**Diseases Of The Prostate** Gland -Part 2 **BENIGN PROSTATIC** HYPERTROPHY OR HYPERPLASIA

- This powerpoint was resurrected and edited from notes made by my medical students, for BARBADOS UNDERGROUND.
- It arose originally from a series of seminars held in a medical school in Curacao in 2005
- It will be in four basic sections
- 1- some basic anatomy and histology of the prostate gland
- 2 some basic pathology of BENIGN PROSTATIC HYPERTROPHY OR HYPERPLASIA
   3- Medical treatment
- 4- Phytotherapy and surgical treatment

## THINGS YOU MUST KNOW ABOUT DISEASES OF THE PROSTATE

- Tell what can cause pain in the prostate.
- Give accounts of bacterial and nonbacterial prostatitis.
- Tell what we know about the etiology, pathogenesis, pathophysiology, anatomic pathology, and consequences of prostatic hyperplasia.
- Describe adenocarcinoma of the prostate in terms of its etiology, pathogenesis, markers, anatomic pathology, patterns of growth and spread, and clinical diagnosis, including the use of the lab.
- Read a prostate needle biopsy, distinguishing cancer from the other common lesions, and do simple grading of adenocarcinoma.

## This presentation is about the etiology, pathogenesis, pathophysiology, anatomic pathology, and consequences of prostatic hyperplasia.

## BENIGN ENLARGEMENT OF THE PROSTATE

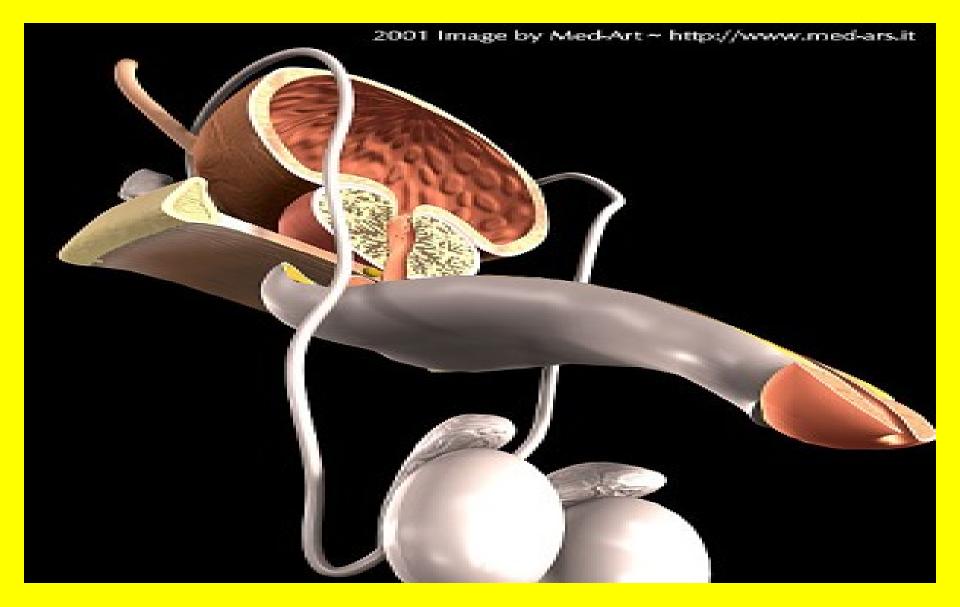
#### **NODULAR HYPERPLASIA**

OR

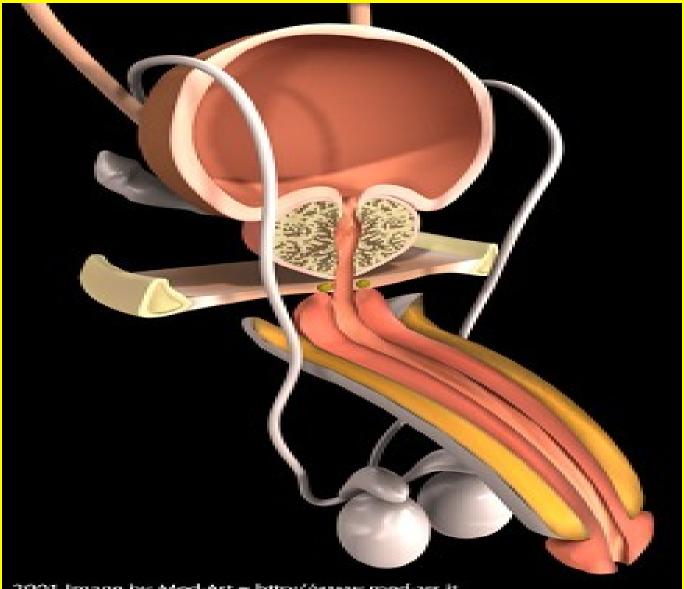
#### BENIGN PROSTATIC HYPERTROPHY OR HYPERPLASIA

But first.....

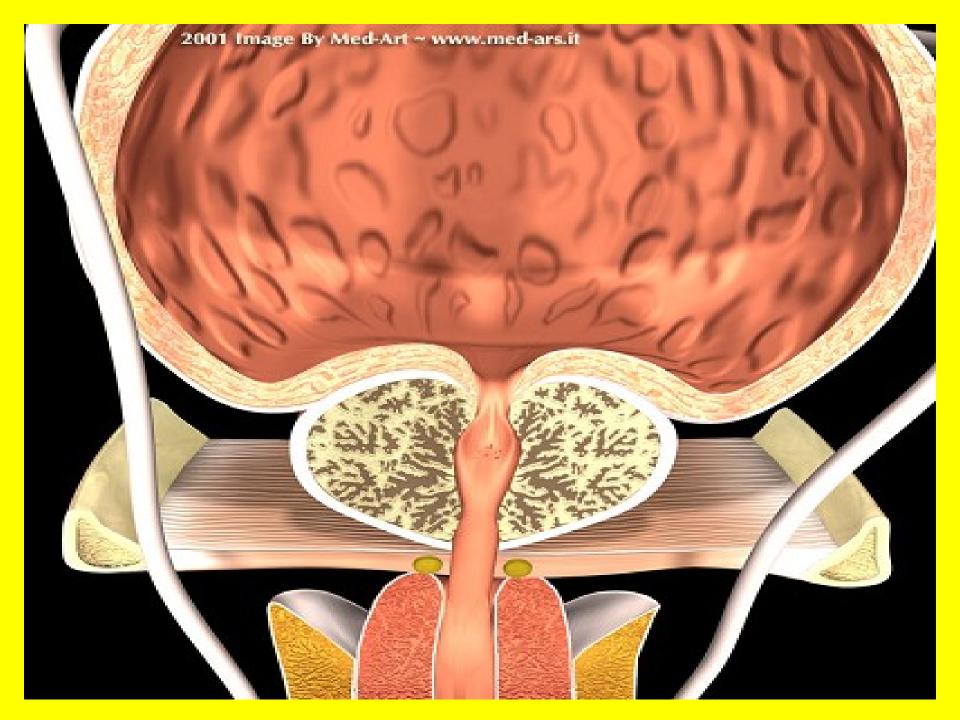
#### Quick Review Of Male genital system



### Quick Review Of Prostate gland

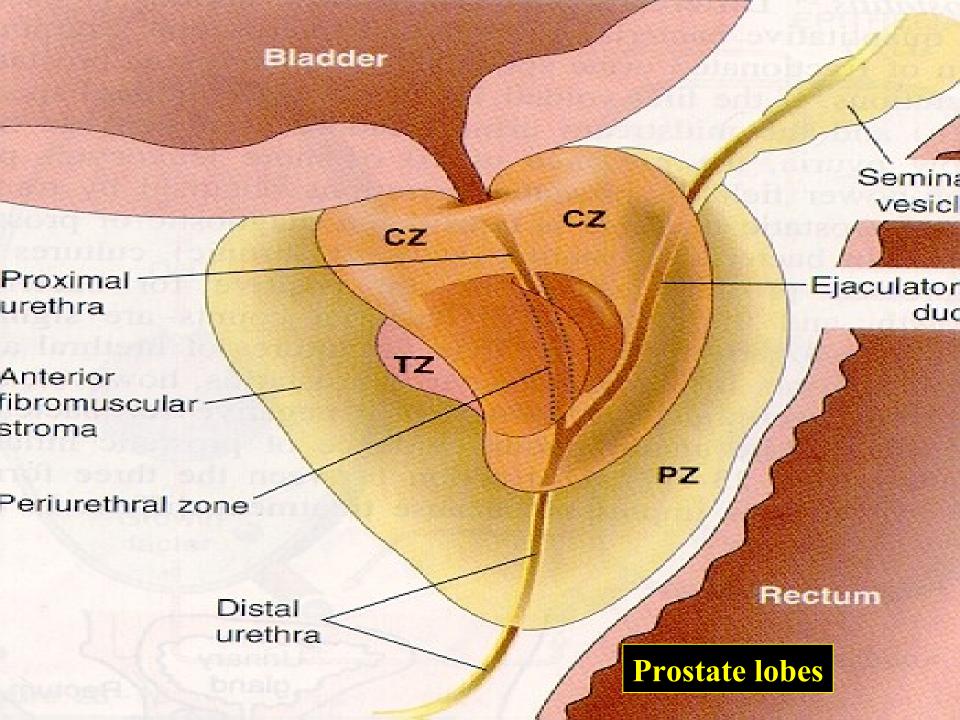


2001 Image by Med-Art ~ http://www.med-ars.it



## Normal prostate

- The prostate is a retroperitoneal organ encircling the neck of the bladder and urethra and is devoid of a distinct capsule.
- In the normal adult, the prostate weighs approximately 20 gm.
- In the adult, prostatic parenchyma can he divided into four biologically and anatomical distinct zones or regions: the peripheral, central, transitional, and periuretheral zones.







The prostate gland is the largest of the accessory glands of the male reproductive tract (approximately 3cm long). The

urethra exits from the bladder and traverses the prostate before exiting to the penile urethra. The glandular part comprises approximately 2/3 of the prostate; the other 1/3 is fibromuscular. It is a collection of 30-50 branched **tubuloalveolar glands**. Their ducts empty into the prostatic urethra, which crosses the prostate.

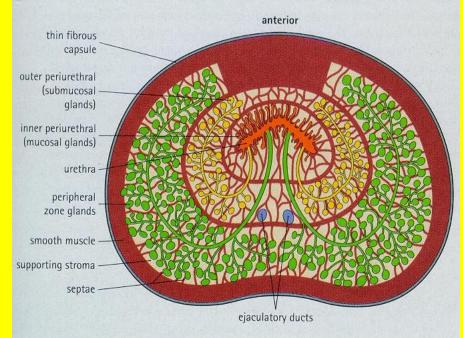
#### Prostate Gland



### Anatomy of...

The prostate has 3 distinct zones:

- central zone which occupies 25% of the gland's volume. This zone consist of mucosal glands which open directly into the urethra.
- peripheral zone which is 70%, and also the major site of prostatic cancer. The glands of this zone open into the urethra via long ducts.
- transition zone which is of medical importance because it is the site where most benign prostatic hyperplasia originates. Glands of this zone are submucosal, and they open into the urethra via short ducts.



#### **Diseases of the Prostate**

- Only three pathologic processes affect the prostate gland with sufficient frequency to merit discussion:
- Inflammation --- The inflammatory processes are, for the most part of less clinical significance
- Benign nodular enlargement or benign prostatic hypertrophy
- Prostatic carcinoma ---Prostatic carcinoma is also an extremely common lesion in men and therefore merits careful consideration.
- Of these three, the benign nodular enlargements are by far the most common and occur so often in advanced age that they can almost be construed as a "normal" aging process.
- This is the subject of this presentation.

## **NODULAR HYPERPLASIA**

- Nodular hyperplasia, or benign prostatic hypertrophy of the prostate is an extremely common disorder in men over age 50, characterized by hyperplasia of prostatic stromal and epithelial cells, which results in the formation of large, fairly discrete nodules in the periurethral region of the prostate.
- When sufficiently large, the nodules compress and narrow the urethral canal to cause partial, or sometimes virtually complete obstruction of' the urethra.

<u>Benign nodular hyperplasia (BNH) /</u> <u>Benign prostatic hyperplasia (BPH)</u>

- Extremely common disorder in men over 50
- Gross distinct circumscribed grey white nodules in the periurethral zone
- Histology proliferation of both glandular and fibromuscular stromal elements + infarct, infection, squamous metaplasia

## Incidence

- PERIURETHRAL NODULES
  - 20% MEN BY 40
  - 70% OF MEN BY 60
  - 90% OF MEN BY 70'S
- 400,000 TUR IN USA PER YEAR
- SECOND MOST COMMON SURGERY AFTER CATARACT EXTRACTION IN MEN OVER 65 YEARS OF AGE
- DHT ACCUMULATES IN PROSTATE

## **Etiology and Pathogenesis**.

- Prostatic hyperplasia is now considered to be related to the action of androgens, especially Dihydrotestosterone (DHT), a metabolite of testosterone, and the ultimate mediator of prostatic growth.
- DHT is synthesized mainly in the stromal cells of the prostate from circulating testosterone by the action of the enzyme 5 alpha reductase type 2, which is principally localized in the stromal cells- the main site for the synthesis of DHT.

- Once synthesized, DHT can act in an autocrine fashion on the stromal cells or in paracrine fashion by diffusing into nearby epithelial cells.
- In both of these cell types, DHT binds to nuclear androgen receptors and signals the transcription of growth factors that are mitogenic to the epithelial and stromal cells.
- Although testosterone can also bind to the androgen receptors and cause growth stimulation. DHT is ten times more potent because it dissociates from the androgen receptor more slowly.

#### The following experimental evidence suggests that DHT-mediated prostatic hyperplasia is aided and abetted by estrogens.

- In castrated young dogs, prostatic hyperplasia can he induced by administration of androgens, an effect markedly enhanced by simultaneous administration of I7 beta-estradiol.
- In aging men, estradiol levels increase, and it is believed that estrogens induce an increase in androgen receptors, thus rendering cells more susceptible to the action of DHT.

- When an inhibitor of 5 alpha reductase was given to men with BPH, it induced a marked reduction of the DHT content of the prostate. and in a proportion of cases, there was a concomitant decrease in both prostatic volume and urinary obstruction.
- The fact that all patients do not benefit from androgen-depriving therapy suggests that prostatic hyperplasia may be etiologically heterogeneous, and that in some cases, factors other than androgens, may be more important.

# **Epidemiology of BPH**

- Benign prostatic hyperplasia
- also called benign prostatic hypertrophy / nodular hyperplasia
- presents in 50% of men more than 50 years of age
- 95% in men of more than 70 years
- in 5-10% of cases, it leads to obstruction of the urethra.
- BPH is an extremely common disorder in men over 50

- Histologic evidence of nodular hyperplasia can he seen in approximately 20% of men 40 years of age, a figure that increases to 70% by age 60 and to 90% by age 70.
- There is no direct correlation, however, between histologic changes and clinical symptoms.
- Only 50% of those who have microscopic evidence of nodular hyperplasia have clinically detectable enlargement of the prostate, and of these individuals, only 50% develop clinical symptoms.
- Nodular hyperplasia of prostate is a problem of enormous magnitude, since more than 400.000 transurethral resections of the prostate are performed every year in the United States.
- In men older than 65 years of age, this surgical procedure is second only to cataract extraction.

## Pathogenesis/ Pathophysiology

- Nodular hyperplasia, or benign prostatic hypertrophy of the prostate is an extremely common disorder in men over age 50, characterized by hyperplasia of prostatic stromal and epithelial cells, which results in the formation of large, fairly discrete nodules in the periurethral region of the prostate.
- There is considerable enlargement of the prostatic glands in the mucous and submucosal gland groups due to an increase in the number and size of the glands and ducts, and an increase in the bulk of the supporting fibromuscular stroma
- When sufficiently large, the nodules compress and narrow the urethral canal to cause partial, or sometimes virtually complete obstruction of' the urethra.

## PATHOLOGY of Nodular hyperplasia of the prostate

- MORPHOLOGY. In cases of prostatic enlargement, the nodules weigh usually between 60 and 100 gm, but weights of up to 200 gm, and even larger masses have been recorded. are encountered, and even larger masses have been recorded.
- Nodular hyperplasia of the prostate originates almost exclusively in the inner aspect of the prostate gland, in the transitional and periurethral zones.
- The first nodules, composed almost entirely of epithelial cells, arise from the transitional zone; later, predominantly stromal nodules arise in the periurethral zone.

- From their origin in this strategic location, the nodular enlargements may encroach on the lateral walls of the urethra to compress it to a slit like orifice.
- In some cases, nodular enlargement may project up into the floor of the urethra as a hemispheric mass directly beneath the mucosa of the urethra.
- On cross-section of the affected prostate, the nodules vary in color and consistency. In nodules with primarily glandular proliferation, the tissue is yellow-pink with a soft consistency, and a milky white prostatic fluid oozes out of these areas.

- In those primarily due to fibromuscular involvement, each nodule is pale gray, is tough, does not exude fluid, and is less clearly demarcated from the surrounding prostatic "capsule".
- The nodules do not have true capsules, but the compressed surrounding prostatic tissue creates a plane of cleavage about them, used by the surgeon in the nucleation of prostatic masses in suprapubic prostatectomies.

A normal prostate gland is about 3 to 4 cm in diameter. This prostate is enlarged due to prostatic hyperplasia, which appears nodular. Thus, this condition is termed either BPH (benign prostatic hyperplasia) or nodular prostatic hyperplasia.



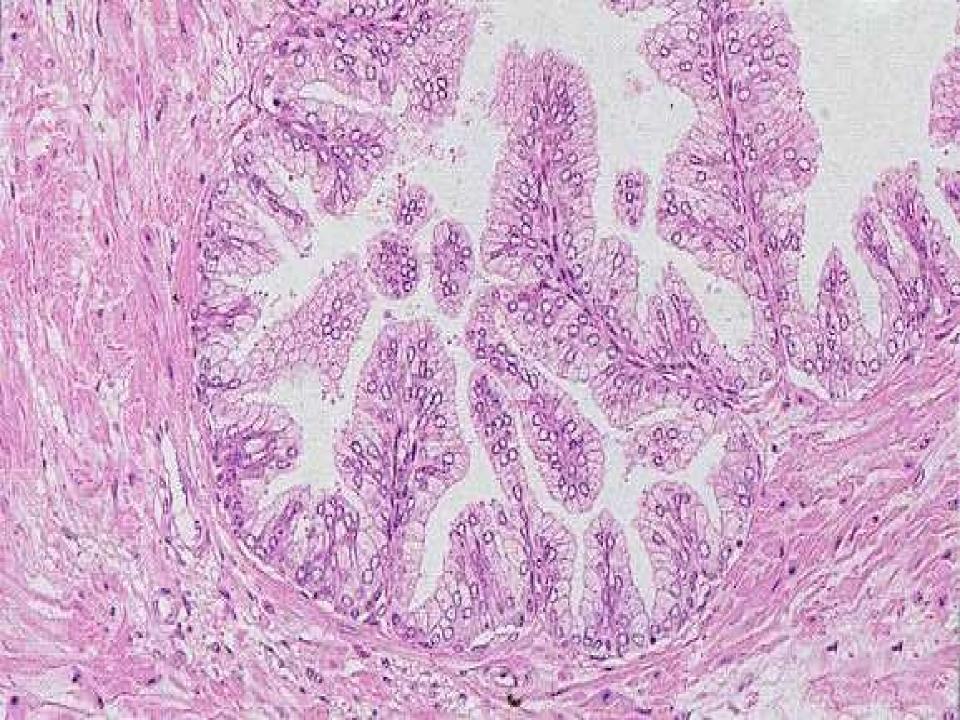
Here is another example of benign prostatic hyperplasia. Nodules appear mainly in the lateral lobes. Such an enlarged prostate can obstruct

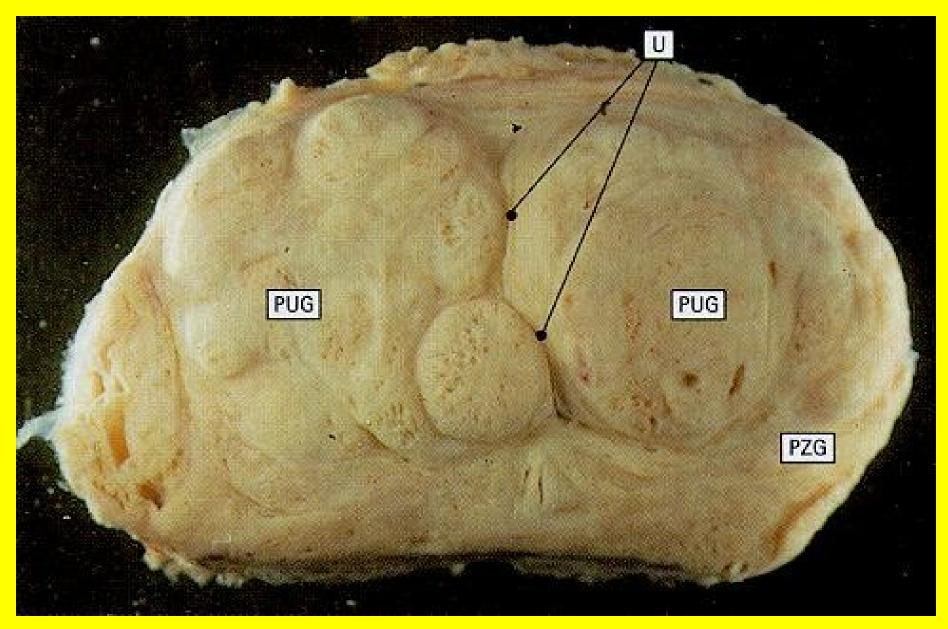
urinary outflow from the bladder and lead to an obstructive uropathy.



## This is what normal prostate tissue looks like under the microscope







Benign prostatic hyperplasia» Nodular overgrowth of the periurethral glands (PUG), which is causing compression and distortion of the urethra (U). Note that the peripheral zone glands (PZG) are not involved. **Benign Prostatic hyperplasia** 





U





Salar 2

A.

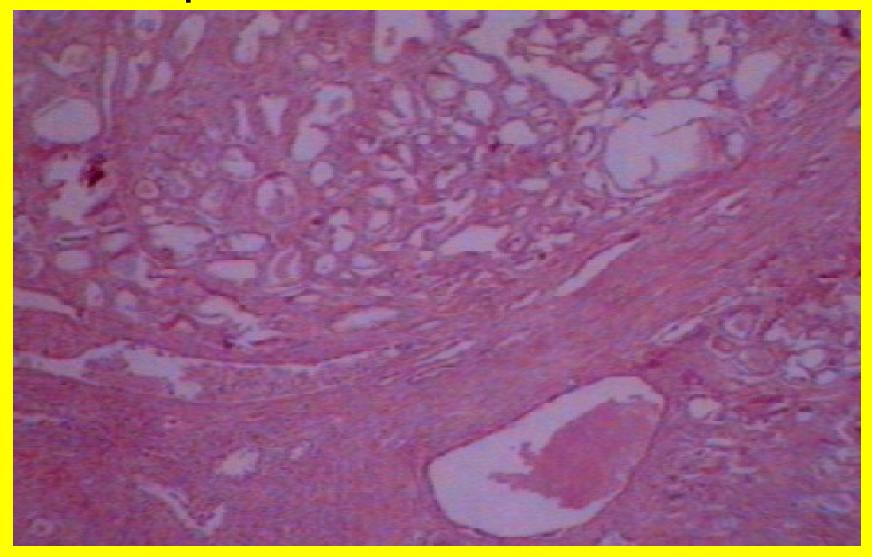


#### BPH ADVANCED

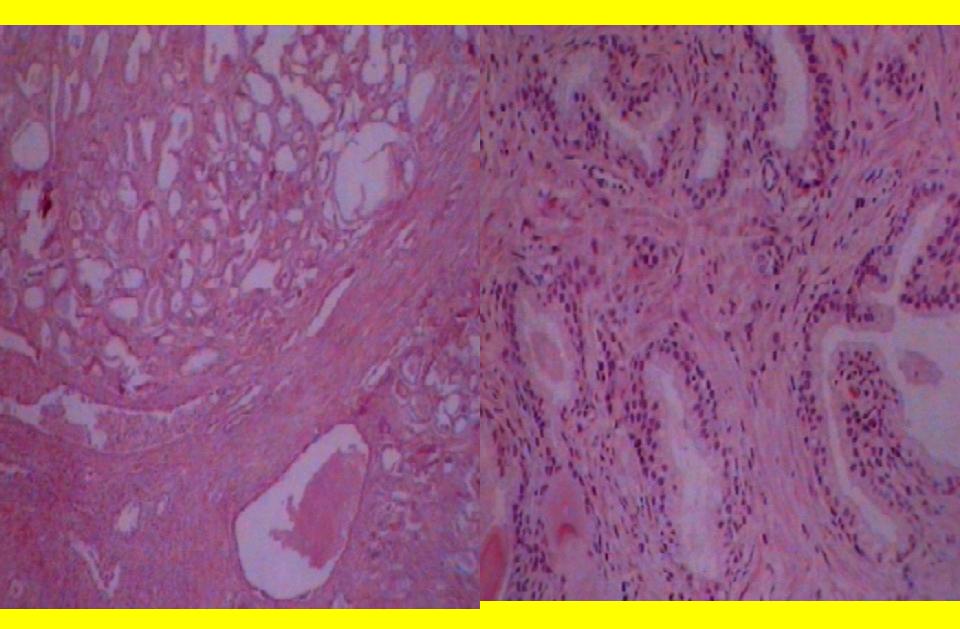
- Microscopically the nodularity may be due to glandular proliferation or dilation or to fibrous or muscular proliferation of the stroma.
- Although all three elements are involved in almost every case, the stromal (fibroblastic) component predominates in most cases.
- Glandular proliferation takes the form of aggregations of small to large to cystically dilated glands, lined by two layers, an inner columnar and an outer cuboidal or flattened epithelium, based on an intact basement membrane.

- The epithelium is characteristically thrown up into numerous papillary buds and infoldings, which are more prominent than in the normal prostate.
- Two other histologic changes are frequently found: (1) foci of squamous metaplasia and
- (2) small areas of infarction. The former tend to occur in the margins of the foci of infarction as nests of metaplastic, but orderly, squamous cells.

#### Next few slides show the appearance of prostatic tissue in BPH



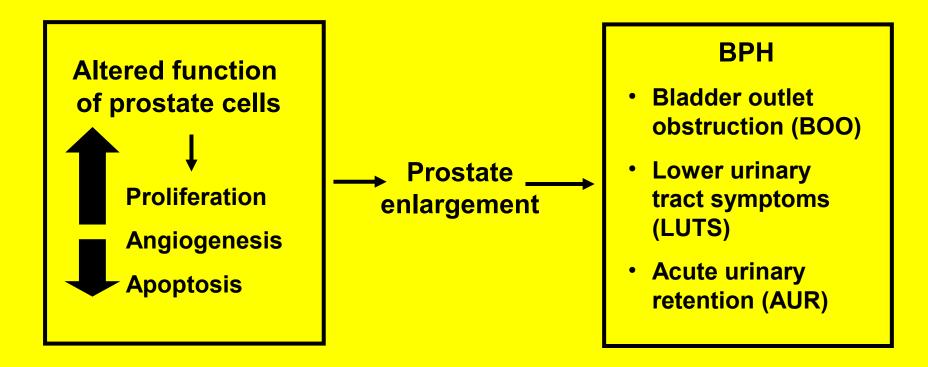




High power view showing hyperplastic glands with two layers – Inner columnar – Outer cuboidal.

Proliferation of glands, some cystically dilated within a well defined nodule

#### Pathophysiology as it relates to clinical manifestations of BPH



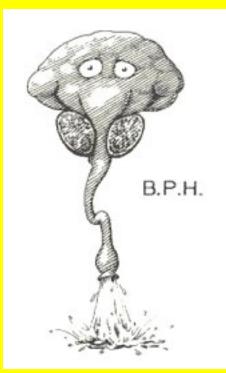
McConnell. Campbell's Urology. 7th ed.

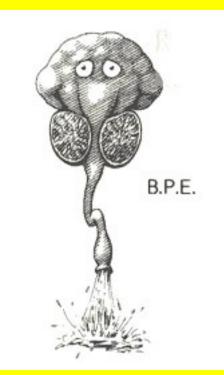
#### **Definitions**

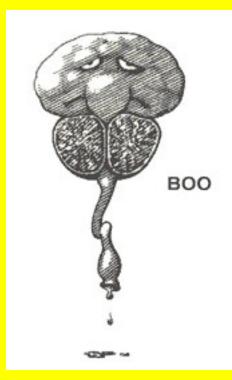
LUTS = Lower Urinary Tract Symptoms

BPH = Benign Prostatic Hyperplasia BPE = Benign Prostatic Enlargement

BOO = Bladder Outlet Obstruction





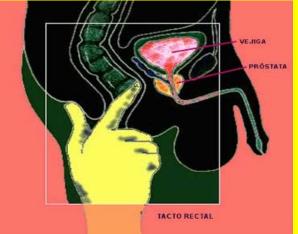


## **CLINICAL PRESENTATION**

- Clinical symptoms (prostatism) is present, hard mass find during rectal examination.
- Incidental finding during microscopic examination of the tissue surgically removed for non-malignant disease, particularly BPH.
- Present with signs and symptoms of metastasis (e.g. back pain due to vertebral metastasis)
- Tumors of the prostate detected during autopsy on patients that showed no clinical evidence of prostatic cancer

### **Symptoms of BPH**

- Symptoms of bladder outlet obstruction caused by BPH include:
- Hesitancy
- Weakness of urinary stream
- Intermittent urinary stream
- A feeling of incomplete



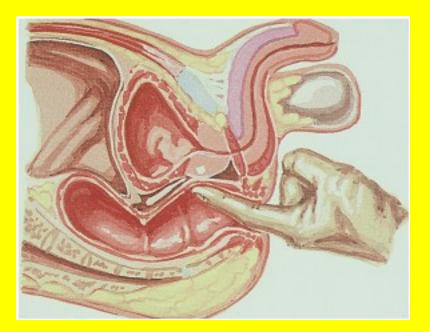
- bladder emptying and need for repeat voiding
- Bladder 'irritability,' as manifested by urinary frequency, nocturia, and urinary urgency

symptoms: -nocturia (need to urinate during night)
 -dysuria (difficulty and/or pain during
 urination)
 -urgency (sudden desire to urinate)
 diagnosis: digital roctal examination





#### Initial Evaluation of Patients Presenting with LUTS/BPH



\*In men with life expectancy of >10 years in whom the diagnosis of prostate cancer can alter management. †Particularly useful in patients with nocturia as the leading symptom.

Chatelain C et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia*. Plymouth, UK: Health Publication Ltd; 2001;522.

#### **Initial Evaluation**

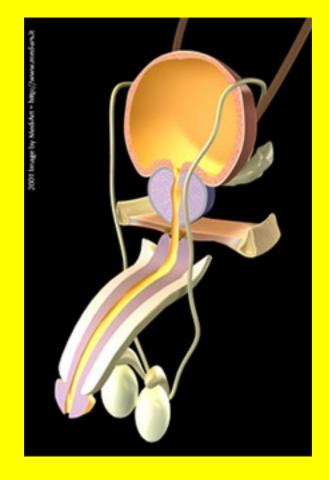
- History
- IPSS and bother question
- PE and DRE
- Urinalysis
- PSA\*
- Voiding diary †

#### LUTS Associated With

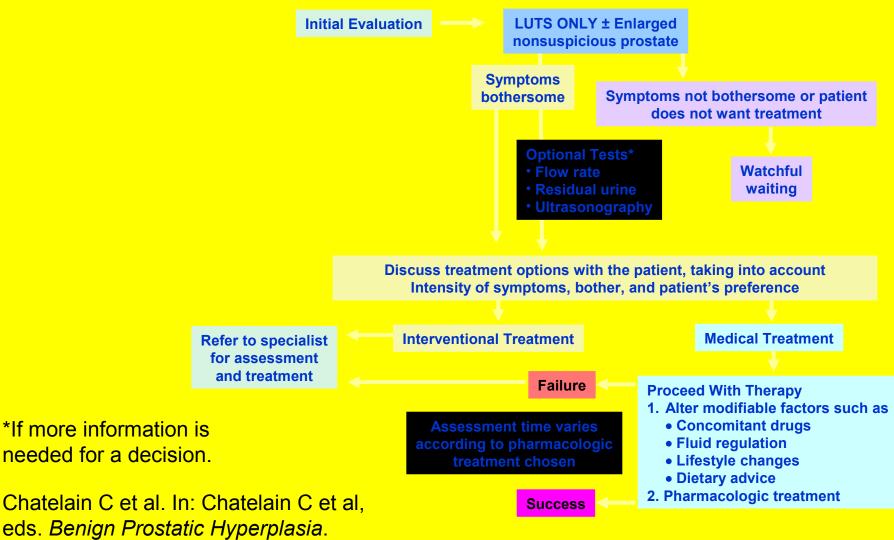
- Suspicious DRE
- Hematuria
- Abnormal PSA
- Pain
- Infection<sup>‡</sup>
- Palpable bladder
- Neurologic disease

#### **BPH: Diagnosis and evaluation**

- Evaluate urinary symptoms using the American Urological Association Symptom Score to assesses severity
- History
- Focused neurovascular exam of the LE and saddle regions
- Digital rectal examination
- Urinalysis: Greater than 4 RBC per high-power filed of uninfected urine requires IV urography and cystoscopy to rule out cancer of the kidney or bladder



#### **Basic Management LUTS**



Plymouth, UK: Health Publication Ltd; 2001;522.

- CLINICAL COURSE & COMPLICATIONS OF BPH
- Symptoms of nodular hyperplasia relate to two secondary effects:
- 1- compression of the urethra with difficulty in urination and
- 2- retention of urine in the bladder with subsequent distention and hypertrophy of the bladder, infection of the urine, and development of cystitis and renal infections.

- **BPH is initially asymptomatic** but with increasing compression of urethra difficulty in urination occurs.
- Patients experience frequency, nocturia, difficulty in starting and stopping the stream of urine, overflow dribbling, and dysuria (painful micturition).
- In many cases, sudden, acute urinary retention appears for unknown reasons, and persists until the patient receives emergency catheterization.
- In addition to these difficulties in urination, prostatic enlargement results in the inability to empty the bladder completely, probably due to the raised level of the urethral floor so that, at the conclusion of micturition, a considerable amount of residual urine is left, which provides a static fluid that is vulnerable to infection.

- On this basis, catheterization or surgical manipulation provides a real danger of the introduction of organisms and the development of pyelonephritis.
- Many secondary changes occur in the bladder, such as hypertrophy, trabeculation. and diverticulum formation.
- Hydronephrosis or acute retention, with secondary urinary tract infection and even azotemia or uremia may develop.

- In addition to these difficulties in urination, prostatic enlargement results in the inability to empty the bladder completely, probably due to the raised level of the urethral floor so that, at the conclusion of micturition, a considerable amount of residual urine is left, which provides a static fluid that is vulnerable to infection.
- On this basis, catheterization or surgical manipulation provides a real danger of the introduction of organisms and the development of pyelonephritis.

#### **Clinical Features & Potential Complications**

• Asymptomatic =>

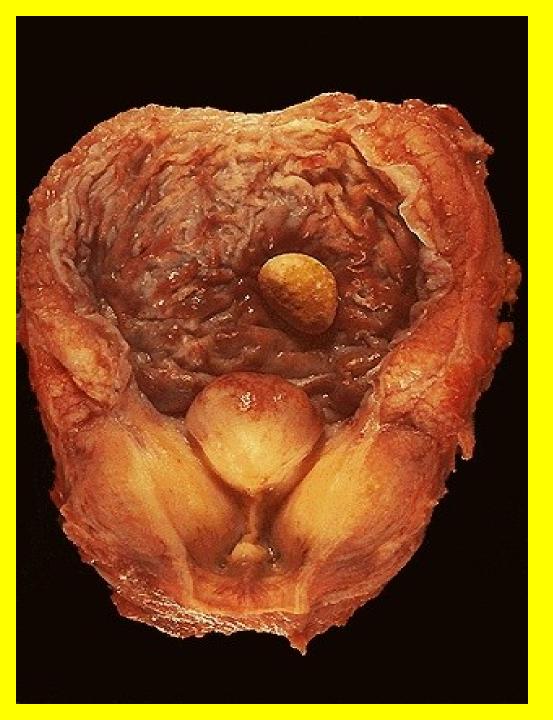
- Compression on Urethra
- Frequency of micturation
- Difficulty in urination
- Nocturia, Dysuria,
- Difficulty in starting & stopping, dribbling

- Urinary retention
- Overflow incontinence and dribbling as a result of retention
- Bladder decompensation--- Distension & Hypertrophy of Bladder, Bladder stones
- Hydroureters and hydronephrosis
- Renal impairment and chronic renal failure
- Superimposed infections (Urinary tract infection, Prostatitis, Cystitis, Urethritis)
- Gross hematuria

Prostate: Nodular Hyperplasia Note: Secondary bladder hypertrophy; nodular prostate; trabeculations of bladder wall

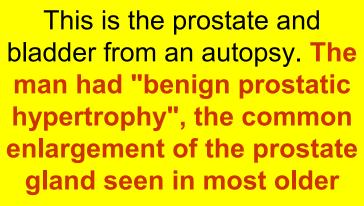






The enlarged prostate gland seen here not only has enlarged lateral lobes, but also a greatly enlarged median lobe that obstructs the prostatic urethra. This led to obstruction with bladder hypertrophy, as evidenced by the prominent trabeculation of the bladder wall seen here from the mucosal surface. **Obstruction with stasis also** led to the formation of the **yellow-brown calculus** (stone). http://www.med.unsw.edu.au/P

athmus/m1147.htm

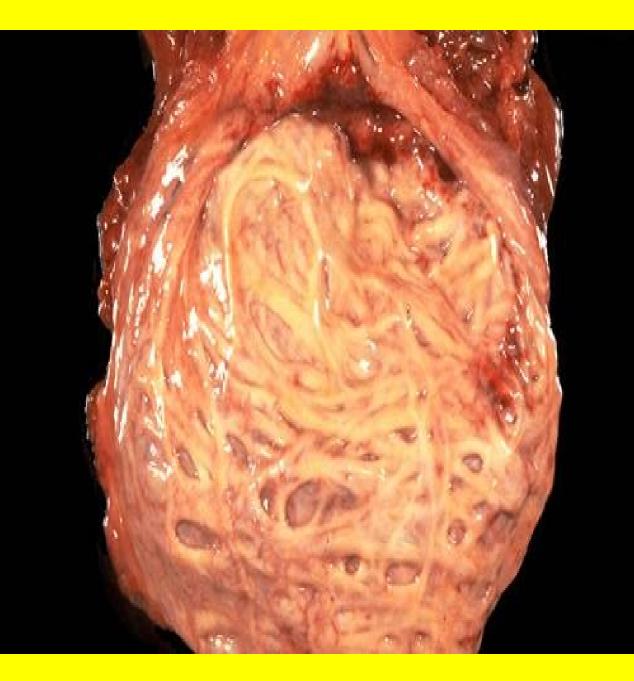


#### men.

The prostate is on the bottom, and the bladder, with its front opened, is on top. You can see the enlarged central lobe of the prostate gland protruding into the bladder cavity. The prostate gland obstructed outflow from the bladder, forcing the bladder wall to become thicker and

stronger.





**Obstruction from** nodular prostatic hyperplasia has led to prominent trabeculation seen on the mucosal surface of this bladder with hypertrophy. The stasis from obstruction predisposes to infection. The obstruction can also lead to bilateral hydroureter and **hydronephrosis** 

 Note that nodular hvperplasia is NOT now considered to be a premalignant condition as was once claimed.

# BPH TREATMENT MEDICAL SURGICAL

- MEDICAL TREATMENT OF BPH
- The goals of pharmacotherapy (medical treatment with drugs) are to reduce morbidity and to prevent complications

- Current Drug Treatments
- A Conventional drug therapies fall into two types of drugs:
- Alpha-blockers, and
- 5 α-reductase inhibitors.

- B Alternative Medicines
- Saw Palmetto berry extracts

- The era of medical therapy for BPH dawned in the mid 1970s with the use of nonselective alpha-blockers such as phenoxybenzamine.
- Alpha-blockers are drugs that were first used to treat high blood pressure.
- But they were pressed into service for the treatment of BPH when they were shown also to relax smooth muscles, including those of the prostate gland.

- Why use Alpha-blockers? Rationale for using USING Alpha-adrenergic blockers (Alpha-blockers)
- Alpha-blockers -- block the effects of postganglionic synapses of smooth muscle and exocrine glands.
- By relaxing the smooth muscles surrounding the prostate, alpha-blockers increase the flow of urine and improve symptoms in patients with BPH.
- Alpha-blockers are also effective in treating the symptoms of BPH in men who don't have significantly enlarged prostates.

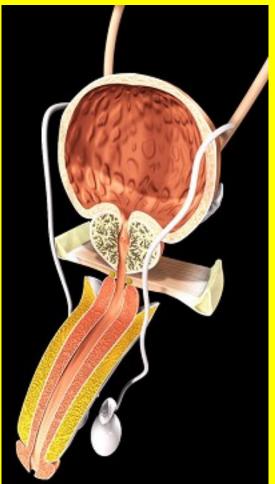
- The medical therapeutic options for BPH have evolved significantly over the last 3 decades, giving rise to the receptor-specific alphablockers that now comprise the first line of therapy.
- So though we still use alpha-blockers, the ones in vogue today act at specific targets in the prostate and NOT on ALL the alpha cells ALL OVER THE BODY!
- So they cause far LESS SIDE EFFECTS!

## α-Blockers: This anatomy relates to Rx

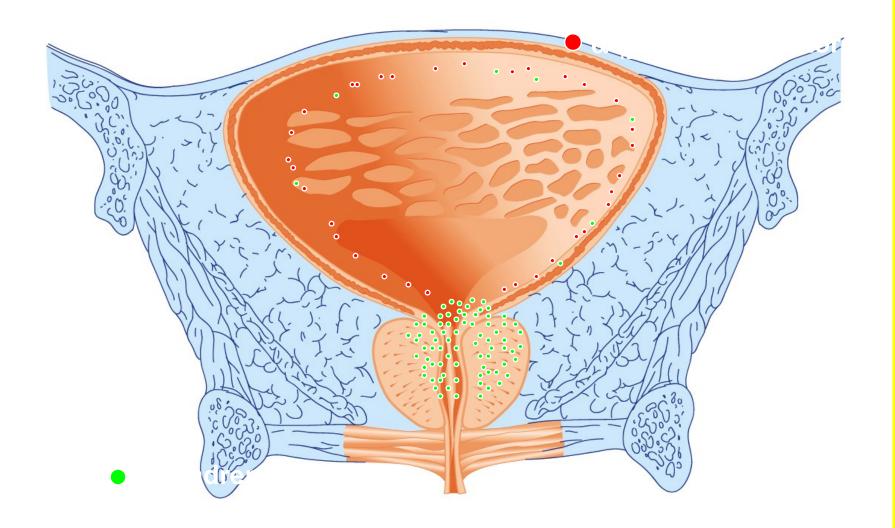
- Prostate smooth muscle tone is mediated via alpha 1 adrenergic receptors
- Increased tone leads to increasing LUTS and reduction in flow rate
- Blockage of the receptor leads to improvement of LUTS and flow rate
- Density of adrenergic receptors changes with prostate size and age
- To this date, three alpha 1 adrenoreceptor subtypes have been identified (a, b, and d)

#### $\alpha_1$ -adrenergic receptors

- Smooth muscle of bladder neck, prostatic capsule, and adenoma have an abundance of α<sub>1</sub>adrenergic receptors
- Stimulation of  $\alpha_1$ -adrenergic receptors on prostate smooth muscle mediates bladder outlet obstruction
- 80% of all receptors in prostate are  $\alpha_{1A}$  subtype

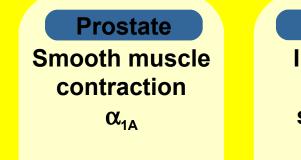


## α-adrenergic receptor distribution in the lower urinary tract



## Localization of $\alpha_1$ -Adrenoreceptors ( $\alpha_1$ -ARs)

 $\alpha_1$ -ARs and Human LUTS



Detrusor Instability; Irritative symptoms  $\alpha_{1D}^{>}$  α1Α Spinal cord Lumbosacral; Control of Urinary function α<sub>1D</sub> VesselsResistancevessels:Younger patients $\alpha_{1A}$ Older patients $\alpha_{1B} > \alpha_{1A}$ 

Jardin A et al. In: Chatelain C et al, eds. *Benign Prostatic Hyperplasia*. Plymouth, UK: Health Publication Ltd; 2001:459-477.

- Rationale for alpha1a-receptor blockade in BPH
- A significant component of the BPH complex and its associated symptoms is believed to be related to the smooth muscle tension in the prostate stroma, urethra, and bladder neck.
- The smooth muscle tension in these areas is mediated by the alpha1-adrenergic receptors; therefore, alpha-adrenergic receptor-blocking agents should theoretically decrease resistance along the bladder neck, prostate, and urethra by relaxing the smooth muscle and allowing passage of urine.
- BPH is predominantly a stromal proliferative process, and a significant component of prostatic enlargement is due to smooth muscle proliferation.
- The stromal-to-epithelial ratio is significantly greater in males with symptomatic BPH relative to those with asymptomatic BPH.

- The 3 subtypes of the alpha-1 receptor are 1a, 1b, and 1c.
- Of these, the alpha-1a receptor is most specifically concentrated in the bladder neck and prostate.
- Since the alpha-1a subtype is predominant in the prostate, bladder neck, and urethra, but not in other tissues, drugs that are selective for this receptor (eg, tamsulosin) may have a potential therapeutic advantage.
- Tamsulosin is thus considered the most pharmacologically uroselective of the commercially available agents because of its highest relative affinity for the alpha1a-receptor subtype.

- The alpha-blocking agents administered in BPH studies can be subgrouped according to receptor subtype selectivity and the duration of serum elimination half-lives.
- Nonselective alpha-blockers include phenoxybenzamine, phentolamine.
- Selective short-acting alpha-1 blockers include prazosin, alfuzosin, and indoramin.
- Selective long-acting alpha-1 blockers include terazosin and doxazosin.
- Partially subtype (alpha-1a)-selective agents include tamsulosin.
- Tamsulosin is considered the most pharmacologically uroselective of the commercially available agents because of its highest relative affinity for the alpha1areceptor subtype.

- Nonselective alpha-blockers
  - Phenoxybenzamine and phentolamine were the first alpha-blockers studied for BPH, but their nonselective nature causes it to antagonize both the alpha1- and alpha2-adrenergic receptors, resulting in a higher incidence of adverse effects.
  - Because of the availability of more alpha1receptor-specific agents, it currently is not often used for the treatment of BPH.
  - Moreover, phenoxybenzamine bonds covalently to receptor sites, and so their prolonged duration of action, also prolongs their disgusting adverse effects which drastically decrease patient's compliance with this drug.

BOTH the short-acting and long-acting alpha-1 blockers are employed today for both hypertension and BPH.

These drugs are listed in the next slide.

- Examples of alpha-blockers in current use
- Drug
- Alfuzosin
- Doxazosin
- Indoramin
- Prazosin
- Terazosin

**Brand Name** Xatral SR & Xatral XL Cardura Doralese Hypovase Hytrin BPH

- Tamsulosin
   Flomax MR
- NOTE THAT Tamsulosin (Flomax MR) is the alpha-blocker drug of choice for the medical therapy of BPH, because tamsulosin is a selective alpha-blocker at alpha1areceptors.

- Advantages of alpha-blockers in Rx of BPH
- Improve urinary flow
- Quick to work
- No adverse effect upon sexual drive

- Disadvantages of alpha-blockers in Rx of BPH
- Short acting
- Usually only delays the need for surgery, no evidence for preventing the progression of BPH
- Only effective on moderately enlarged prostates
- Lowers concomitant blood pressure ...... BUT
- Can cause fatigue, nasal congestion, headache
- Can decrease ejaculate

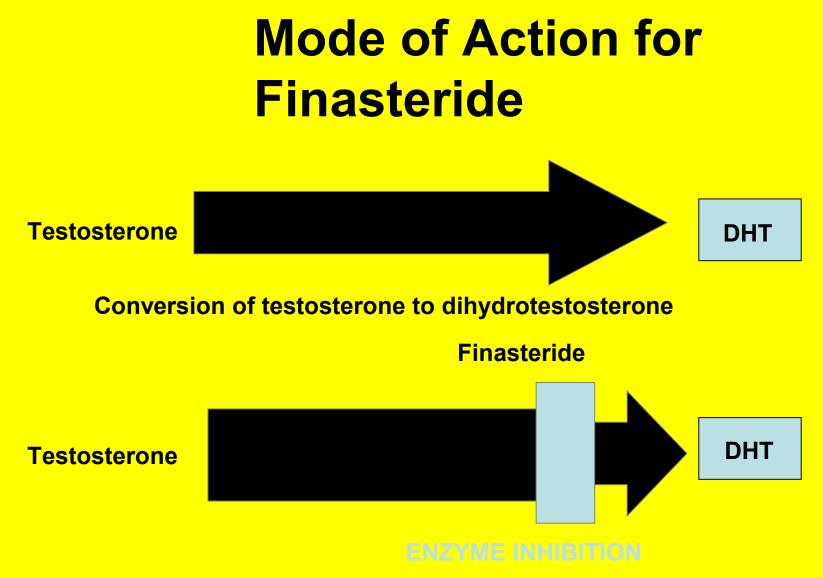
- Can you answer these two questions?
- Do you see the KEY words in these two questions?

- Which of the following drugs <u>can be used</u> for the treatment of benign prostatic hypertrophy?
- a) phenoxybenzamine
- b) phentotamine
- c) prazosin
- d) terazosin and doxazosin.
- e) tamsulosin.
- f) all of the above

- Which of the following drugs is the best choice for the treatment of benign prostatic hypertrophy?
- a) phenoxybenzamine
- b) phentotamine
- c) prazosin
- d) terazosin and doxazosin.
- e) tamsulosin.
- f) all of the above

## **5 α-reductase inhibitors.**

- Why use 5 α-reductase inhibitors.
- Because prostatic hyperplasia is now considered to be related to the action of androgens, especially dihydro-testosterone (DHT), a metabolite of testosterone, and the ultimate mediator of prostatic growth.
- DHT is synthesized mainly in the stromal cells of the prostate from circulating testosterone by the action of the enzyme 5 alpha reductase type 2, which is principally localized in the stromal cells- the main site for the synthesis of DHT.



finasteride reduces the amount of testosterone converted to dihydrotestosterone

**Diagrammatic Representation** 

- Hormonally inspired medical management emerged from the discovery of a congenital form of pseudohermaphroditism secondary to DHT deficiency (due to a lack of 5-alpha reductase activity).
- This deficiency produced a hypoplastic prostate.
- Type II 5-alpha reductase is an enzyme responsible for the conversion of testosterone to DHT.
- DHT promotes growth of prostatic tissue.
- The 5-alpha reductase inhibitors block the conversion of testosterone to DHT, causing lower intraprostatic levels of DHT.
- This leads to inhibition of prostatic growth, apoptosis, and involution.

- The 5alpha-reductase inhibitors
  - The inhibition of 5-alpha reductase selectively blocks androgen action in tissues whose function is dependent on continuing production of DHT, including prostate and hair follicles.
  - Finasteride, has demonstrated type II 5alpha-reductase blocking activity resulting in the inhibition of DHT-receptor complex formation. This effect causes a profound decrease in the concentration of DHT in plasma, which, in turn, results in a consistent decrease in prostate size. A third of men treated with this agent exhibit improvements in urine flow and symptomatology.
  - A newer agent recently introduced, dutasteride, has affinity for both type I and type II 5alpha-reductase receptors.
  - Both agents actively reduce serum DHT levels by more than 80%, improve symptoms, reduce the incidence of urinary retention, and decrease the likelihood of surgery for BPH. These agents may not work in all men and may take several months before activity is noted. However, for those in whom they are effective, the impact may be profound.
- The goals of pharmacotherapy are to reduce morbidity and to prevent complications.

- 5 Alpha-reductase inhibitors [e.g Finasteride (Proscar)]
- 5 α-reductase inhibitors like finasteride selectively block androgen action in tissues whose function is dependent on continuing production of DHT, resulting in the inhibition of DHT II receptor complex formation.
- They block the conversion of testosterone to DHT within the prostate cells (and hair follicles). This causes a profound decrease in the concentration of DHT in plasma. As DHT levels drop, this in turn results in a consistent decrease in prostate size by 20%

 5 α-reductase inhibitors are more effective in men with larger prostate glands than alpha-blockers and have been found to reduce prostate volume by 20% resulting in an improvement in symptoms.

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   However, for those in whom they are effective, the impact may be profound.

- Finasteride (Proscar) is a steroid- like inhibitor of the enzyme 5 alpha reductase. It is orally active and inhibits conversion of testosterone to DHT, causing serum DHT levels to decrease within 8 hours after administration. This effect lasts for about 24 hours. The half-life is about 8 hours (longer in elderly individuals). Forty to 50 percent of the dose is metabolized; more than half is excreted in the feces.
- Finasteride has been reported to be moderately effective in reducing prostate size in men with benign prostatic hyperplasia, being most beneficial in men with prostates >40 g
- It improves symptoms and reduces prostatic size by 20-30%. Reduction in prostate size sustained 5 y following treatment.
- Improves urinary flow rate by 2 mL/s.
- The dosage is 5 mg/d.

- A minimum of 6 mo treatment necessary to determine response.
- Documented hypersensitivity; lactation, children
- Caution in liver function abnormalities; monitor patients with severely diminished urinary flow for obstructive uropathy (may not be candidates for this therapy); generally well tolerated with few adverse effects; rare headache, loss of libido, and impotence may occur; lowers serum PSA level by 50% after 6 mo of therapy
- Its use in advanced prostatic carcinoma is under study. The drug is not approved for use in women or children, though it has been used successfully in the treatment of hirsutism in women and early male pattern baldness in men (1 mgld).

## Advantages of Finasteride in the treatment of BPH

- More effective on larger prostates
- Longer acting
- Less side effects than alpha blockers
- Can reverse male pattern balding

- Disadvantages of Finasteride in the treatment of BPH
- Not effective on slight and moderately enlarged prostates
- Slow to act can take up to six months to work
- Can affect sexual function
- Can cause breast swelling
- Can be transmitted in semen and cause birth defects, users should have protected sex

- Dutasteride (Avodart) is another newer 5alphareductase inhibitor used to treat symptomatic BPH in men with an enlarged prostate. Improves symptoms, reduces urinary retention, and may decrease need for BPH-related surgery.
- Inhibits 5alpha-reductase isoenzymes types I and II. Suppresses >95% conversion of testosterone to DHT, causing serum DHT levels to decrease.
- Dose 0.5 mg PO qd
- Adverse effects
- Documented hypersensitivity; pregnancy or lactation; women or children
- CYP450 3A4 substrate; data limited, caution with potent CYP450 3A4 inhibitors (eg, ketoconazole, ritonavir, erythromycin) or inducers (eg, rifampin, phenytoin)