present one of the following:

-obstructive score (AUA part A) ≥ 14 (8.5+1SD at peak flow <-2 SD)
-irritative score (AUA part A) ≥12 (7.97 +1 SD at peak flow <-3 SD)
-Total objective score (AUA part A) ≥ 22 (15.54 +1SD at peak flow <-2 SD)
-urethral resistance ≥ 42 cm H_2O (100) which corresponded to post void residuals above 200 cc., thus patients in chronic retention.

Using these guidelines, we would treat about 10 to 15 % of the ambulatory BPH patients consulting urologists. However, there are important individual variations regarding uroflow results in a given patient over time. It would have been interesting to follow these same two hundreds and forteen patients over a few years to determine those with spontaneous symtomatic and urodynamic improvements.

Considering the fact that no lesion was seen on transrectal ultrasound when the digital rectal examination was normal and the serum PSA was below 4 ng./cc., considering the fact that only 1 out of 152 patients had a prostate PSA density above 0.15 ng./cc./gr. (at .19 ng./cc./gr.) at a serum PSA below 4 ng./cc., the transrectal ultrasound and the measurement of prostate PSA density (serum PSA/prostate volume) should be reserved for those with a suspicious rectal exam or with a serum PSA $\geq$ 4 ng./cc. Six sextants biopsies of the peripheral zone should be done in those patients with a PSA prostate density $\geq$ .2 ng./cc./gr. (obtained from the mean density (.12ng./cc./gr.) observed in patients with adenocarcinoma on random biopsies - 1sd).

This work does not answer the issue of transition zone biopsies : 20% of prostate adenocarcinomas arise from this area. Strategic biopsies of the neurovascular bundle which can be useful in documenting extracapsular prostatic adenocarcinomas (thus locally advanced prostate cancer) to stage a given tumor have not been evaluated in this study.

TABLE 1A
Correlation analysis

Relationship between symtom scores

AUA part A-irritative vs. obstructive: r=0.506, r^2=0.256
AUA part B-irritative vs. obstructive: r=0.686, r^2=0.47
Boyarsky irritative vs. obstructive : r=.363, r^2=.132
Boyarsky irritative vs. AUA part A irritative : r=.735, r^2=.54
Boyarsky irritative vs. AUA part A obstructive: r=.344, r^2=.119
Boyarsky total score vs. AUA part A total score: r=.766r^2=.587

Table 1B
Simple regression analysis
Relationship between symtom scores

AUA part A irritative vs. AUA part B irritative: r=.694 r^2=.481, p<.0001
AUA part A-irritative vs. part C: r=.641, r^2=.411, p=.0001
AUA part A- obstructive vs. part C: r=.456, r^2=.208, p=.0001
AUA part A total score vs. part C: r=.623, r^2=.389, p=.0001
AUA part B-irritative vs. part C: r=.715, r^2=.512, p=.0001
AUA part B obstructive vs. part C: r=.582, r^2=.339, p=.0001
AUA part B total vs. part C: r= .699, r^2=.489, p=.0001
AUA part A total vs. AUA part B total: r= .763, r^2=.582, p=.0001
Boyarsky total score vs. AUA part B total score: r=.695, r^2=.484,p=.0001
Boyarsky total score vs. part C: r=.667, r^2=.445, p=.0001

Table 2

Regression analysis of symptom scores vs. peak flow

At voided volume > 50 cc.

Part A-irritative	$r=-.029$	$r^2=.001$	$p=.6994$
obstructive	$r=-.246$	$r^2=.06$	$p=.0008$
total	$r=-.144$	$r^2=.021$	$p=.05$
Part B-irritative	$r=-.071$	$r^2=.005$	$p=.34$
obstructive	$r=-.14$	$r^2=.005$	$p=.34$
total	$r=-.12$	$r^2=.014$	$p=.105$
Part C	$r=-.051$	$r^2=.003$	$p=.51$
Boyarski-irritative	$r=-.071$	$r^2=.005$	$p=.34$
obstructive	$r=-.22$	$r^2=.047$	$p=.003$
total	$r=-.17$	$r^2=.03$	$p=.02$

Table 3

Regression analysis of symptom scores vs. mean flow.

Voided volume > 50cc.

Part A-irritative	$r=.056$	$r^2=.003$	$p=.446$
obstructive	$r=-.23$	$r^2=.053$	$p=.002$
total	$r=-.12$	$r^2=.014$	$p=.11$
Part B-irritative	$r=-.077$	$r^2=.006$	$p=.3$
obstructive	$r=-.16$	$r^2=.024$	$p=.03$
total	$r=-.132$	$r^2=.017$	$p=.074$
Part C	$r=-.032$	$r^2=.001$	$p=.7$
Boyarski-irritative	$r=.003$	$r^2=9\times10^{-6}$	$p=1$
obstructive	$r=-.208$	$r^2=.043$	$p=.005$
total	$r=-.149$	$r^2=.022$	$p=.04$

Table 4

Regression analysis of symptom scores vs. bladder residual.

Voided volume > 50 cc.

Part A-irritative	r= .12	r^2=.014	p=.13
obstructive	r= .13	r^2= .018	p=.08
total	r=.145	r^2=.021	p=.06
Part B-irritative	r= .041	r^2=.002	p=.6
obstructive	r=.09	r^2=.008	p=.2
total	r=.08	r^2=.006	p=.3
Part C	r= .071	r^2=.005	p=.4
Boyarski-irritative	r= .02	$r^2=4x10^{-4}$	p=.8
obstructive	r= .04	r^2=.001	p=.6
total	r=.02	$r^2=3.6x10^{-4}$	p=.8

Table 5

Regression analysis of symptom scores vs. peak flow.

Voided volume >100cc.

Part A-irritative	$r=.033$	$r^2=.001$	$p=.67$
obstructive	$r=-.272$	$r^2=.074$	$p=.0004$
total	$r=-.157$	$r^2=.025$	$p=.0448$
Part B-irritative	$r=-.095$	$r^2=.009$	$p=.2262$
obstructive	$r=-.134$	$r^2=.018$	$p=.088$
total	$r=-.127$	$r^2=.016$	$p=.1$
Part C	$r=-.042$	$r^2=.002$	$p=.61$
Boyarski-irritative	$r=.024$	$r^2=.001$	$p=.76$
obstructive	$r=-.22$	$r^2=.049$	$p=.004$
total	$r=-.17$	$r^2=.03$	$p=.028$

Table 6

Regression analysis of symptom scores vs. mean flow.

Voided volume >100cc.

Part A-irritative	r= .064	r^2=.004	p=.4
obstructive	r=-.25	r^2=.062	p=.001
total	r=-.127	r^2=.016	p=.11
Part C-irritative	r=-.09	r^2=.008	p=.25
obstructive	r=-.137	r^2=.02	p=.08
total	r=-.13	r^2=.02	p=.105
Part C	r=.02	r^2= 3.5×10^{-4}	p= .8
Boyarski-irritative	r=.001	r^2= 7.5×10^{-4}	p=.99
obstructive	r= -.2	r^2=.04	p=.01
total	r=.15	r^2=.02	p=.06

Table 7

Regression analysis of symptom scores vs. bladder residual.

Voided volume >100cc.

Part A-irritative	r= .10	r^2=.012	p=.2
obstructive	r= .15	r^2=.022	p=.07
total	r=.15	r^2=.022	p=.07
Part B-irritative	r=.08	r^2=.006	p=.36
obstructive	r=.1	r^2=.01	p=.23
total	r=-.13	r^2=.02	p=.105
Part C	r=.1	r^2= .009	p= .24
Boyarski-irritative	r=-.018	r^2= 3.2×10^{-4}	p=.8
obstructive	r= -.045	r^2=.002	p=.6
total	r=-.041	r^2=.002	p=.6

Table 8

Regression analysis of symptom scores vs. peak flow.

Voided volume >150cc.

Part A-irritative	r= .005	$r^2=2.7X10^{-5}$	p=.95
obstructive	r= -.3	$r^2=.9$	p=.007
total	r=-.2	$r^2=.035$	p=.03
Part B-irritative	r=-.101	$r^2=.01$	p=.25
obstructive	r=-.15	$r^2=.022$	p=.095
total	r=-.138	$r^2=.019$	p=.12
Part C	r=-.03	$r^2= .001$	p= .74
Boyarski-irritative	r=.029	$r^2=.001$	p=.74
obstructive	r= .24	$r^2=.06$	p=.006
total	r=.19	$r^2=.035$	p=.03

Table 9

Regression analysis of symptom scores vs. mean flow.

Voided volume >150cc.

Part A-irritative	$r = .035$	$r^2 = .001$	$p = .7$
obstructive	$r = -.28$	$r^2 = .08$	$p = .0013$
total	$r = .16$	$r^2 = .026$	$p = .07$
Part B-irritative	$r = -.101$	$r^2 = .01$	$p = .25$
obstructive	$r = -.16$	$r^2 = .025$	$p = .07$
total	$r = -.144$	$r^2 = .021$	$p = .1$
Part C	$r = -.011$	$r^2 = 1.3 \times 10^{-4}$	$p = .9$
Boyarski-irritative	$r = .005$	$r^2 = 2.8 \times 10^{-5}$	$p = .95$
obstructive	$r = -.224$	$r^2 = .05$	$p = .01$
total	$r = -.17$	$r^2 = .03$	$p = .06$

Table 10

Regression analysis of symptom scores vs.bladder residual.

Voided volume >150cc.

Part A-irritative	r= .099	r^2=.01	p=.28
obstructive	r= .09	r^2=.007	p=.35
total	r=.105	r^2=.011	p=.26
Part B-irritative	r=.144	r^2=.021	p=.12
obstructive	r=.08	r^2=.006	p=.38
total	r=.119	r^2=.014	p=.199
Part C	r=.143	r^2= .02	p= .14
Boyarski-irritative	r=.06	r^2=.003	p=.54
obstructive	r= -.066	r^2=.004	p=.48
total	r=-.02	$r^2=4X10^{-4}$	p=.83

Table 11

T-test of average symptoms scores at given standart deviation of peak flows from nomograms (ref. 114-115)

AUA part A-irritative

-3 sd vs -2 sd: p>.125
-3 sd vs -1 sd: p>.125
-1 sd vs -2 sd: p>.125
≤-3sd vs ≥-1 sd: p=.055
≤-3 sd vs >-3 sd: p=.015
≤-3 sd vs ≥-2sd: p=.025
<-2 sd vs ≥-2sd: p=.115

Table 12
T-test of average symptoms scores at given standart deviation of peak flows from nomograms (ref. 114-115)

AUA part A-obstructive

-3 sd vs -2 sd: p=.025
-3 sd vs -1 sd: p=.05
-1 sd vs -2 sd: p=.0075
≤-3sd vs ≥-1 sd: p=.1
≤-3 sd vs >-3 sd: p=.1
≤-3 sd vs ≥-2sd: p=.0005
<-2 sd vs ≥-2sd: p =.0015

Table 13

T-test of average symptoms scores at given standart deviation of peak flows from nomograms (ref. 114-115)

AUA part A- total score

-3 sd vs -2 sd: p=.05
-3 sd vs -1 sd: p=.125
-1 sd vs -2 sd: p>.125
≤-3sd vs ≥-1 sd: p>.125
≤-3 sd vs >-3 sd: p=.00125
≤-3 sd vs ≥-2sd: p=.0005
<-2 sd vs ≥-2sd: p=.004

Table 14

T-test of average symptoms scores at given standart deviation of peak flows from nomograms (ref. 114-115)

AUA part B-irritative

-3 sd vs -2 sd: p=.015
-3 sd vs -1 sd: p=.125
-1 sd vs -2 sd: p>.125
≤-3sd vs ≥-1 sd: p>.125
≤-3 sd vs >-3 sd: p=.003
≤-3 sd vs ≥-2sd: p=.0035
<-2 sd vs ≥-2sd: p=.02

Table 15

T-test of average symptoms scores at given standart deviation of peak flows from nomograms (ref. 114-115)

AUA part B-obstructive

-3 sd vs -2 sd: p>.125
-3 sd vs -1 sd: p>.125
-1 sd vs -2 sd: p>.125
≤-3sd vs ≥-1 sd: p=.045
≤-3 sd vs >-3 sd: p=.025
≤-3 sd vs ≥-2sd: p=.015
<-2 sd vs ≥-2sd: p=.025

Table 16

T-test of average symptoms scores at given standart deviation of peak flows from nomograms (ref. 114-115)

AUA part B-total

-3 sd vs -2 sd: p=.04
-3 sd vs -1 sd: p>.125
-1 sd vs -2 sd: p>.125
≤-3sd vs >-1 sd: p=.075
≤-3 sd vs >-3 sd: p=.0075
≤-3 sd vs ≥-2sd: p=.0045
<-2 sd vs ≥-2sd: p=.019

Table 17

T-test of average symptoms scores at given standart deviation of peak flows from nomograms (ref. 114-115)

AUA part C- total

-3 sd vs -2 sd: p=.05
-3 sd vs -1 sd: p=.04
-1 sd vs -2 sd: p=.04
≤-3sd vs >-1 sd: p=.1
≤-3 sd vs >-3 sd: p=.0038
≤-3 sd vs ≥-2sd: p=.005
<-2 sd vs ≥-2sd: p=.05

Table 18

T-test of average symptoms scores at given standart deviation of peak flows from nomograms (ref. 114-115)

Boyarski-irritative

-3 sd vs -2 sd: p=.025
-3 sd vs -1 sd: p=.019
-1 sd vs -2 sd: p=.063
≤-3sd vs ≥-1 sd: p>.125
≤-3 sd vs >-3 sd: p<.0025
≤-3 sd vs ≥-2sd: p=.005
<-2 sd vs ≥-2sd: p>.125

Table 19

T-test of average symptoms scores at given standart deviation of peak flows from nomograms (ref. 114-115)

Boyarsky-obstructive

-3 sd vs -2 sd: p=.0075
-3 sd vs -1 sd: p=.06
-1 sd vs -2 sd: p>.125
≤-3sd vs ≥-1 sd: p=.0125
≤-3 sd vs >-3 sd: p=.005
<-2 sd vs ≥-2sd: p=.0005
≤-3 sd vs ≥-2sd: p=.0013

Table 20

T-test of average symptoms scores at given standart deviation of peak flows from nomograms (ref. 114-115)

Boyarsky-total

-3 sd vs -2 sd: p=.0038
-3 sd vs -1 sd: p>.125
-1 sd vs -2 sd: p>.125
≤-3sd vs ≥-1 sd: p=.025
≤-3 sd vs >-3 sd: p=.0005
<-2 sd vs ≥-2sd: p=.003
≤-3 sd vs ≥-2sd: p=.00025

Table 21

T-test of average symptoms scores at given standart deviation of mean flows from nomograms (ref. 114-115)

AUA part A-irritative

-3 sd vs -2 sd: p>.125
-3 sd vs -1 sd: p>.125
-1 sd vs -2 sd: p=.11
≤-3sd vs ≥-1 sd: p=.019
≤-3 sd vs >-3 sd: p>.125
<-2 sd vs ≥-2sd: p=.09
≤-3sd vs >-2 sd: p>.125

Table 22

T-test of average symptoms scores at given standart deviation of mean flows from nomograms (ref. 114-115)

AUA part A- obstructive

-3 sd vs -2 sd: p>.125
-3 sd vs -1 sd: p=.1
-1 sd vs -2 sd: p=.1
≤-3sd vs ≥-1 sd: p=.06
≤-3 sd vs >-3 sd: p=.01
<-2 sd vs ≥-2sd: p=.0005
≤-3sd vs >-2 sd: p=.0038

Table 23

T-test of average symptoms scores at given standart deviation of mean flows from nomograms (ref. 114-115)

AUA part A-total

-3 sd vs -2 sd: p>.125
-3 sd vs -1 sd: p>.125
-1 sd vs -2 sd: p>.125
≤-3sd vs ≥-1 sd: p>.125
≤-3 sd vs >-3 sd: p=.025
<-2 sd vs ≥-2sd: p=.0025
≤-3sd vs >-2 sd: p=.0125

Table 24

T-test of average symptoms scores at given standart deviation of mean flows from nomograms (ref. 114-115)

AUA part B-irritative

-3 sd vs -2 sd: p=.1
-3 sd vs -1 sd: p>.125
-1 sd vs -2 sd: p>.125
≤-3sd vs ≥-1 sd: p=.125
≤-3 sd vs >-3 sd: p>.125
<-2 sd vs ≥-2sd: p=.08
≤-3sd vs >-2 sd: p=.1

Table 25

T-test of average symptoms scores at given standart deviation of peak flows from nomograms (ref. 114-115)

AUA part B-obstructive

-3 sd vs -2 sd: p>.125
-3 sd vs -1 sd: p>.125
-1 sd vs -2 sd: p>.125
≤-3sd vs ≥-1 sd: p=.08
≤-3 sd vs >-3 sd: p=.05
<-2 sd vs ≥-2sd: p=.019
≤-3sd vs >-2 sd: p=.038

Table 26

T-test of average symptoms scores at given standart deviation of peak flows from nomograms (ref. 114-115)

AUA part B-total

-3 sd vs -2 sd: p>.125
-3 sd vs -1 sd: p>.125
-1 sd vs -2 sd: p>.125
≤-3sd vs ≥-1 sd: p>.125
≤-3 sd vs >-3 sd: p=.07
<-2 sd vs ≥-2sd: p=.025
≤-3sd vs >-2 sd: p=.05

Table 27

T-test of average symptoms scores at given standart deviation of mean flows from nomograms (ref. 114-115)

AUA part C- total

-3 sd vs -2 sd: p=.038
-3 sd vs -1 sd: p=.05
-1 sd vs -2 sd: p=.1
≤-3sd vs ≥-1 sd: p=.025
≤-3 sd vs >-3 sd: p>.125
<-2 sd vs ≥-2sd: p>.125
≤-3sd vs >-2 sd: p=.37

Table 28

T-test of average symptoms scores at given standart deviation of mean flows from nomograms (ref. 114-115)

Boyarski-irritative

-3 sd vs -2 sd: p=.1
-3 sd vs -1 sd: p=.125
-1 sd vs -2 sd: p>.125
≤-3sd vs ≥-1 sd: p=.025
≤-3 sd vs >-3 sd: p>.125
<-2 sd vs ≥-2sd: p=.075
≤-3sd vs >-2 sd: p>.125

Table 29

T-test of average symptoms scores at given standart deviation of mean flows from nomograms (ref. 114-115)

Boyarsky-obstructive

-3 sd vs -2 sd: p>.125
-3 sd vs -1 sd: p=.11
-1 sd vs -2 sd: p=.09
≤-3sd vs ≥-1 sd: p=.05
≤-3 sd vs >-3 sd: p=.075
<-2 sd vs ≥-2sd: p=.02
≤-3sd vs >-2 sd: p=.06

Table 30

T-test of average symptoms scores at given standart deviation of mean flows from nomograms (ref. 114-115)

Boyarsky-total

-3 sd vs -2 sd: p>.125
-3 sd vs -1 sd: p>.125
-1 sd vs -2 sd: p=.05
≤-3sd vs ≥-1 sd: p>.125
≤-3 sd vs >-3 sd: p=.11
<-2 sd vs ≥-2sd: p=.0125
≤-3sd vs >-2 sd: p=.05

Table 31

Sensitivity and specificity of digital rectal exam, transrectal ultrasonography and the combination of both.

	DRE	TRUS	DRE+TRUS
Sensitivity	66.6% (6/9)	66.6% (6/9)	66.6% (6/9)
Specificity (15/21)	81% (17/21)	76% (16/21)	71%

Table 32
Correlation analysis between symptom scores and serum PSA

AUA part	A-irritative	r=-.016	$r^2=2.5X10^{-4}$
	obstructive	r=-.007	$r^2=5.2X10^{-5}$
	total	r=-.013	$r^2=1.62X10^{-4}$
AUA part B-irritative		r=-.014	$r^2=1.9X10^{-4}$
	obstructive	r=.01	$r^2=9.5X10^{-5}$
	total	r=-.001	$r^2=6.3X10^{-7}$
AUA part C		r=-.037	$r^2=.001$

Table 33
Regression analysis of symptom scores vs. prostate volume

AUA part a-irritative	r=.11	r^2=.012	p=.12
obstructive	r=.035	r^2=.001	p=.63
total	r=.079	r^2=.006	p=.27
AUA part B-irritative	r=.094	r^2=.009	p=.19
obstructive	r=.028	r^2= 001	p=.7
Total	r=.063	r^2=.004	p=.38
AUA part C	r=.06	r^2=.004	p=.42

Table 34
Student t-test of average symptom scores regarding the developement of transition zone (well, moderately or poorly developed on transrectal ultrasound)

	TZ well dev. vs. TZ mod. dev.	TZ mod.dev. vs. TZ poorly dev.
AUA symptom score		
part A-irritative	p>.125	p>.125
obstructive	p=.08	p=.015
total	p=.1	p=.09
part B-irritative	p>.125	p=.125
obstructive	p>.125	p>.125
total	p>.125	p>.125
partC	p=.06	p=.02

Table 35
Student t-test of average symptom scores regarding the developement of transition zone (well, moderately or poorly developed on transrectal ultrasound)

	TZ poorly dev. vs. TZ well dev.
AUA symptom score	
part A-irritative	p = .125
obstructive	p >.125
total	p>.125
part B-irritative	p=.11
obstructive	p >.125
total	p >.125
partC	p=.125

Table 36
Student t test of average post void residual and prostate volume regarding the development of the transition zone (well, moderately and poorly developed)

	TZ well dev. vs. TZ mod. dev.	TZ mod. dev vs. TZ poorly dev.	TZ poorly dev vs. TZ well dev.
Residual	p>.125	p=.125	p=.05
Prostate volume	p=.00025	p<.0005	p<.0005

Table 37
Student t test of average peak and mean flows regarding the development of the transition zone (well, moderately and poorly developed)

	TZ well dev. vs TZ mod. dev.	TZ mod. dev vs. TZ poorly dev.	TZ poorly dev vs. TZ well dev.
Peak flow	p=.002	p=.008	p<.0005
Mean flow	p=.011	p=.002	p<.0005

Table 38
Serum PSA, tissue density PSA (serum PSA/volume) encountered in positive and negative random prostate biopsies (mean ± st. dev.).
Non parametric Wilcoxon sign rank sum test.

Serum PSA in positive vs negative random biopsies: p=.09 (40.04 ± 58.6 vs. 11.48±6.71)

PSA density in positive vs. negative random biopsies: p<.0005 (1.24 ng./cc./gr. ±1.934 vs. 0.209 ng./cc./gr. ±.057)

Table 39
Serum PSA, tissue density PSA (serum PSA/volume) encountered in positive and negative suspicious lesion biopsies (mean ± st.dev.).
Non parametric Wilcoxon sign rank sum test.

Serum PSA in positive vs negative suspicious lesion biopsies: p=.1 (49.16±68.53 vs. 9.58±10.64)

PSA density in positive vs. negative suspicious lesion biopsies: p<.0005 (1.32 ng./cc./gr. ± 2.11 vs. 0.116 ng./cc./gr. ±.09)

Table 40
AUA part A-irritative vs. urodynamic parameters
Simple regression analysis

Capacity	r=.088	r^2=.008
p=.71		
Urethral opening pressure	r=.285	r^2=.08
p=.26		
Urethral resistance	r=.472	r^2=.22
p=.036		
Detrusor pressure at max. flow	r=.29	r^2=.087
p=.2		
Detrusor power at max. flow	r=.27	r^2=.075
p=.24		
Detrusor pressure at beginning	r=.033	r^2=.001
p=.89		

Table 41
AUA part A-obstructive vs. urodynamic parameters
Simple regression analysis

Capacity	r=.07	r^2=.005
p=.77		
Urethral opening pressure	r=.038	r^2=.001
p=.88		
Urethral resistance	r=.269	r^2=.073
p=.25		
Detrusor pressure at max. flow	r=.002	$r^2=2.37\times10^{-6}$
p=.99		
Detrusor power at max. flow	r=.44	r^2=.191
p=.05		
Detrusor pressure at beginning	r=.12	r^2=.014
p=.61		

Table 42
AUA part A total vs. urodynamic parameters
simple regression analysis

Capacity	r=.083	r^2=.007
p=.72		
Urethral opening pressure	r=.16	r^2=.026
p=.53		
Urethral resistance	r=.39	r^2=.15
p=.093		
Detrusor pressure at max. flow	r=.146	r^2=.021
p=.54		
Detrusor power at max. flow	r=.38	r^2=.147
p=.09		
Detrusor pressure at beginning	r=.085	r^2=.007
p=.72		

Table 43
AUA part B -irritative vs. urodynamic parameters
Simple regression analysis

Capacity	r=.25	r^2=.064
p=.28	Urethral opening pressure	r=.112
r^2=.013	p=.68	
Urethral resistance	r=.41	r^2=.17
p=.07		
Detrusor pressure at max. flow	r=.103	r^2=.011
p=.66		
Detrusor power at max. flow	r=.36	r^2=.131
p=.12		
Detrusor pressure at beginning	r=.161	r^2=.026
p=.5		

Table 44
AUA part B-obstructive vs. urodynamic parameters
simple regression analysis

Capacity	r=.029	r^2=.001
p=.9		
Urethral opening pressure	r=.012	$r^2=1.4X10^{-4}$
p=.96		
Urethral resistance	r=.32	r^2=.102
p=.17		
Detrusor pressure at max. flow	r=.041	r^2=.002
p=.86		
Detrusor power at max. flow	r=.36	r^2=.13
p=.12		
Detrusor pressure at beginning	r=.17	r^2=.03
p=.46		

Table 45
AUA part B -total vs. urodynamic parameters
Simple regression analysis

Capacity	r=.145	r^2=.021
p=.54		
Urethral opening pressure	r=.064	r^2=.004
p=.8		
Urethral resistance	r=.4	r^2=.164
p=.08		
Detrusor pressure at max. flow	r=.077	r^2=.006
p=.75 Detrusor power at max. flow		r=.41
r^2=.16 p=.08		
Detrusor pressure at beginning	r=.19	r^2=.035
p=.42		

Table 46
AUA part C vs. urodynamic parameters
Simple regression analysis

Capacity	r=.33	r^2=.111	p=.16
Urethral opening pressure	r=.19	r^2=.037	p=.48
Urethral resistance	r=.57	r^2=.32	p=.01
Detrusor pressure at max. flow	r=.34	r^2=.12	p=.16
Detrusor power at max. flow	r=.29	r^2=.09	p=.23
Detrusor pressure at beginning	r=.05	r^2=.003	p=.84

Table 47
Simple regression analysis
Peak flow vs urodynamic parameters

Capacity	r=.335	r^2=.112	p=.14
Urethral opening pressure	r=.069	r^2=.005	p=.78
Urethral resistance	r=-.46	r^2=.21	p=.03
Detrusor pressure at max. flow	r=.26	r^2=.07	p=.24
Detrusor power	r=.92	r^2=.84	p=.0001

Table 48
Simple regression analysis
Mean flow vs urodynamic parameters

Capacity	r=.42	r^2=.177	p=.06
Urethral opening pressure	r=.282	r^2=.079	p=.24
Urethral resistance	r=-.5	r^2=.25	p=.02
Detrusor pressure at max. flow	r=.023	r^2=.001	p=.9
Detrusor power	r=.48	r^2=.23	p=.02

Table 49
Simple regression analysis
Standardized Peak flow vs urodynamic parameters

Capacity	r=.4	r^2=.163	p=.07
Urethral opening pressure	r=.12	r^2=.014	p=.63
Urethral resistance	r=-.54	r^2=.29	p=.01
Detrusor pressure at max. flow	r=.06	r^2=.004	p=.79
Detrusor power	r=.66	r^2=.43	p=.001

Table 50
Simple regression analysis
Standardized mean flow vs urodynamic parameters

Capacity	r=.615	r^2=.38	p=.003
Urethral opening pressure	r=.21	r^2=.046	p=.39
Urethral resistance	r=-.4	r^2=.103	p=.07
Detrusor pressure at max. flow	r=.03	r^2=.001	p=.89
Detrusor power	r=.52	r^2=.27	p=.02

Table 51
Averages and standard deviations of the twenty-two patients who underwent pressure-flow studies

AUA part A-irritative	6.45 (±4.26)
obstructive	8.2 (±4.94)
total	14.65 (±8.67)
AUA part B -irritative	4.45 (±3.73)
obstructive	4.75 (±4.66)
total	9.2 (±7.47)
AUA part C	6.9 (±5.16)
Peak flow	10.37 (±8.98)
Mean flow	5.44 (±3.06)
Voided volume	228.23 (±113.35)
Post void residual	165.33 (±196.38)
Urethral resistance	39.68 (±31.15)
Urethral opening pressure	70.11 (±53.02)
Detrusor pressure at maximum flow	78.63 (±50.35)
Detrusor power at maximum flow	927.32 (±1494.55)
Bladder capacity	374.05 (±191.86)
Standardized peak flow	10.19 (±4.71)
Standardized mean flow	10.59 (±3.26)

Table 52
Simple linear regression analysis of post void residuals vs. urodynamic pressure-flow studies parameters.

capacity	r= .777	r^2=.603	p=.0001
Urethral opening pressure	r=.524	r^2=.274	p=.0213
Urethral resistance	r=.578	r^2=.334	p=.0048
Detrusor pressure at max. flow	r=.35	r^2=.123	p=.11
Detrusor power	r=.159	r^2=.025	p=.48

Table 53
Correlation analysis between stromal/glandular cell ratio vs. symptoms and flows

irritative symptoms	r=.988	r^2=.976
obstructive symtoms	r=-.359	r^2=.129
mean flow	r=-.849	r^2=.72
peak flow	r=-.547	r^2=.299

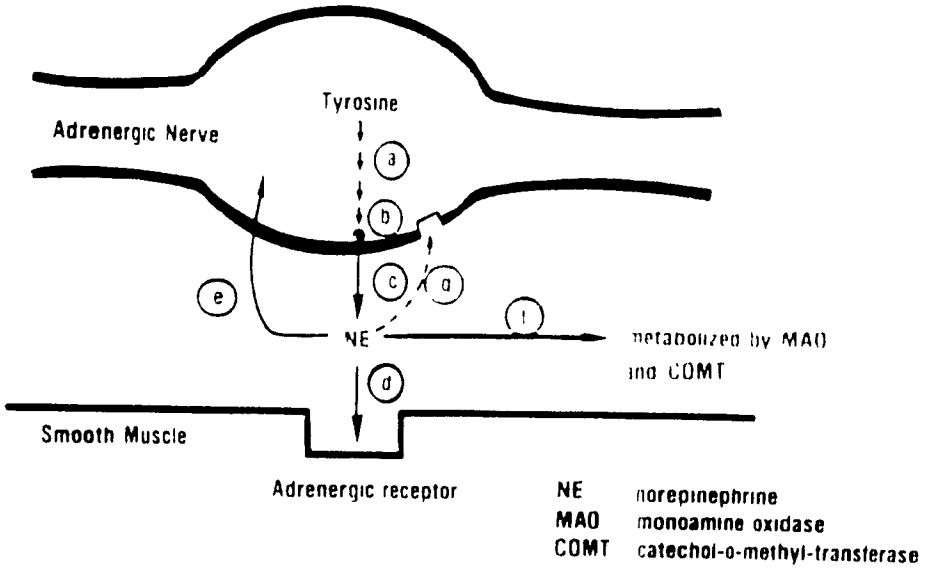
Table 54
Non parametric wilcoxon rank sum test
Stromal cells predominant prostate vs. glandular cells predominant prostate

peak flow	p=.09	(10.27±.99 vs. 9.88±3.26)
mean flow	p=.0075	(5.5±.46 vs. 4 ±1.71)
Standardized peak flow	p>.125	(11.3±1.15 vs.10.55±1.8)
Standardized mean flows	p=.05	(12.5 ±1.5 vs. 13.9 ±5.58)
Irritative symtoms	p=.0125	(5.5 ±4.73 vs 8.25±1.71)
Obstructive symtoms	p>.125	(10.25±3.95 vs. 9.5±6.03)
Total objective symtoms (AUA part A)	p>.125	(15.75±4.6 vs17.75±7.4)
Prostate volume	p>.125	(40.9±10.14 vs 29.4±15.45)

Table 55
Simple linear regression analysis of prostate volume vs. flows

peak flow	r=-.019	$r^2=3.4X10^{-4}$	p=.8
mean flows	r=.007	$r^2=4.29X10^{-4}$	p=.9
Standardized peak flow	r=.005	$r^2=2.28X10^{-5}$	p=.95
standardized mean flow	r=.075	$r^2=.006$	p=.31

VII- Figure 1



Norepinephrine is synthesised from tyrosine through synthesis of dopa and dopamine (a). The norepinephrine is then stored in granular vesicle (b). The transmitter is released from the nerve terminal (c) and diffuses to a receptor site on the smooth membrane (d) called **alpha-1 receptor** Inactivation occurs largely through active reuptake into peripheral nerve terminals (e) where granular reincorporation and degradation by monoamine oxidase and catechol-O-methyltransferase occurs. **Site g** depicts the ability, via presynaptic **alpha-2 receptors**, of norepinephrine to interact with presynaptic receptors and regulate its own rate of release from the nerve terminal.

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