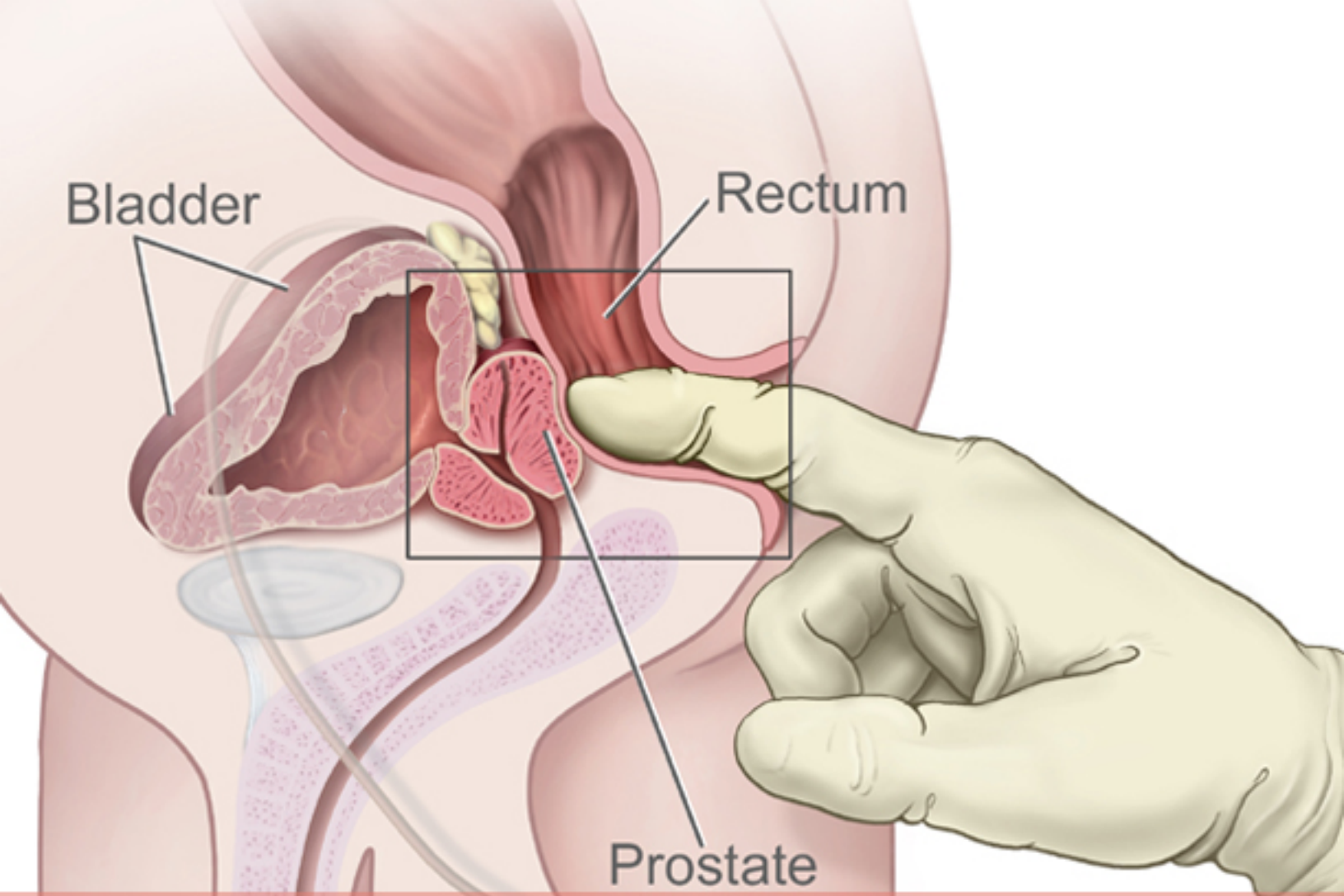

Prostate

(Exocrine gland of the male reproductive system)

Lorina Goforth

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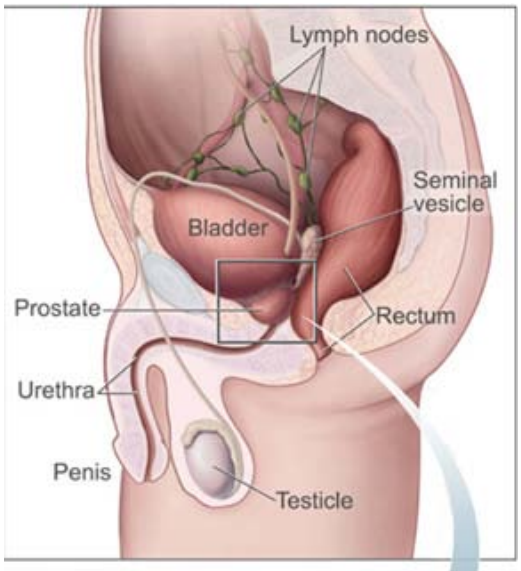
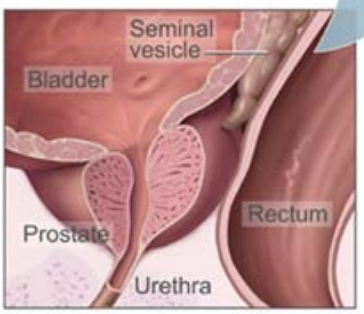
Prostate

Prostate

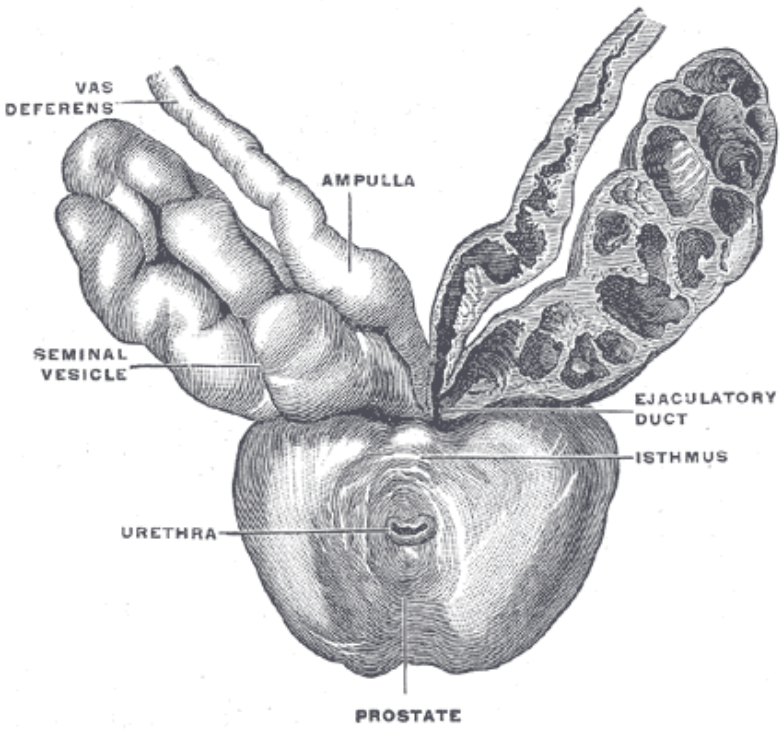


This shows the prostate and nearby organs.



This shows the inside of the prostate, urethra, rectum, and bladder.

Male Anatomy



Prostate with seminal vesicles and seminal ducts, viewed from in front and above.

Latin *prostata*

Artery	internal pudendal artery, inferior vesical artery, and middle rectal artery
Vein	prostatic venous plexus, pudendal plexus, vesicle plexus, internal iliac vein
Nerve	inferior hypogastric plexus
Lymph	external iliac lymph nodes, internal iliac lymph nodes, sacral lymph nodes
Precursor	Endodermic evaginations of the urethra

MeSH *Prostate*

Dorlands/Elsevier *Prostate*

The **prostate** (from Greek *προστάτης* - *prostates*, literally "one who stands before", "protector", "guardian") is a compound tubuloalveolar exocrine gland of the male reproductive system in most mammals.

In 2002, female paraurethral glands, or Skene's glands, were officially renamed the female prostate by the Federative International Committee on Anatomical Terminology.

The prostate differs considerably among species anatomically, chemically, and physiologically.

Function

The function of the prostate is to store and secrete a slightly alkaline fluid, milky or white in appearance, that usually constitutes 20-30% of the volume of the semen along with spermatozoa and seminal vesicle fluid. The alkalinity of semen helps neutralize the acidity of the vaginal tract, prolonging the lifespan of sperm. The alkalinization of semen is primarily accomplished through secretion from the seminal vesicles. The prostatic fluid is expelled in the first ejaculate fractions, together with most of the spermatozoa. In comparison with the few spermatozoa expelled together with mainly seminal vesicular fluid, those expelled in prostatic fluid have better motility, longer survival and better protection of the genetic material (DNA).

The prostate also contains some smooth muscles that help expel semen during ejaculation.

Secretions

Prostatic secretions vary among species. They are generally composed of simple sugars and are often slightly alkaline.

In human prostatic secretions, the protein content is less than 1% and includes proteolytic enzymes, prostatic acid phosphatase, and prostate-specific antigen. The secretions also contain zinc with a concentration 500-1,000 times the concentration in blood.

Regulation

To work properly, the prostate needs male hormones (androgens), which are responsible for male sex characteristics.

The main male hormone is testosterone, which is produced mainly by the testicles. Some male hormones are produced in small amounts by the adrenal glands. However, it is dihydrotestosterone that regulates the prostate.

Development

The prostatic part of the urethra develops from the *pelvic* (middle) part of the urogenital sinus (endodermal origin). Endodermal outgrowths arise from the prostatic part of the urethra and grow into the surrounding mesenchyme. The glandular epithelium of the prostate differentiates from these endodermal cells, and the associated mesenchyme differentiates into the dense stroma and the smooth muscle of the prostate. The prostate

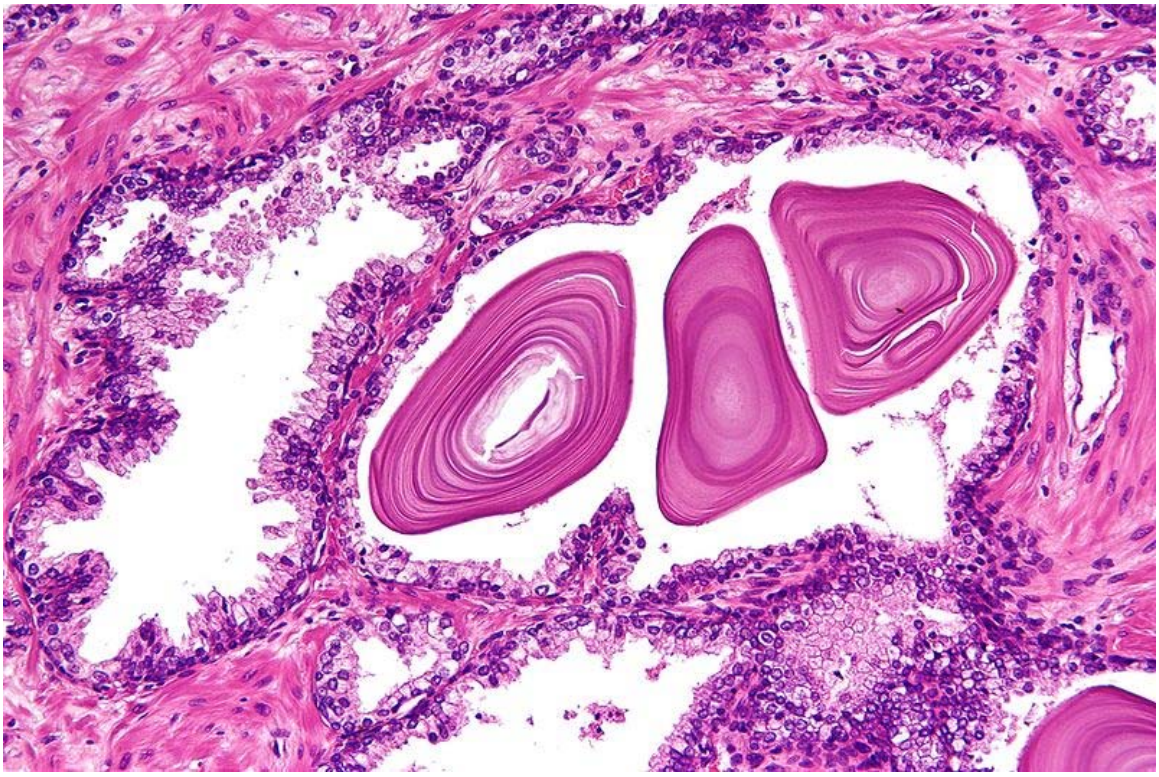
glands represent the modified wall of the proximal portion of the male urethra and arises by the 9th week of embryonic life in the development of the reproductive system. Condensation of mesenchyme, urethra and Wolffian ducts gives rise to the adult prostate gland, a composite organ made up of several glandular and non-glandular components tightly fused within a common capsule.

Female prostate gland

The Skene's gland, also known as the paraurethral gland, found in females, is homologous to the prostate gland in males. However, evolutionarily, the uterus is in the same position as the prostate gland. In 2002 the Skene's gland was officially renamed the prostate by the *Federative International Committee on Anatomical Terminology*.

The female prostate, like the male prostate, secretes PSA and levels of this antigen rise in the presence of carcinoma of the gland. The gland also expels fluid, like the male prostate, during orgasm.

Structure



Micrograph of benign prostatic glands with corpora amylacea. H&E stain.

Urinary bladder (black butterfly-like shape) and hyperplastic prostate (BPH) visualized by Medical ultrasonography technique

A healthy human prostate is classically said to be slightly larger than a walnut. In actuality, it is approximately the size of a kiwifruit. The mean weight of the "normal" prostate in adult males is about 11 grams, usually ranging between 7 and 16 grams. It surrounds the urethra just below the urinary bladder and can be felt during a rectal exam. It is the only exocrine organ located in the midline in humans and similar animals.

The ducts are lined with transitional epithelium.

Within the prostate, the urethra coming from the bladder is called the prostatic urethra and merges with the two ejaculatory ducts. The prostate is sheathed in the muscles of the pelvic floor, which contract during the ejaculatory process.

The prostate can be divided in two ways: by zone, or by lobe.

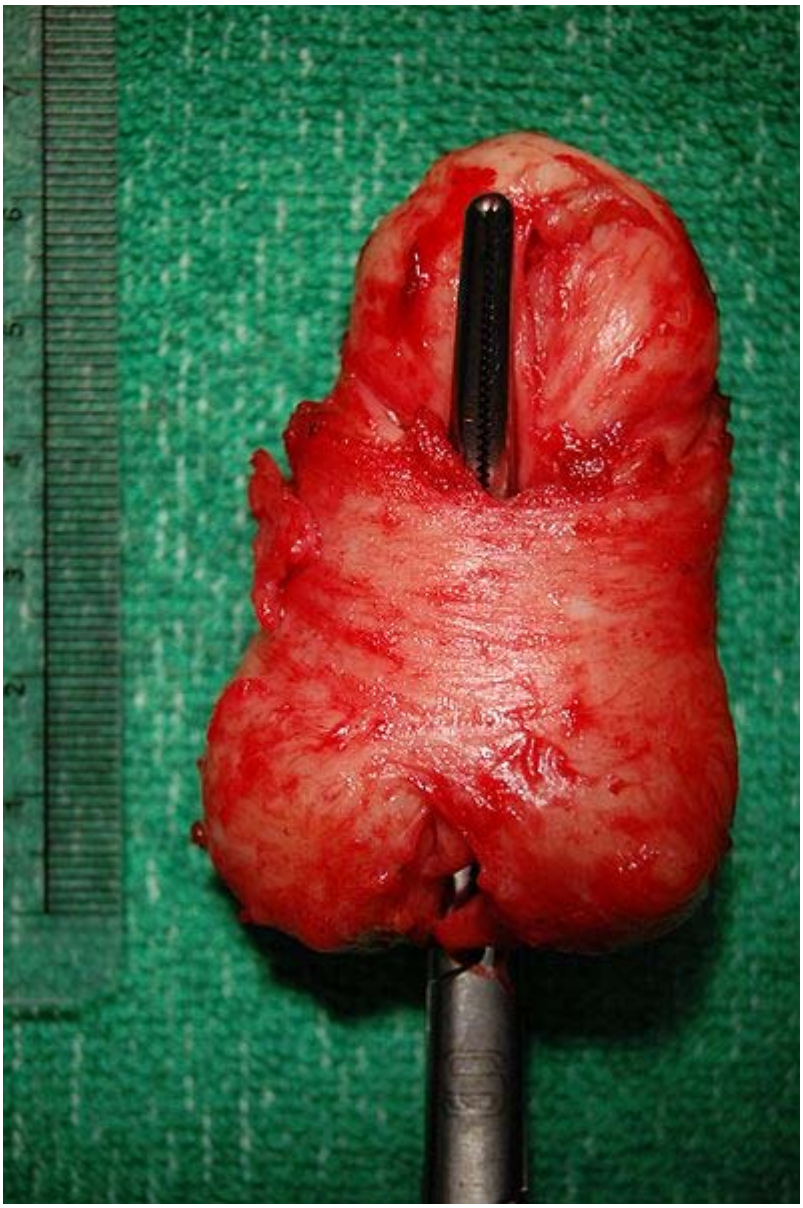
Zones

The "zone" classification is more often used in pathology. The idea of "zones" was first proposed by McNeal in 1968. McNeal found that the relatively homogeneous cut surface of an adult prostate in no way resembled "lobes" and thus led to the description of "zones."

The prostate gland has four distinct glandular regions, two of which arise from different segments of the prostatic urethra:

Name	Fraction of gland	Description
Peripheral zone (PZ)	Up to 70% in young men	The sub-capsular portion of the posterior aspect of the prostate gland that surrounds the distal urethra. It is from this portion of the gland that ~70-80% of prostatic cancers originate.
Central zone (CZ)	Approximately 25% normally	This zone surrounds the ejaculatory ducts. The central zone accounts for roughly 2.5% of prostate cancers although these cancers tend to be more aggressive and more likely to invade the seminal vesicles.
Transition zone (TZ)	5% at puberty	~10-20% of prostate cancers originate in this zone. The transition zone surrounds the proximal urethra and is the region of the prostate gland that grows throughout life and is responsible for the disease of benign prostatic enlargement. (2)
Anterior fibro-muscular zone (or stroma)	Approximately 5%	This zone is usually devoid of glandular components, and composed only, as its name suggests, of muscle and fibrous tissue.

Lobes



Prostate with a large median lobe bulging upwards. A metal instrument is placed in the urethra which passes through the prostate. This specimen was almost 7 centimeters long with a volume of about 60 cubic centimetres on transrectal ultrasound and was removed during a Hryntschak procedure or transvesical prostatectomy (removal of the prostate through the bladder) for benign prostatic hyperplasia.

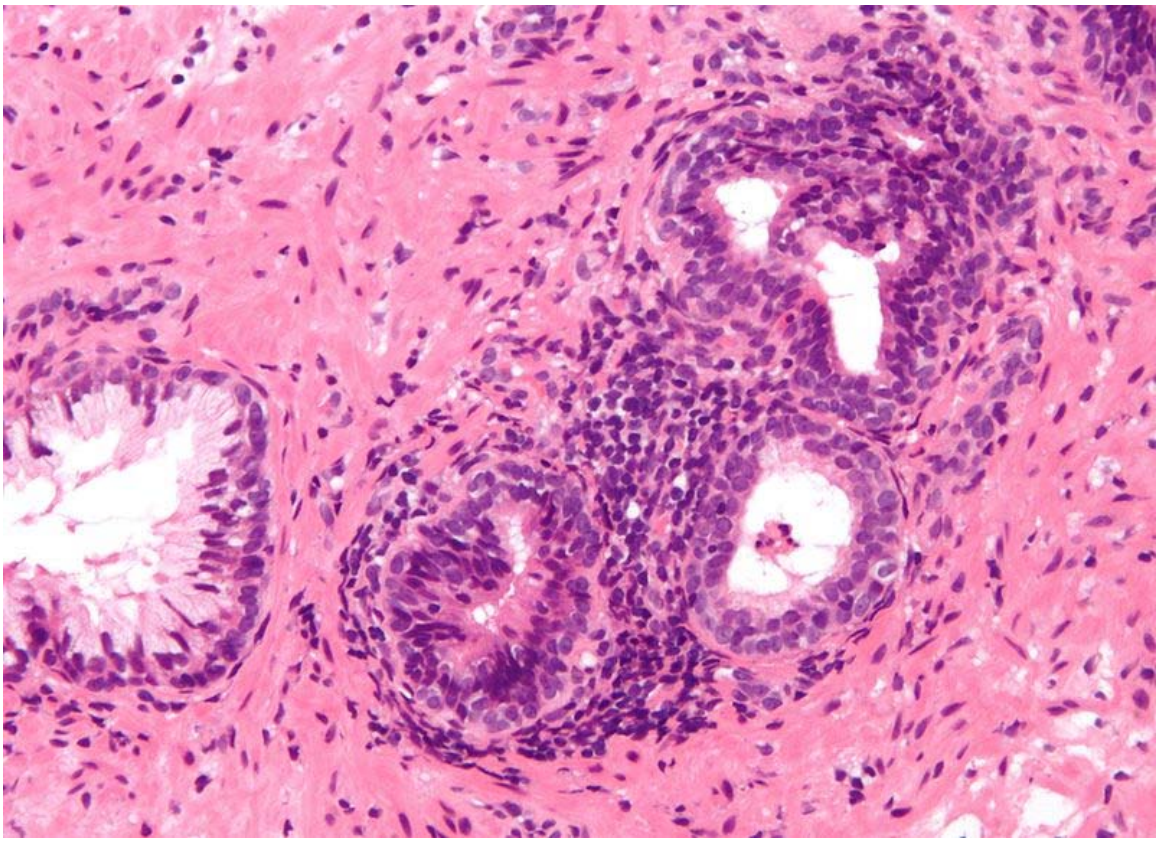
The "lobe" classification is more often used in anatomy.

Anterior lobe (or isthmus)	roughly corresponds to part of transitional zone
Posterior lobe	roughly corresponds to peripheral zone
Lateral lobes	spans all zones

Median lobe (or middle lobe) roughly corresponds to part of central zone

Prostate disorders

Prostatitis



Micrograph showing an inflamed prostate gland, the histologic correlate of **prostatitis**. A normal non-inflamed prostatic gland is seen on the left of the image. H&E stain.

Prostatitis is inflammation of the prostate gland. There are primarily four different forms of prostatitis, each with different causes and outcomes. Two relatively uncommon forms, acute prostatitis and chronic bacterial prostatitis, are treated with antibiotics (category I and II, respectively). Chronic non-bacterial prostatitis or male chronic pelvic pain syndrome (category III), which comprises about 95% of prostatitis diagnoses, is treated by a large variety of modalities including alpha blockers, phytotherapy, physical therapy, psychotherapy, antihistamines, anxiolytics, nerve modulators, surgery, and more. More recently, a combination of trigger point and psychological therapy has proved effective for category III prostatitis as well. Category IV prostatitis, relatively uncommon in the general population, is a type of leukocytosis.

Benign prostatic hyperplasia

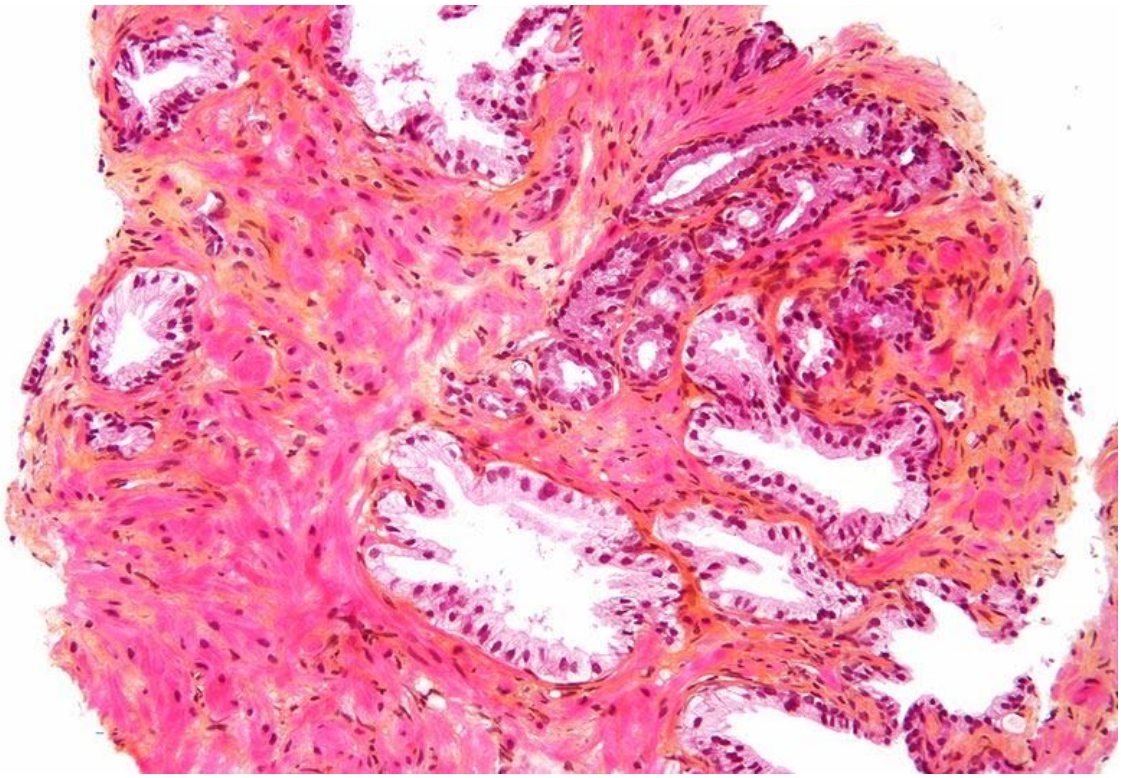
Benign prostatic hyperplasia (BPH) occurs in older men; the prostate often enlarges to the point where urination becomes difficult. Symptoms include needing to urinate often (frequency) or taking a while to get started (hesitancy). If the prostate grows too large, it may constrict the urethra and impede the flow of urine, making urination difficult and painful and, in extreme cases, completely impossible.

BPH can be treated with medication, a minimally invasive procedure or, in extreme cases, surgery that removes the prostate. Minimally invasive procedures include Transurethral needle ablation of the prostate (TUNA) and Transurethral microwave thermotherapy (TUMT). These outpatient procedures may be followed by the insertion of a temporary Prostatic stent, to allow normal voluntary urination, without exacerbating irritative symptoms.

The surgery most often used in such cases is called transurethral resection of the prostate (TURP or TUR). In TURP, an instrument is inserted through the urethra to remove prostate tissue that is pressing against the upper part of the urethra and restricting the flow of urine. TURP results in the removal of mostly transitional zone tissue in a patient with BPH. Older men often have *corpora amylacea* (amyloid), dense accumulations of calcified proteinaceous material, in the ducts of their prostates. The corpora amylacea may obstruct the lumens of the prostatic ducts, and may underlie some cases of BPH.

Urinary frequency due to bladder spasm, common in older men, may be confused with prostatic hyperplasia. Statistical observations suggest that a diet low in fat and red meat and high in protein and vegetables, as well as regular alcohol consumption, could protect against BPH.

Prostate cancer



Micrograph showing normal prostatic glands and glands of prostate cancer (prostate adenocarcinoma) - right upper aspect of image. HPS stain. Prostate biopsy.

Prostate cancer is one of the most common cancers affecting older men in developed countries and a significant cause of death for elderly men (estimated by some specialists at 3%). Regular rectal exams, as well as measurement of Prostate Specific Antigen are recommended for men, usually ages 40 and up to detect prostate cancer early.

Male sexual response

During male orgasm, sperm is transmitted from the ductus deferens into the male urethra via the ejaculatory ducts, which lie within the prostate gland.

It is possible for men to achieve orgasm solely through stimulation of the prostate gland, such as prostate massage or receptive anal intercourse.

Vasectomy and risk of prostate cancer

In 1993, the Journal of the American Medical Association revealed a connection between vasectomy and an increased risk of prostate cancer. Reported studies of 48,000 and 29,000 men who had vasectomies showed 66 percent and 56 percent higher rates of prostate cancer, respectively. The risk increased with age and the number of years since the vasectomy was performed.

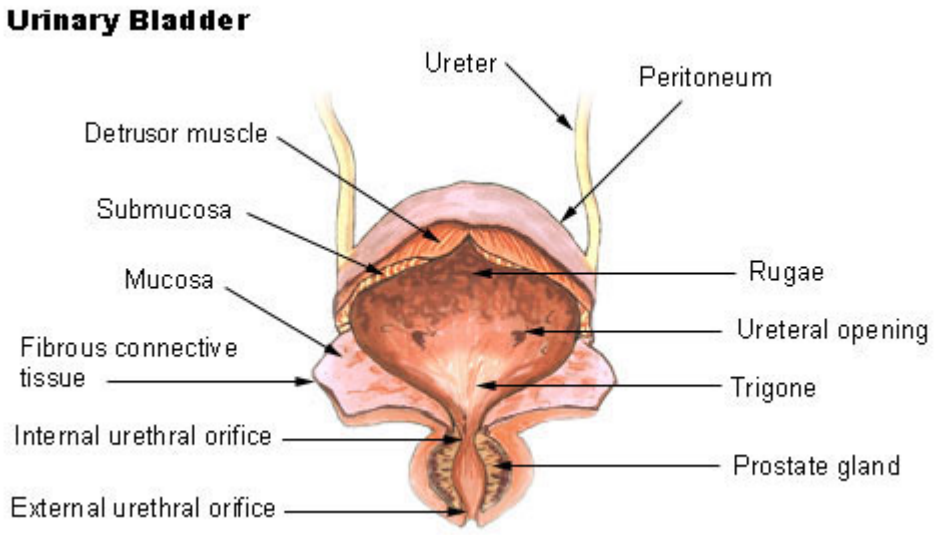
However, in March of the same year, the National Institute of Child Health and Human Development held a conference cosponsored by the National Cancer Institute and others to review the available data and information on the link between prostate cancer and vasectomies. It was determined that an association between the two was very weak at best, and even if having a vasectomy increased one's risk, the risk was relatively small.

In 1997, the NCI held a conference with the prostate cancer Progressive Review Group (a committee of scientists, medical personnel, and others). Their final report, published in 1998 stated that evidence that vasectomies help to develop prostate cancer was weak at best.

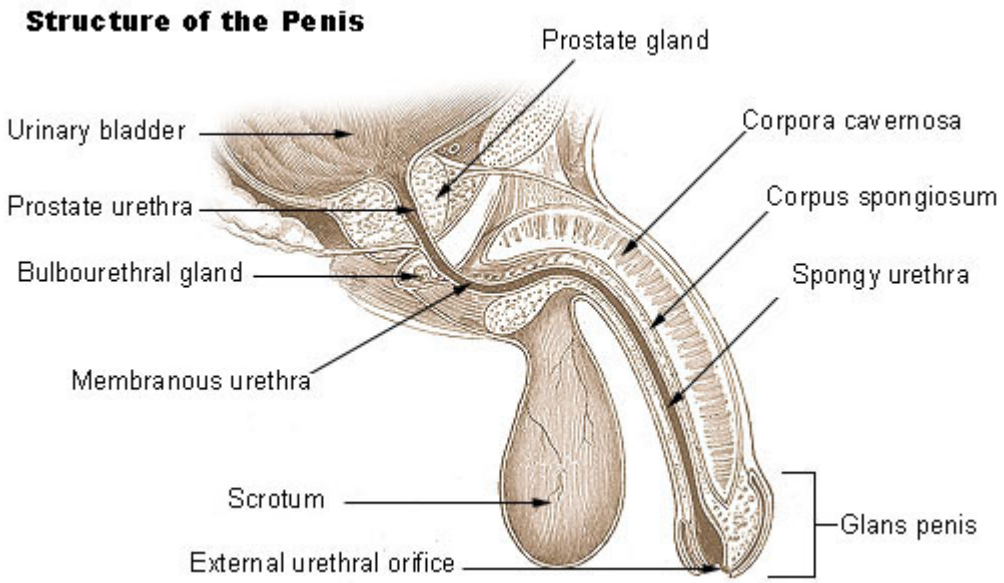
Stenting the prostate

Recent scientific breakthroughs have now meant using a Prostatic stent is a viable method of dis-obstructing the prostate. Stents are devices inserted into the urethra to widen it and keep it open. Stents can be temporary or permanent, and insertion is mostly done on an outpatient basis under local or spinal anesthesia and usually takes about 30 minutes.

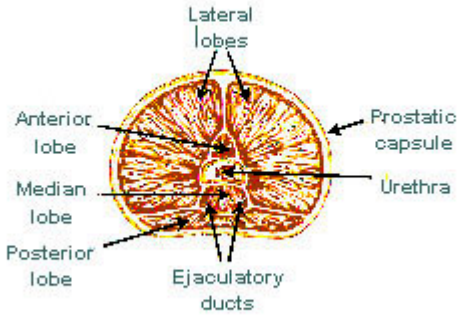
Additional images



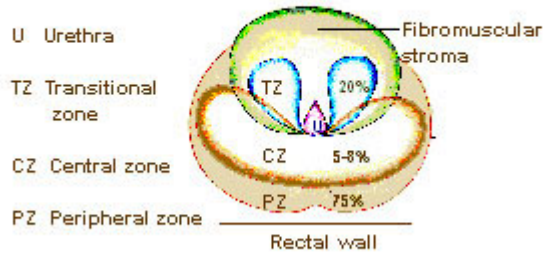
Urinary bladder



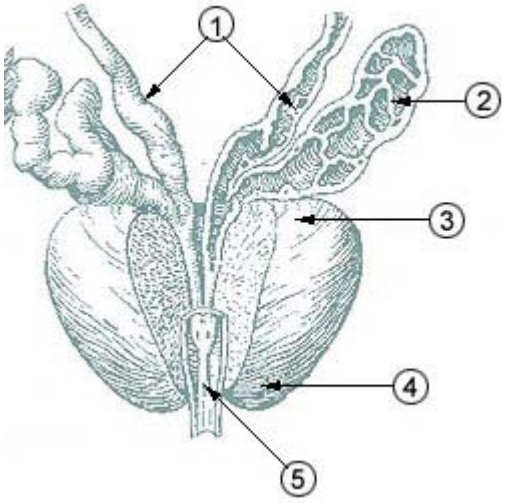
Structure of the penis



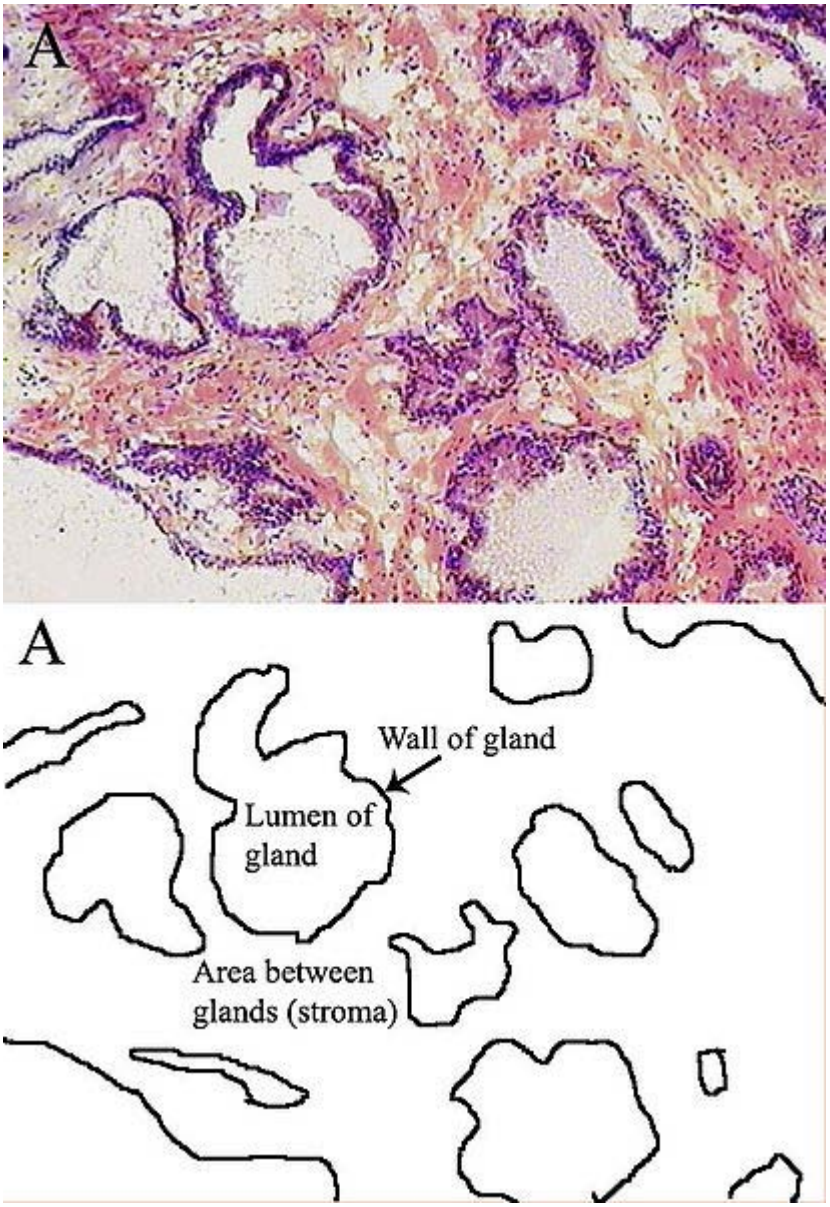
Lobes of prostate



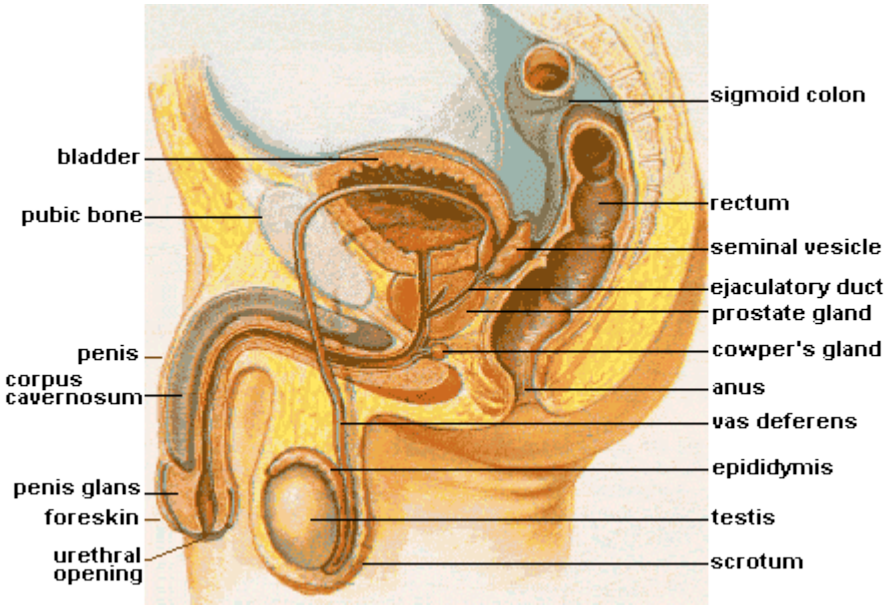
Zones of prostate



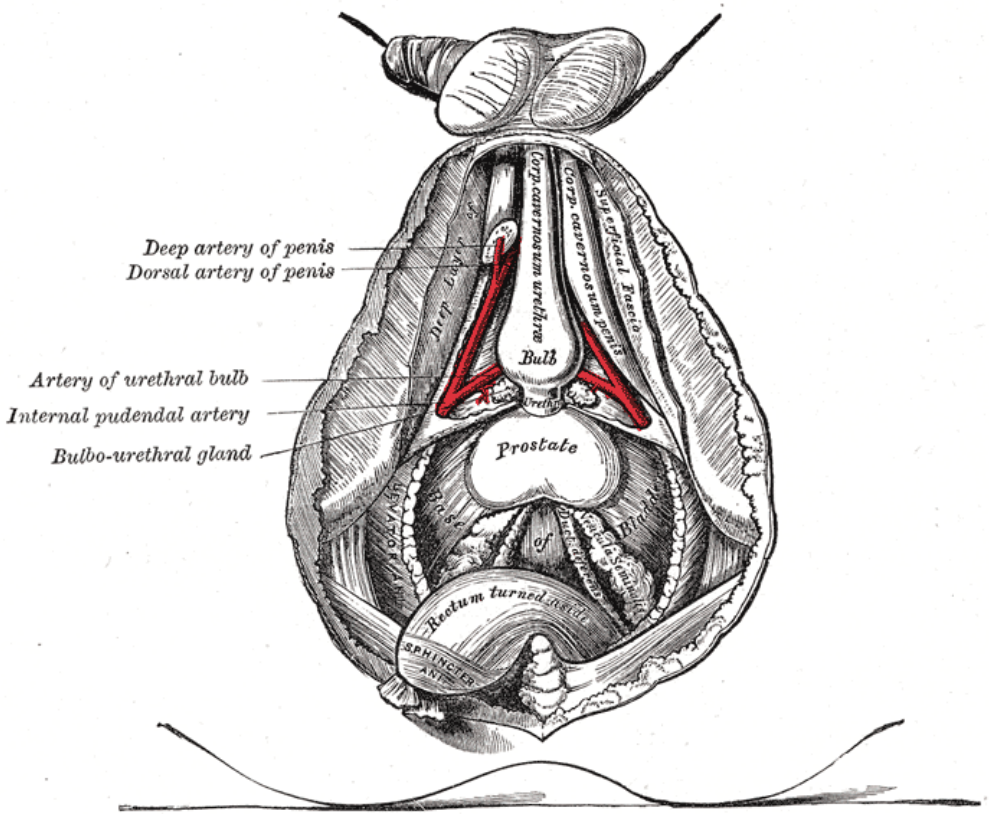
Prostate



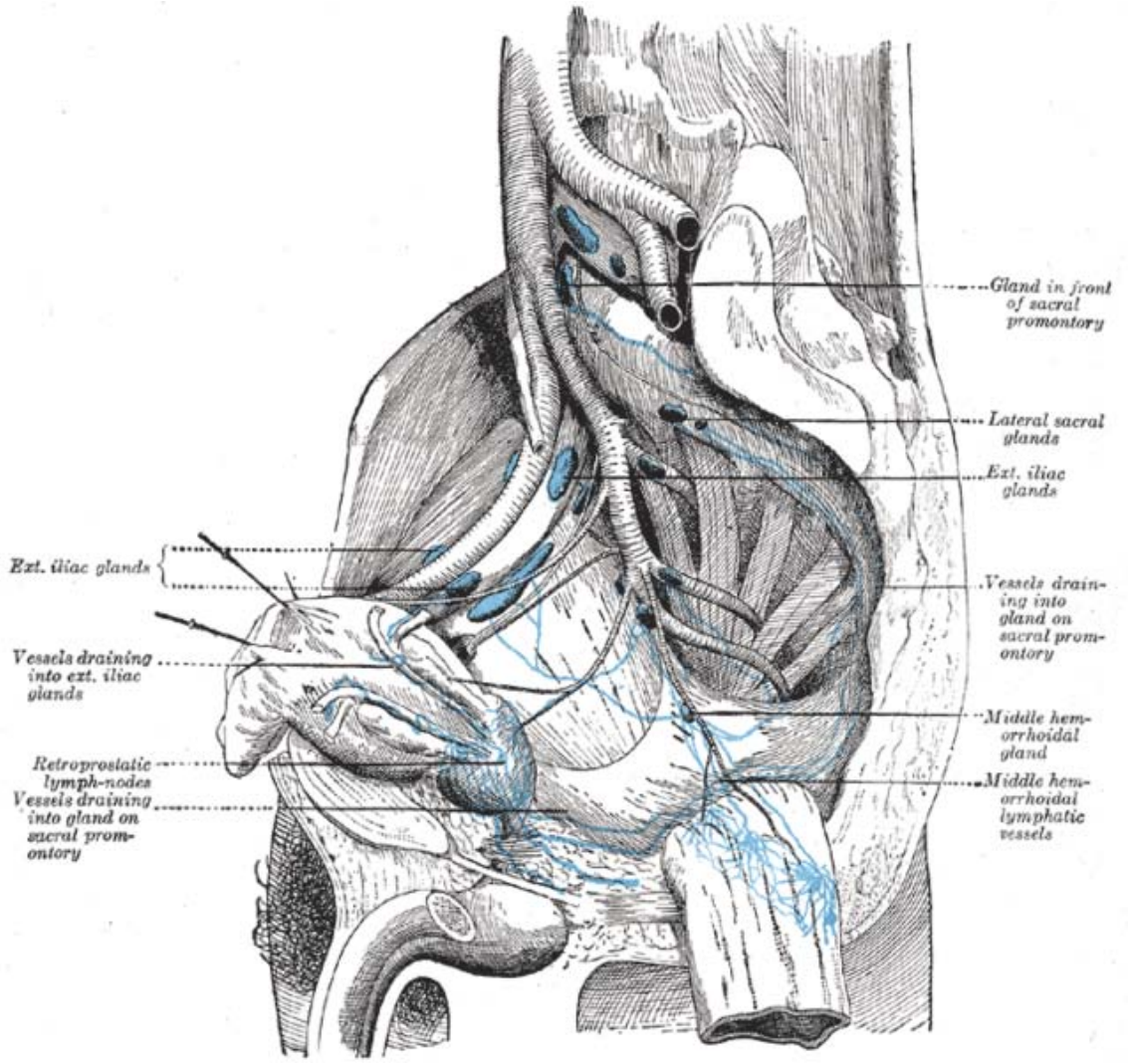
Microscopic glands of the prostate



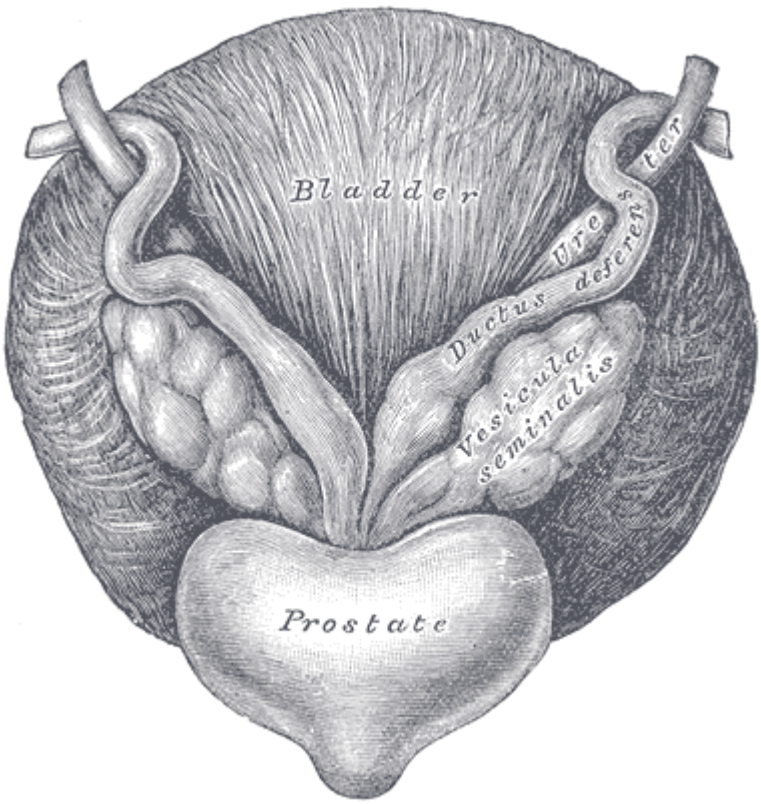
Male Anatomy



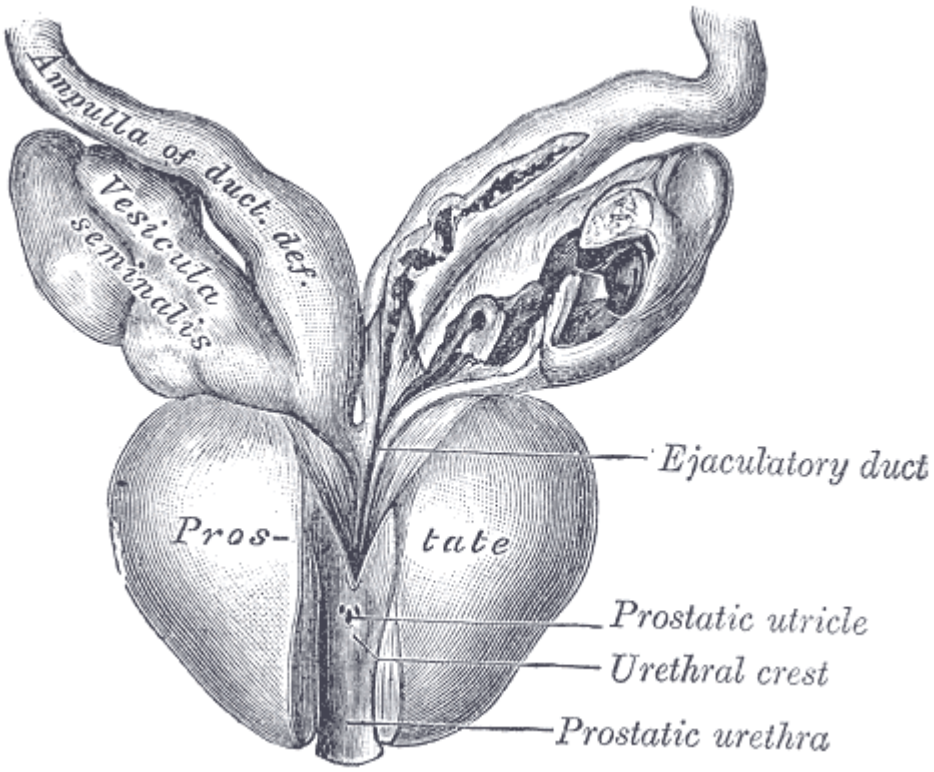
The deeper branches of the internal pudendal artery.



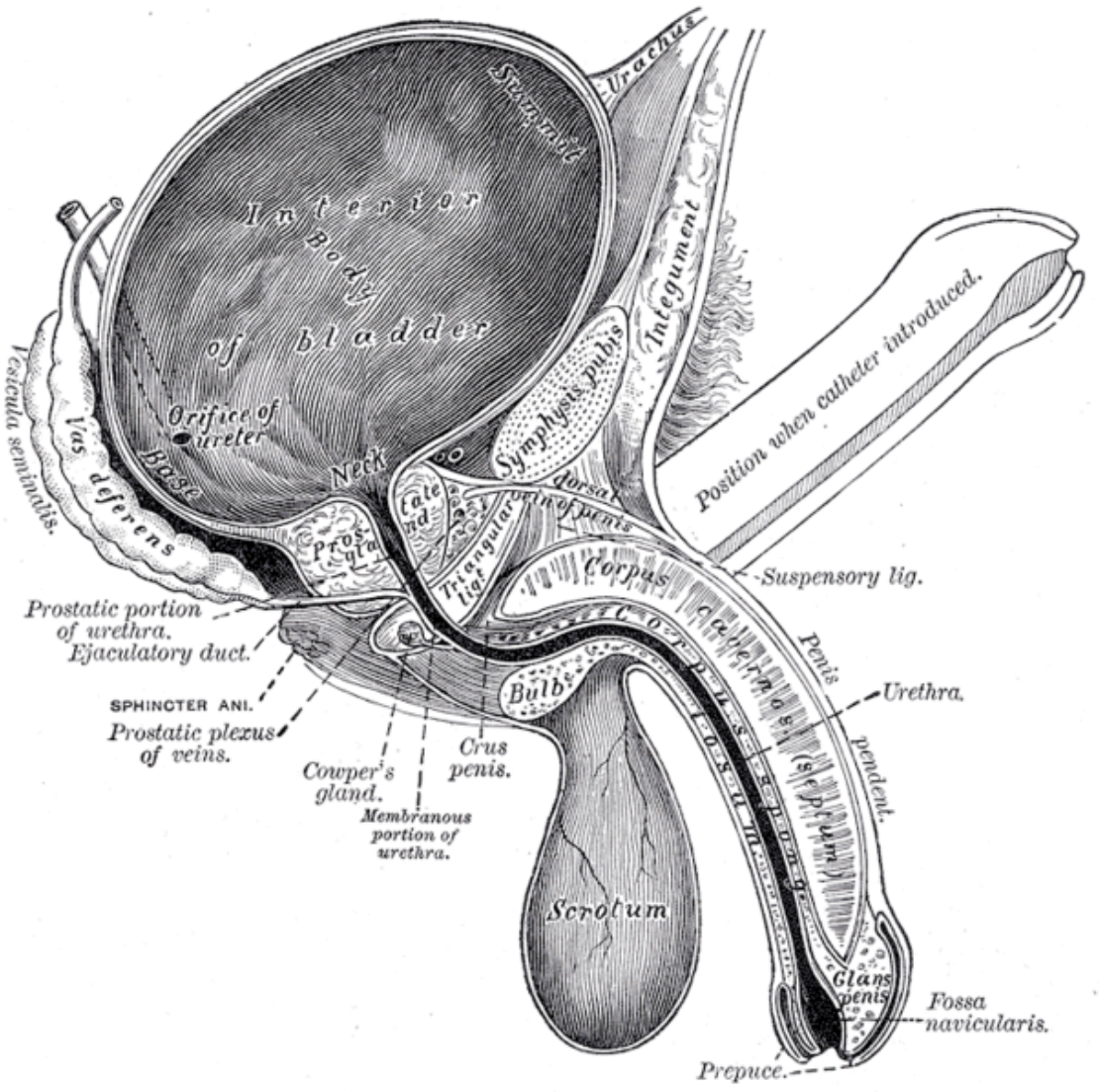
Lymphatics of the prostate.



Fundus of the bladder with the vesiculæ seminales.



Vesiculae seminales and ampullae of ductus deferentes, front view.

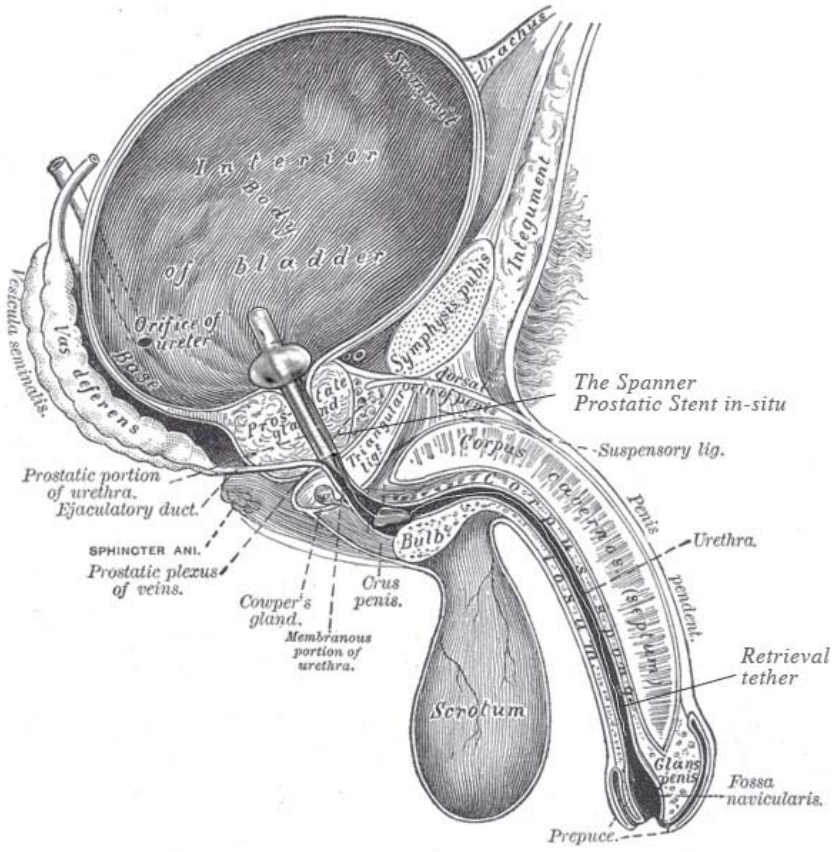


Vertical section of bladder, penis, and urethra.

Chapter 2

Prostatic Stent

Prostatic stent for treatment of BPH



Prostatic stent use in the treatment of BPH

ICD-10	N40.
ICD-9	600

DiseasesDB	10797
eMedicine	med/1919
MeSH	D

A **prostatic stent** is a stent used to keep open the male urethra and allow the passing of urine in cases of prostatic obstruction and lower urinary tract symptoms (LUTS). Prostatic obstruction is a common condition with a variety of etiologies. Benign prostatic hyperplasia (BPH) is the most common cause, but obstruction may also occur acutely after treatment for BPH such as Transurethral needle ablation of the prostate (TUNA), Transurethral resection of the prostate (TURP), transurethral microwave thermotherapy (TUMT), prostate cancer or after radiation therapy.

Classification

There are two types of prostatic stent: temporary and permanent.

Although a permanent prostatic stent is not a medical treatment, it falls under the classification of a surgical procedure. Placement of a permanent prostatic stent is carried out as an outpatient treatment under local, topical or spinal anesthesia and usually takes about 15–30 minutes.

A temporary prostatic stent can be inserted in a similar manner to a Foley catheter, requiring only topical anesthesia.

Food and drug administration approved stents

At the present time, there is one temporary prostatic stent that has received U.S. Food and Drug Administration (FDA) approval. The Spanner temporary prostatic stent maintains urine flow and allows natural voluntary urination. The prostatic stent is a completely internal device and can be inserted and removed as easily as a Foley catheter. It permits normal bladder and sphincter functioning and can be worn comfortably by patients. The temporary prostatic stent is typically used to help patients maintain urine flow after procedures that cause prostatic swelling, such as brachytherapy, cryotherapy, TUMT, TURP. It has also become an effective differential diagnostic tool for identifying poor bladder function separate from prostatic obstruction.

Permanent stents are often metal coils, which are inserted into the male urethra. The braided mesh is designed to expand radially, applying constant gentle pressure to hold open the sections of the urethra that obstruct the flow of urine. The open, diamond-shape cell design of the stent allows the stent to eventually become embedded in the urethra, thus minimizing the risk for encrustation and migration. Permanent stents are used to relieve urinary obstructions secondary to benign prostatic hyperplasia (BPH), recurrent bulbar Urethral stricture (RBUS), or detrusor external sphincter dyssynergia (DESD). The main motive for removal of permanent stents is worsening of symptoms even with

device fitted. Other reasons have been migration, clot retention, hematuria, and urinary retention. The only FDA approved permanent stent is the Urolume. Usually, permanent stents are used only for men who are unwilling or unable to take medications or who are reluctant or unable to have surgery. Most doctors do not consider permanent stents a viable long-term treatment for most men.

Not yet approved in the USA but available in Europe and several other countries are the nickel-titanium stents. These stents place themselves between temporary and permanent stents since they can remain in place for several years and still easily be removed. The reason for this feature is that nickel-titanium becomes super-soft when cooled with cold water.

Advantages and disadvantages to permanent prostatic stents

Advantages

- They can be placed in less than 15 minutes under regional anesthesia.
- Bleeding during and after surgery is minimal.
- The patient can be discharged the same day.

Disadvantages

- They may cause increased urination and limited incontinence.
- They may cause mild discomfort
- They can become dislodged, leading to urinary obstruction or total incontinence.
- They can become infected and can be very difficult to remove.
- Their fixed diameter limits subsequent endoscopic surgical options.

Advantages and disadvantages to temporary prostatic stents

Advantages

- They can be placed in less than 15 minutes in a manner similar to Foley catheter placement.
- They can be easily removed, also in a manner similar to Foley catheter removal.
- They allow the patient to retain volitional voiding.
- Patients prefer a temporary stent to Foley catheter use.

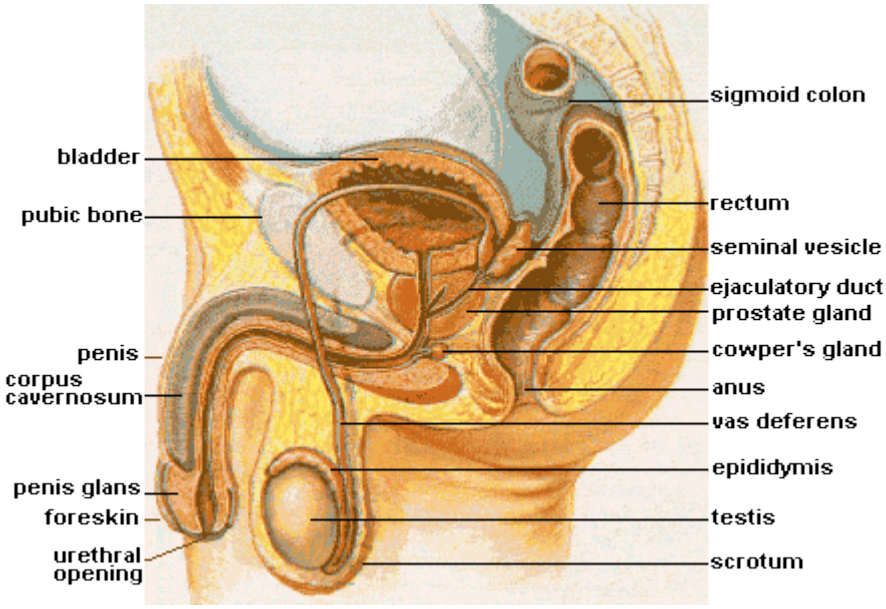
Disadvantages

- A temporary stent will not provide voiding function if the patient does not have a working bladder and external sphincter.
- The stent may cause mild discomfort.
- They may cause urinary frequency which usually subsides after the first 78 hours.

- If the stent is not sized correctly or placed correctly, the patient may experience urinary retention or slight incontinence until the problem is corrected.

Chapter 3

Prostate Massage



Male genital anatomy

Prostate massage is the massage or stimulation of the male prostate gland for sexual stimulation or medical purposes.

The prostate takes part in the sexual response cycle, and is essential for ejaculation. Normally, in mammals found to be most active during the time of ejaculation, this organ also faces many threats from disease. Due to its close proximity to the anterior rectal wall, it can be stimulated manually via the anus.

Medical uses

Digital rectal examination (DRE)

Prostate massage is part of the digital rectal examination (DRE) routinely given to men by urologists in order to look for nodules of prostate cancer and to obtain an expressed prostatic secretion (EPS) specimen for microscopy and microbiological culture to screen for prostatitis.

Prostatitis

In the late 1990s, doctors tried prostate massage in conjunction with antibiotics for the treatment of chronic bacterial prostatitis with uncertain results. In recent trials, however, prostate massage was not shown to improve outcomes compared to antibiotics alone. As a consequence of these findings, prostate massage is not used in the treatment of any medical disorder today, and prostate massage should *never* be performed on patients with acute prostatitis, because the infection can spread elsewhere in the body if massage is performed.

Risks

In addition, prostate massage can be risky. Some of the documented consequences are life-threatening periprostatic hemorrhage, cellulitis, Fournier's gangrene, septicaemia, possible disturbance and metastasis of prostate cancer to other parts of the body, and hemorrhoidal flare-up.

Animal husbandry

Electroejaculation is a procedure in which nerves are stimulated via an electric probe, which is inserted into the rectum adjacent to the prostate. It is most commonly encountered in animal husbandry for the purpose of collecting semen samples for testing or breeding.

Prostate massage as alternative therapy

Prostate massage was once the most popular therapeutic maneuver used to treat prostatitis, but abandoned as primary therapy in the early 1970s. Continuing research in emerging medical communities, published articles in non-medical circles, and anecdotal evidence on the internet shows that there is still interest in the technique as alternative therapy. In China, a 2008 survey of 627 urologists found that prostate massage is used prevalently as a nonpharmacological therapy for chronic prostatitis.

Prostate massage as sexual practice

Prostate massage is also used for sexual stimulation, often in order to reach orgasm.

The prostate is sometimes referred to as the "male G-spot". Some men are able to achieve orgasm solely through stimulation of the prostate gland, such as prostate massage or receptive anal intercourse. Men who report the sensation of prostate stimulation often give descriptions similar to females' accounts of G-spot stimulation.

Prostate massage has become a common sexual practice in couples' sexual lives as men seem to experience high levels of pleasure from it. Also, the advent of equipment and products for prostate massage encourages people to try it. Many couples though do not purchase such devices but use the finger for anal penetration and prostate stimulation to enhance the man's orgasm. The finger or the prostate massager is introduced into the rectum through the anus and the prostate gland is gently massaged. The main problem in using the finger is that it may be too short to reach the prostate gland.

Prostate massage can be performed individually or with the help of a partner. Some men prefer being anally stimulated by their partner during foreplay or after intercourse. Men can excite their own prostates while masturbating using anal penetration devices.

There are a few safety matters concerning prostate stimulation and anal penetration. It is strongly recommended that plenty of lubricant is used with prostate massagers to prevent rectal lining damage. A smaller instrument or finger may be introduced gradually to minimize the discomfort that some may feel. Massagers may be used with or without a condom; however, because of the bacteria found in the rectum, if a condom is not used, it is very important to clean the tool with antibacterial soap before use in another orifice or by a partner.

Equipment

A *prostate massager* refers to devices for massaging the prostate gland, mainly for sexual purposes.

The shape of a prostate massager is similar to a finger, since prostate massages are traditionally given digitally. They usually have a slightly curved head to effectively massage the prostate. Lubricant is usually inserted into the anus. A prostate massager should be used with care because of the sensitivity of the prostate. Correct use involves a medium to light repetitive massage, or circular motion—the tool should not be thrusted.

Prostate massage equipment ranges from dildos to butt plugs and G-spot vibrators. When used in sexual practice, prostate massagers are commonly referred to as "prostate toys", "prostate sex toys", and "anal toys". These prostate massagers are inserted into the rectum through the anus and are intended to stimulate the prostate by simple massaging or vibrating. They are used during foreplay by many couples.

Prostate stimulation is thought to produce stronger and more powerful orgasms similar to orgasms in women produced by G-spot stimulation.

Prostate dildos are similar to the vaginal dildos, but they tend to be more curved, slimmer and with a softer texture. Some of the new prostate dildos on the market are driven by batteries and offer vibration at the tip, which may be changed depending on the personal preference. Unlike the vaginal dildos, the anal prostate massager has a flared end to prevent from being lost in the rectum.

Most men prefer butt plugs, which are easy to use, can be inserted freely and left in place while the man's hands are free for other sexual activities such as masturbation. Anal plugs come also in various shapes, sizes and designs and although they are not commonly intended to stimulate the prostate, newer models of more angled butt plugs are now developed to provide a more vigorous massage to the prostate. The new butt plugs have a more curved shape and they are slightly longer than the regular anal plugs. They commonly have a narrow neck and a flared end to prevent losing it in the rectum. Some of the newer models come with batteries and vibrations that increase sexual pleasure.

The G-spot vibrator can be used as a prostate massager as long as it is handled carefully and are provided with a safety base that will not allow to be lost in the rectum. Vibrators for prostate stimulation usually have a pronounced curve at the end.

Chapter 4

Development of the Reproductive System

The **development of the reproductive system** is a part of prenatal development, and concerns the sex organs. It is a part of the stages of sexual differentiation. Because its location to a large extent overlaps the urinary system, the development of them can also be described together as the development of the urinary and reproductive organs.

The reproductive organs are developed from the intermediate mesoderm. The permanent organs of the adult are preceded by a set of structures which are purely embryonic, and which with the exception of the ducts disappear almost entirely before the end of fetal life. These embryonic structures are the Wolffian and Müllerian ducts, also known as mesonephric and paramesonephric ducts, respectively. The Wolffian duct remains as the duct in males, and the Müllerian as that of the female.

Wolffian (mesonephric) Duct

The Wolffian duct originates from a part of the ovary where the urinary system grows.

Origin

In the outer part of the intermediate mesoderm, immediately under the ectoderm, in the region from the fifth cervical segment to the third thoracic segment, a series of short evaginations from each segment grows dorsally and extends caudally, fusing successively from before backward to form the pronephric duct. This continues to grow caudalward until it opens into the ventral part of the cloaca; beyond the pronephros it is termed the Wolffian duct. Thus, the Wolffian duct is what remains of the pronephric duct after the atrophy of the pronephros.

Development in male

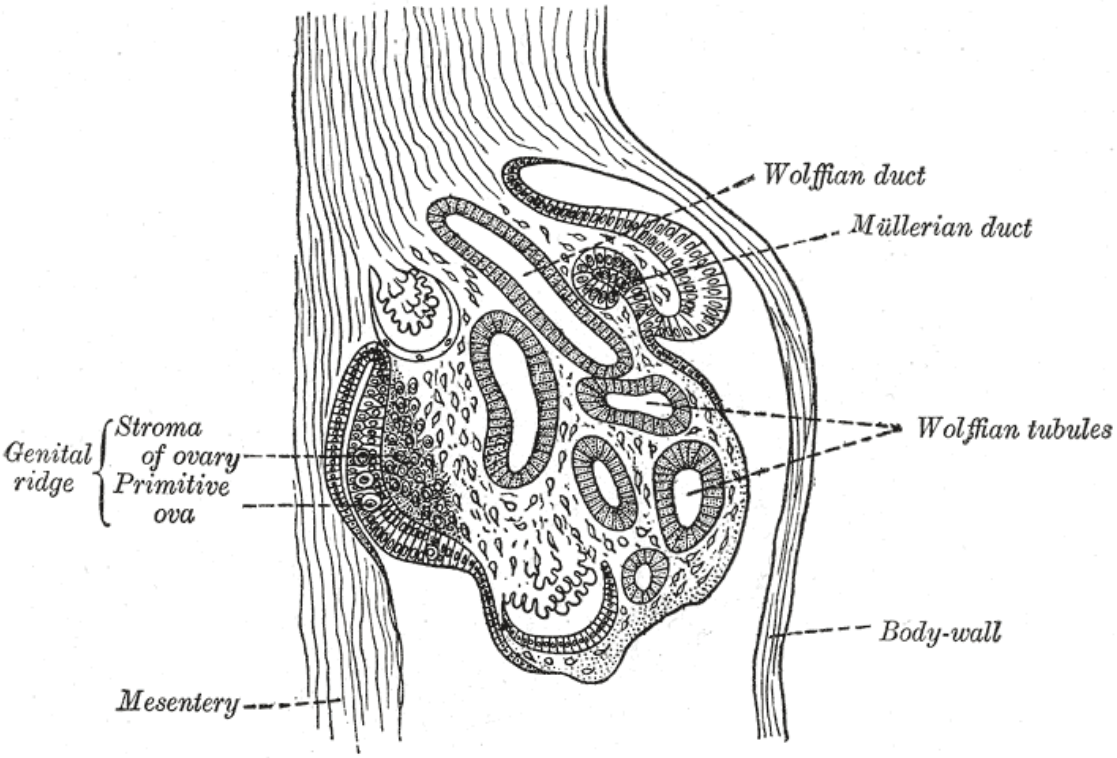
In the male the Wolffian duct persists, and forms the tube of the epididymis, the ductus deferens and the ejaculatory duct, while the seminal vesicle arises during the third month as a lateral diverticulum from its hinder end. A large part of the head end of the

mesonephros atrophies and disappears; of the remainder the anterior tubules form the efferent ducts of the testis; while the posterior tubules are represented by the ductuli aberrantes, and by the paradidymis, which is sometimes found in front of the spermatic cord above the head of the epididymis.

Atrophy in female

In the female the Wolffian bodies and ducts atrophy. The nonfunctional remains of the Wolffian tubules are represented by the epoophoron, and the paroöphoron, two small collections of rudimentary blind tubules which are situated in the mesosalpinx.

Remnants

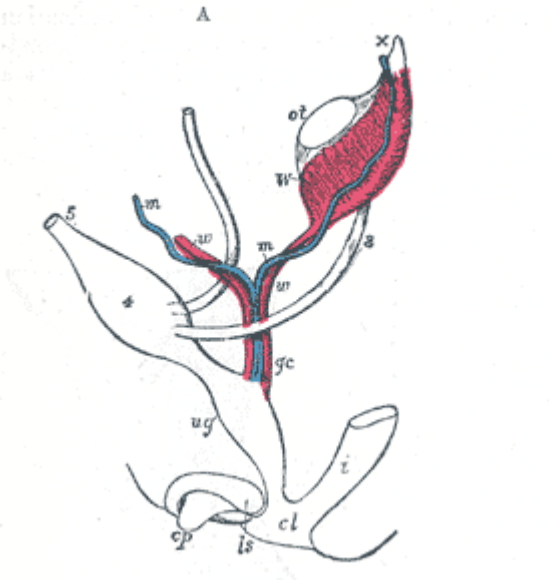


Section of the fold in the mesonephros of a chick embryo of the fourth day.

The lower part of the Wolffian duct disappears, while the upper part persists as the longitudinal duct of the epoöphoron, called Gartner's duct.

There are also developments of other tissues from the Wolffian duct that persist, e.g. the development of the suspensory ligament of the ovary.

The Müllerian (paramesonephric) Duct



A.—Diagram of the primitive urogenital organs in the embryo previous to sexual distinction. The common genital cord is labeled with gc.
* 3. Ureter.
* 4. Urinary bladder.
* 5. Urachus.
* cl. Cloaca.
* cp. Elevation which becomes clitoris or penis.
* i. Lower part of the intestine.
* ls. Fold of integument from which the labia majora or scrotum are formed.
* m, m. Right and left Müllerian ducts uniting together and running with the Wolffian ducts in gc, the common genital cord.
* ot. The gonadal ridge from which either the ovary or testis is formed.
* ug. Sinus urogenitalis.
* W. Left Wolffian body.
* w, w. Right and left Wolffian ducts.

Shortly after the formation of the Wolffian ducts a second pair of ducts is developed; these are the Müllerian ducts. Each arises on the lateral aspect of the corresponding Wolffian duct as a tubular invagination of the cells lining the abdominal cavity. The orifice of the invagination remains open, and undergoes enlargement and modification to form the abdominal ostium of the fallopian tube. The ducts pass backward lateral to the Wolffian ducts, but toward the posterior end of the embryo they cross to the medial side of these ducts, and thus come to lie side by side between and behind the latter—the four ducts forming what is termed the *common genital cord*, to distinguish it from the *genital cords of the germinal epithelium* seen later. The Müllerian ducts end in an epithelial elevation, the Müllerian eminence, on the ventral part of the cloaca between the orifices of the Wolffian ducts. At a later stage the eminence opens in the middle, connecting the Müllerian ducts with the cloaca.

Atrophy in males

In the male the Müllerian ducts atrophy, but traces of their anterior ends are represented by the appendices testis (hydatids of Morgagni of the male), while their terminal fused portions form the utriculus in the floor of the prostatic urethra. This is due to the production of Anti-Müllerian hormone by the Sertoli cells of the testes.

Development in females

In the female the Müllerian ducts persist and undergo further development. The portions which lie in the *genital cord* fuse to form the uterus and vagina. This fusion of the Müllerian ducts begins in the third month, and the septum formed by their fused medial walls disappears from below upward.

The parts outside this cord remain separate, and each forms the corresponding Fallopian tube. The ostium of the fallopian tube remains from the anterior extremity of the original tubular invagination from the abdominal cavity.

About the fifth month a ring-like constriction marks the position of the cervix of the uterus, and after the sixth month the walls of the uterus begin to thicken. For a time the vagina is represented by a solid rod of epithelial cells. A ring-like outgrowth of this epithelium occurs at the lower end of the uterus and marks the future vaginal fornix. At about the fifth or sixth month the lumen of the vagina is produced by the breaking down of the central cells of the epithelium. The hymen represents the remains of the Müllerian eminence .

Gonads

The gonads are the precursors of the testes in males and ovaries in females. They initially develop from the mesothelial layer of the peritoneum.

Ovaries

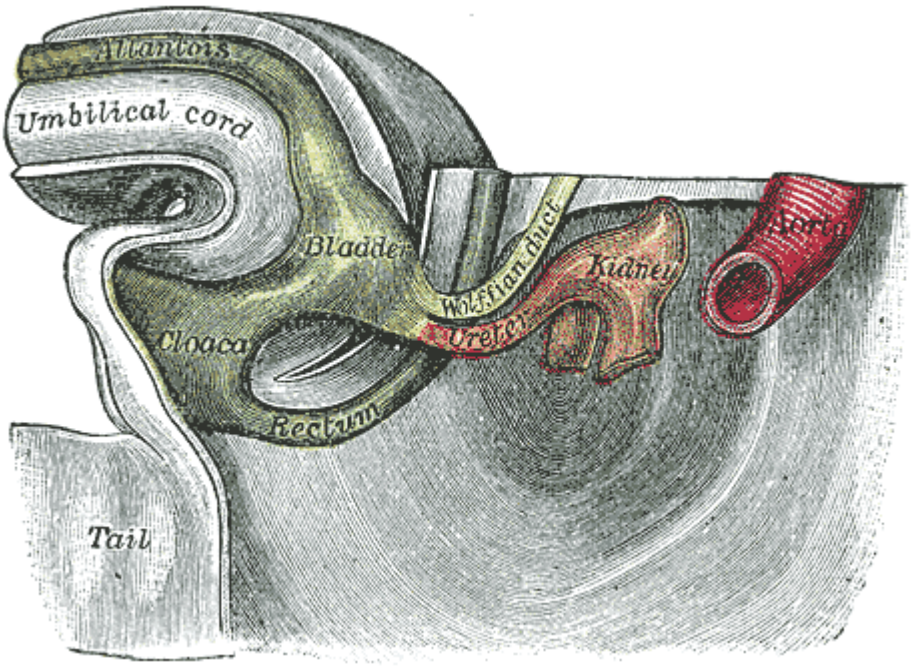
The ovary is differentiated into a central part, the medulla of ovary, covered by a surface layer, the germinal epithelium. The immature ova originate from cells from the dorsal endoderm of the yolk sac. Once they have reached the gonadal ridge they are called oogonia. Development proceeds and the oogonia become fully surrounded by a layer of connective tissue cells (pre-granulosa cells) In this way, the rudiments of the ovarian follicles are formed. The embryological origin of granulosa cells, on the other hand, remains controversial. Just as in the male, there is a gubernaculum in the female, which pulls it downward, albeit not as much as in males. The gubernaculum later becomes the proper ovarian ligament and the round ligament of the uterus.

Testes

The periphery of the testes are converted into the tunica albuginea. Cords of the central mass run together and form a network which becomes the rete testis, and another network, which develops the seminiferous tubules. Via the rete testis, the seminiferous tubules become connected with outgrowths from the mesonephros, which form the efferent ducts of the testis.

In short, the descent of the testes consists of the opening of a connection from the testis to its final location at the anterior abdominal wall, followed by the development of the gubernaculum, which subsequently pulls and translocates the testis down into the developing scrotum. Ultimately, the passageway closes behind the testis. A failure in this process can cause indirect inguinal hernia or an infantile hydrocoele.

Division of cloaca



Tail end of human embryo thirty-two to thirty-three days old. The entodermal cloaca is visible at center left, labeled in green

After the separation of the rectum from the dorsal part of the cloaca, the ventral part becomes the primary urogenital sinus. The urogenital sinus, in turn, divides into the superficial definitive urogenital sinus and the deeper anterior vesico-urethral portion.

Definitive urogenital sinus

The definitive urogenital sinus consists of a caudal cephallic portion and an intermediate narrow channel, the pelvic portion.

Vesico-urethral portion

The vesico-urethral portion is the deepest portion, continuous with the allantois. It absorbs the ends of the Wolffian ducts and the associated ends of the renal diverticula, and these give rise to the trigone of urinary bladder and part of the prostatic urethra. The remainder of the vesico-urethral portion forms the body of the bladder and part of the prostatic urethra; its apex is prolonged to the umbilicus as a narrow canal, the urachus, which later is obliterated and becomes the median umbilical ligament of the adult.

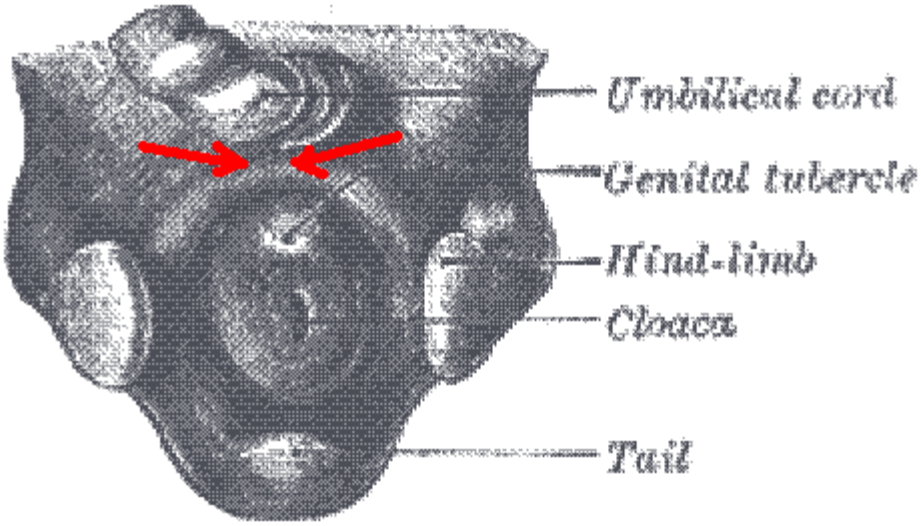
The Prostate

The prostate originally consists of two separate portions, each of which arises as a series of diverticular buds from the epithelial lining of the urogenital sinus and vesico-urethral part of the cloaca, between the third and fourth months. These buds become tubular, and form the glandular substance of the two lobes, which ultimately meet and fuse behind the urethra and also extend on to its ventral aspect. The median lobe of the prostate is formed as an extension of the lateral lobes between the common ejaculatory ducts and the bladder.

Skene's glands in the female urethra are regarded as the homologues of the prostatic glands.

The bulbourethral glands in the male, and Bartholin's gland in the female, also arise as diverticula from the epithelial lining of the urogenital sinus.

External genitalia



The mesoderm extends to the midventral line

Until about the ninth week of gestational age the external genitalia of males and females look the same, and follow a common development. This includes the development of a genital tubercle and a membrane dorsally to it, covering the developing urogenital opening, and the development of labioscrotal folds.

Even after differentiation can be seen between the sexes, some stages are common, e.g. the disappearing of the membrane. On the other hand, sex-dependent development include further protrusion of the genital tubercle in the male to form the penis. Furthermore, the labioscrotal folds evolve into the scrotum in males, while they evolve into labia in females.

Common development

Before differentiation

Urogenital membrane

There is initially a cloacal membrane, composed of ectoderm and endoderm, reaching from the umbilical cord to the tail, separating the cloaca from the exterior. After the separation of the rectum from the dorsal part of the cloaca, the ventral part of the cloacal membrane becomes the *urogenital membrane*.

Genital tubercle

Mesoderm extends to the midventral line for some distance behind the umbilical cord, and forms the lower part of the abdominal wall; it ends below in a prominent swelling, the cloacal tubercle, which after the separation of the rectum becomes the genital tubercle. Dorsally to this tubercle the sides aren't really fused. Rather, the urogenital part of the cloacal membrane separates the ingrowing sheets of mesoderm.

Phallus

The genital tubercle develops into the phallus, the first rudiment of the penis or clitoris.

The terminal part of the phallus, representing the future glans becomes solid. The remainder of the phallus, which remains hollow, is converted into a longitudinal groove by the absorption of the urogenital membrane.

The term genital tubercle, however, still remains, but only refers to the future glans

Urogenital opening

In both sexes the phallic portion of the urogenital sinus extends on to the under surface of the cloacal tubercle as far forward as the apex. At the apex the walls of the phallic portion come together and fuse, obliterating the urogenital opening. Instead, a solid plate, the urethral plate, is formed. The remainder of the phallic portion is for a time tubular, and

then, by the absorption of the urogenital membrane, it establishes a communication with the exterior. This opening is for a while the primitive urogenital opening, and it extends forward to the corona glandis.

After differentiation

|500px|Development of external genitalia. A: common development. C,E: male development. B,D, F: female development]]

The following developments occur in both males and females, although a difference in the development between the sexes already can be seen:

- The corpora cavernosa of the penis or clitoris and of the urethra arise from the mesodermal tissue in the phallus; they are at first dense structures, but later vascular spaces appear in them, and they gradually become cavernous.

- The prepuce in both sexes is formed by the growth of a solid plate of ectoderm into the superficial part of the phallus; on coronal section this plate presents the shape of a horseshoe. By the breaking down of its more centrally situated cells the plate is split into two lamellæ. Thus, a cutaneous fold, the prepuce, is liberated and forms a hood over the glans.

Female

In the female, a deep groove forms around the phallus. The sides of it grow dorsalward as the labioscrotal folds, which ultimately form the labia majora in females. The labia minora, in contrast, arise by the continued growth of the lips of the groove on the under surface of the phallus; the remainder of the phallus forms the clitoris. The immature glans becomes the clitoral glans.

Male

In the male the pelvic portion of the cloaca undergoes much greater development, pushing before it the phallic portion.

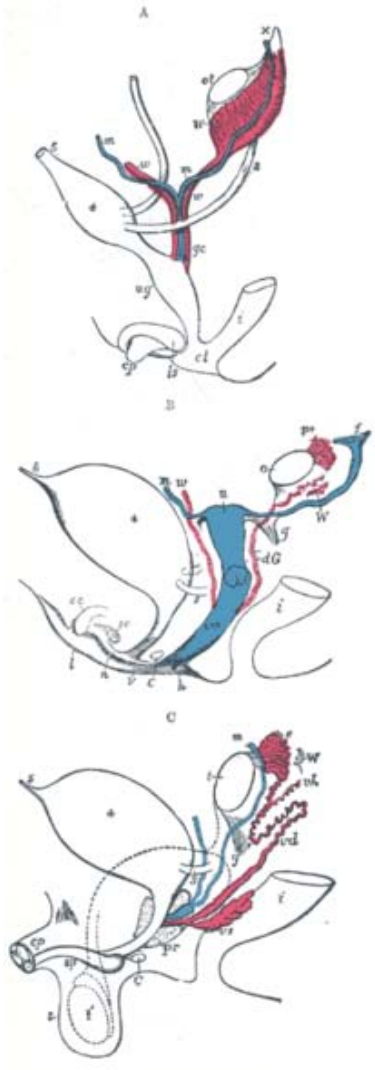
The labioscrotal folds extend around between the pelvic portion and the anus, and form a scrotal area. During the changes associated with the descent of the testes this scrotal area is drawn out to form the scrotal sacs. The penis is developed from the phallus.

As in the female, the urogenital membrane undergoes absorption, forming a channel on the under surface of the phallus; this channel extends only as far forward as the corona glandis.

Urogenital opening

In the male, by the greater growth of the pelvic portion of the cloaca, a longer urethra is formed, and the primitive opening is carried forward with the phallus, but it still ends at the corona glandis. Later, this opening, which is located on the dorsal ide of the penis, closes from behind forward. Meanwhile, the urethral plate of the glans breaks down centrally to form a median groove continuous with the primitive ostium. This groove also closes from behind forward, leaving only a small pipe running in the middle of the penis. Thus, the urogenital opening is shifted forward to the end of the glans.

Diagram of internal differentiation



Diagrams to show the development of male and female generative organs from a common type.

A.—Diagram of the primitive urogenital organs in the embryo previous to sexual distinction.

- 3. Ureter.
- 4. Urinary bladder.
- 5. Urachus.
- cl. Cloaca.
- cp. Elevation which becomes clitoris or penis.
- i. Lower part of the intestine.
- ls. Fold of integument from which the labia majora or scrotum are formed.
- m, m. Right and left Müllerian ducts uniting together and running with the Wolffian ducts in gc, the genital cord.
- ot. The genital ridge from which either the ovary or testis is formed.
- ug. Sinus urogenitalis.
- W. Left Wolffian body.
- w, w. Right and left Wolffian ducts.

B.—Diagram of the female type of sexual organs.

- C. Greater vestibular gland, and immediately above it the urethra.
- cc. Corpus cavernosum clitoridis.
- dG. Remains of the left Wolffian duct, such as give rise to the duct of Gärtner, represented by dotted lines; that of the right side is marked w.
- f. The abdominal opening of the left uterine tube.
- g. Round ligament, corresponding to gubernaculum.
- h. Situation of the hymen.
- i. Lower part of the intestine.
- l. Labium major.
- n. Labium minus.
- o. The left ovary.
- po. Epoophoron.
- sc. Corpus cavernosum urethrae.
- u. Uterus. The uterine tube of the right side is marked m.
- v. Vulva.
- va. Vagina.
- W. Scattered remains of Wolffian tubes near it (paroöphoron of Waldeyer).

C.—Diagram of the male type of sexual organs.

- C. Bulbo-urethral gland of one side.
- cp. Corpora cavernosa penis cut short.
- e. Caput epididymis.
- g. The gubernaculum.
- i. Lower part of the intestine.

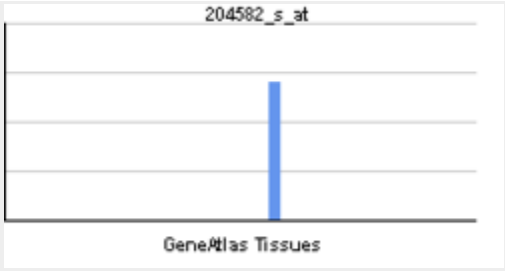
- m. Müllerian duct, the upper part of which remains as the hydatid of Morgagni; the lower part, represented by a dotted line descending to the prostatic utricle, constitutes the occasionally existing cornu and tube of the uterus masculinus.
- pr. The prostate.
- s. Scrotum.
- sp. Corpus cavernosum urethrae.
- t. Testis in the place of its original formation.
- t', together with the dotted lines above, indicates the direction in which the testis and epididymis descend from the abdomen into the scrotum.
- vd. Ductus deferens.
- vh. Ductus aberrans.
- vs. The vesicula seminalis.
- W. Scattered remains of the Wolffian body, constituting the organ of Giraldès, or the paradidymis of Waldeyer.

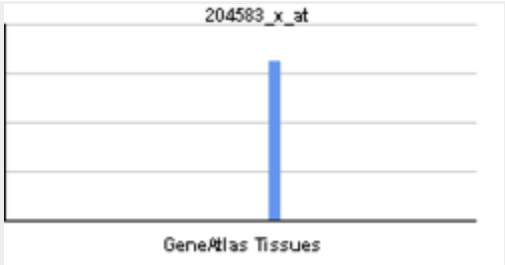
Chapter 5

Prostate-Specific Antigen

Kallikrein-related peptidase 3

Identifiers	
Symbols	KLK3; APS; KLK2A1; PSA; hK3
External IDs	OMIM: 176820 MGI: 892021 HomoloGene: 84789 GeneCards: KLK3 Gene
Gene Ontology	
RNA expression pattern	





Orthologs		
Species	**Human**	**Mouse**
Entrez	354	16617
Ensembl	ENSG00000142515	ENSMUSG00000063713

UniProt	P07288	O35307
RefSeq (mRNA)	NM_001030047	XM_001000656
RefSeq (protein)	NP_001025218	XP_001000656
Location (UCSC)	Chr 19: 56.05 - 56.06 Mb	Chr 7: 44.06 - 44.06 Mb
PubMed search		

Prostate-specific antigen (**PSA**) is a protein produced by the cells of the prostate gland. PSA is present in small quantities in the serum of men with healthy prostates, but is often elevated in the presence of prostate cancer and in other prostate disorders. A blood test to measure PSA is considered the most effective test currently available for the early detection of prostate cancer, but this effectiveness has also been questioned.

Rising levels of PSA over time are associated with both localized and metastatic prostate cancer (CaP).

Biochemistry

Prostate-specific antigen (PSA, also known as **kallikrein III**, **seminin**, **semenogelase**, **γ-seminoprotein** and **P-30 antigen**) is a 34 kD glycoprotein manufactured almost exclusively by the prostate gland; PSA is produced for the ejaculate where it liquifies the semen in the seminal coagulum and allows sperm to swim freely. It is also believed to be instrumental in dissolving the cervical mucous cap, allowing the entry of sperm.

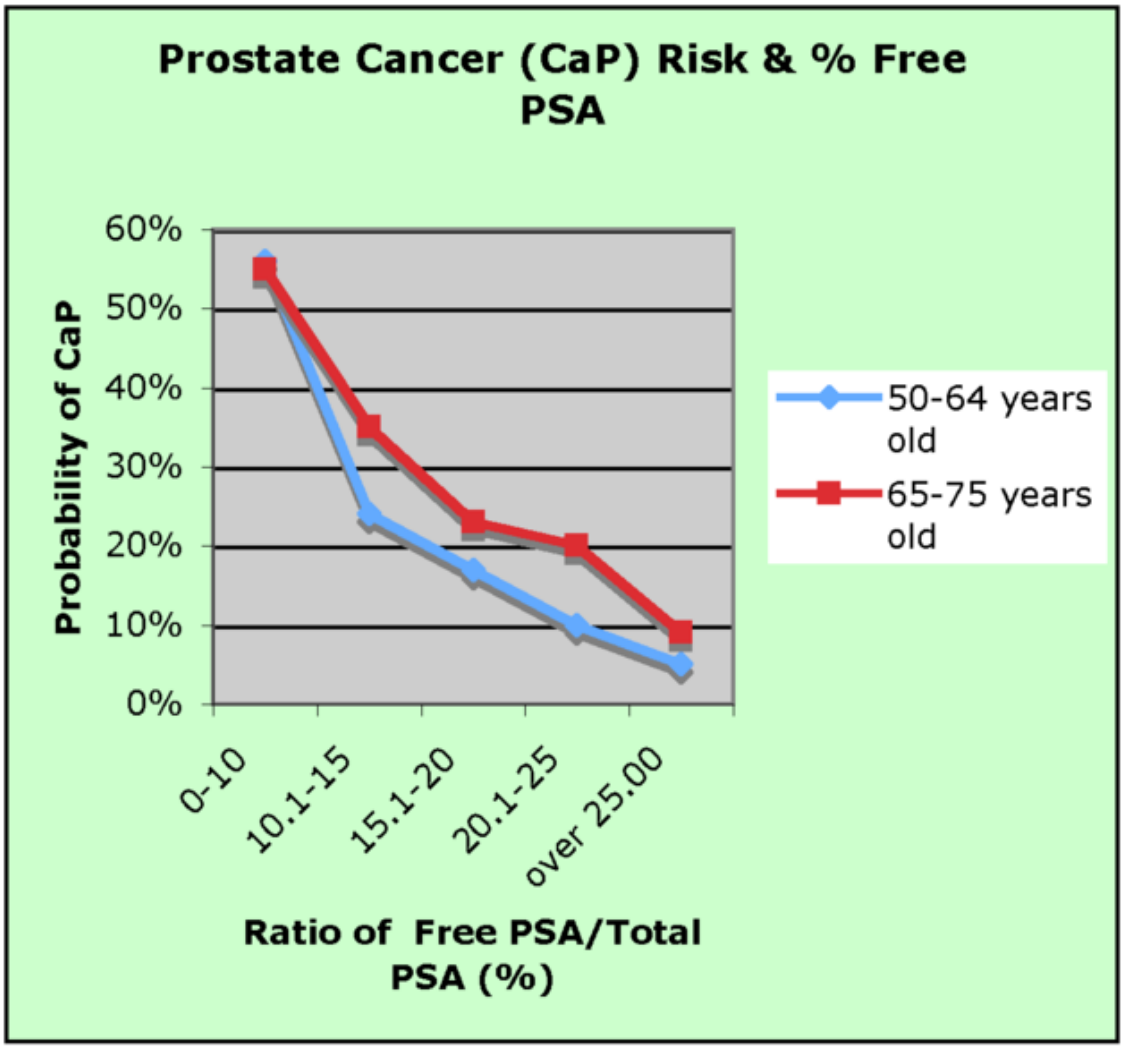
It is a serine protease (EC 3.4.21.77) enzyme, the gene of which is located on the nineteenth chromosome (19q13).

Discovery

The discovery of prostate-specific antigen (PSA) is beset with controversy; as PSA is present in prostatic tissue and semen, it was independently discovered and given different names, thus adding to the controversy. Flocks was the first to experiment with antigens in the prostate and 10 years later Ablin reported the presence of precipitation antigens in the prostate. In 1971, Hara characterized a unique protein in the semen fluid, gamma-seminoprotein. Li and Beling, in 1973, isolated a protein, E1, from human semen in an attempt to find a novel method to achieve fertility control. In 1978, Sensabaugh identified semen-specific protein p30, but proved that it was similar to E1 protein, and that prostate was the source. In 1979, Wang purified a tissue-specific antigen from the prostate

('prostate antigen'). PSA was first measured quantitatively in the blood by Papsidero in 1980, and Stamey carried out the initial work on the clinical use of PSA as a marker of prostate cancer.

Serum PSA



Risk of prostate cancer in two age groups based on **Free PSA** as % of Total PSA

PSA is normally present in the blood at very low levels. The reference range of less than 4 ng/mL for the first commercial PSA test, the Hybritech Tandem-R PSA test released in February 1986, was based on a study that found 99% of 472 apparently healthy men had a total PSA level below 4 ng/mL—the upper limit of normal is much less than 4 ng/mL. Increased levels of PSA may suggest the presence of prostate cancer. However, prostate cancer can also be present in the complete absence of an elevated PSA level, in which case the test result would be a false negative. Obesity has been reported to reduce serum PSA levels. Delayed early detection may partially explain worse outcomes in obese men with early prostate cancer.

PSA levels can be also increased by prostatitis, irritation, benign prostatic hyperplasia (BPH), and recent ejaculation, producing a false positive result. Digital rectal examination (DRE) has been shown in several studies to produce an increase in PSA. However, the effect is clinically insignificant, since DRE causes the most substantial increases in patients with PSA levels already elevated over 4.0 ng/mL.

The "normal" reference ranges for prostate-specific antigen increase with age, as do the usual ranges in cancer:

Age	**<50**		**50 - 59**		**60 - 69**		**>70**		**(years)**
	Cancer	No cancer	Cancer	No cancer	Cancer	No cancer	Cancer	No cancer	
5th percentile	0.4	0.3	1.2	0.3	1.7	0.3	2.3	0.4	**(ng/mL)**
95th percentile	163.0	2.5	372.5	4.7	253.2	8.3	613.2	17.8	

Despite earlier findings, recent research suggests that the rate of increase of PSA (the **PSA velocity**) is not a more specific marker for prostate cancer. However, the PSA rate of rise may have value in prostate cancer prognosis. Men with prostate cancer whose PSA level increased by more than 2.0 ng per milliliter during the year before the diagnosis of prostate cancer have a higher risk of death from prostate cancer despite undergoing radical prostatectomy.

Most PSA in the blood is bound to serum proteins. A small amount is not protein bound and is called **free PSA**. In men with prostate cancer the ratio of free (unbound) PSA to total PSA is decreased. The risk of cancer increases if the free to total ratio is less than 25%. The lower the ratio the greater the probability of prostate cancer. Measuring the ratio of free to total PSA appears to be particularly promising for eliminating unnecessary biopsies in men with PSA levels between 4 and 10 ng/mL. However, both total and free PSA increase immediately after ejaculation, returning slowly to baseline levels within 24 hours.

PSA in other biologic fluids and tissues

Concentration of PSA in human body fluids

Fluid	**PSA (ng/mL)**
semen	200,000 to 5.5 million
amniotic fluid	0.60-8.98
breast milk	0.47-100
saliva	0
female urine	0.12-3.72
female serum	0.01-.53

It is now clear that the term prostate-specific antigen is a misnomer. It is neither an antigen nor specific to the prostate. Although present in large amounts in prostatic tissue and semen, it has been detected in other body fluids and tissues.

In women, PSA is found in female ejaculate at concentrations roughly equal to that found in male semen. Other than semen and female ejaculate, the greatest concentrations of PSA in biological fluids are detected in breast milk and amniotic fluid. Low concentrations of PSA have been identified in the urethral glands, endometrium, normal breast tissue and salivary gland tissue. PSA also is found in the serum of women with breast, lung, or uterine cancer and in some patients with renal cancer.

Tissue samples can be stained for the presence of PSA in order to determine the origin of malignant cells that have metastasized.

Uses of PSA

Prostate cancer

Screening

In the United States, the U.S. Food and Drug Administration (FDA) has approved the PSA test for annual screening of prostate cancer in men of age 50 and older. The patient needs to be informed of the risks and benefits of PSA testing prior to performing the test. PSA levels between 4 and 10 ng/mL (nanograms per milliliter) are considered to be suspicious and consideration should be given to confirming the abnormal PSA with a repeat test. If indicated, prostate biopsy is performed to obtain tissue sample for histopathological analysis. The independent US Preventive Services Task Force rated the PSA test as "I", meaning it "found insufficient evidence to recommend either for or against screening"; for men aged 75 years or older, the rating is "D", meaning it found more reasons to advise against it. In the United Kingdom, the National Health Service does not mandate, nor advise for PSA test, but allows patients to decide based on their doctor's advice. PSA is false positive-prone (7 out of 10 men in this category will still not have prostate cancer) and false negative-prone (2.5 out of 10 men with prostate cancer have no elevation in PSA). Recent reports indicate that refraining from ejaculation 24 hours or more prior to testing will improve test accuracy.

Risk stratification and staging

Patients with localized (non-metastatic) prostate cancer have traditionally been characterized as low-, intermediate-, or high-risk for failure of curative treatment and prostate cancer mortality. PSA level is one of three variables on which the risk-stratification is based; the others are the grade of prostate cancer (Gleason score) and the stage of cancer based on clinical investigations (as opposed to examination of surgical pathology). Criteria for each risk category are as follows:
• Low-risk: PSA < 10, Gleason score ≤ 6, AND clinical stage ≤ T2a

• Intermediate-risk: PSA 10-20, Gleason score 7, OR clinical stage T2b/c
• High-risk: PSA > 20, Gleason score ≥ 8, OR clinical stage ≥ T3

Researchers are working to identify more accurate prognostic variables for risk-stratification of men with prostate cancer.

Post-treatment monitoring

PSA levels are monitored periodically (usually every 6-12 months) after treatment for prostate cancer. If surgical therapy (i.e., radical prostatectomy) is successful at removing all prostate tissue (and prostate cancer), PSA becomes undetectable within a few weeks. A subsequent rise in PSA level above 0.2 ng/dL is generally regarded as evidence of recurrent prostate cancer after a radical prostatectomy; less commonly, it may simply indicate residual benign prostate tissue.

Following radiation therapy of any type for prostate cancer, PSA levels do not become undetectable, even when the treatment ultimately proves to be successful. This makes it more difficult to interpret the relationship between PSA levels and recurrence/persistence of prostate cancer after radiation therapy. PSA levels may continue to decrease for several years after radiation therapy. The lowest level is referred to as the PSA nadir. A subsequent increase in PSA levels by 2.0 ng/dL above the nadir is the currently accepted definition of prostate cancer recurrence after radiation therapy.

If recurrent prostate cancer is detected by a rise in PSA levels after curative treatment, it is referred to as a "biochemical recurrence." The likelihood of developing recurrent prostate cancer after curative treatment is correlated to various risk factors, such as the grade of prostate cancer (Gleason score), PSA level prior to treatment, and the stage of disease prior to treatment. Patients with low-grade cancer (Gleason score ≤ 6), PSA < 10, and tumors that are not palpable by digital rectal examination are at the lowest risk of recurrence.

Forensic identification of semen

PSA was first identified by researchers attempting to find a substance in seminal fluid that would aid in the investigation of rape cases. PSA is now used to indicate the presence of semen in forensic serology. The semen of adult males has PSA levels far in excess of those found in other tissues; therefore, a high level of PSA found in a sample is an indicator that semen may be present. Because PSA is a biomarker that is expressed independently of spermatozoa, it remains useful in identifying semen from vasectomized and azoospermic males.

It is important to note that PSA can also be found at low levels in other body fluids, such as urine and breast milk, thus setting a high minimum threshold of interpretation to rule out false positive results and conclusively state that semen is present. While traditional tests such as crossover electrophoresis have a sufficiently low sensitivity to detect only seminal PSA, newer diagnostics tests developed from clinical prostate cancer screening

methods have lowered the threshold of detection down to 4 ng/mL. This level of antigen has been shown to be present in the peripheral blood of males with prostate cancer, and rarely in female urine samples and breast milk. No studies have been performed to assess the PSA levels in the tissues and secretions of pre-pubescent children. Therefore, the presence of PSA from a high sensitivity (4 ng/mL) test cannot conclusively identify the presence of semen, so care must be taken with the interpretation of such results.

Interactions

Prostate-specific antigen has been shown to interact with Protein C inhibitor.

Chapter 6

Benign Prostatic Hyperplasia

Benign prostatic hyperplasia

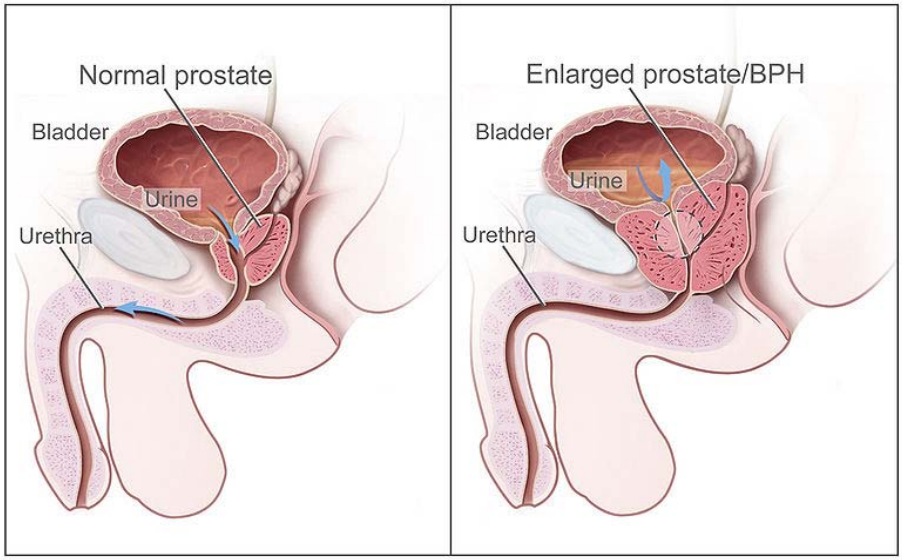


Diagram illustrating normal prostate (left) and benign prostatic hyperplasia (right).

ICD-10	N40.
ICD-9	600
DiseasesDB	10797
eMedicine	med/1919
MeSH	D011470

Benign prostatic hyperplasia (**BPH**) also known as **benign prostatic hypertrophy** (technically a misnomer), **benign enlargement of the prostate (BEP)**, and **adenofibromyomatous hyperplasia**, refers to the increase in size of the prostate.

To be accurate, the process is one of hyperplasia rather than hypertrophy, but the nomenclature is often interchangeable, even amongst urologists. It is characterized by hyperplasia of prostatic stromal and epithelial cells, resulting in the formation of large, fairly discrete nodules in the periurethral region of the prostate. When sufficiently large, the nodules compress the urethral canal to cause partial, or sometimes virtually complete, obstruction of the urethra, which interferes the normal flow of urine. It leads to symptoms of urinary hesitancy, frequent urination, dysuria (painful urination), increased risk of urinary tract infections, and urinary retention. Although prostate specific antigen levels may be elevated in these patients because of increased organ volume and inflammation due to urinary tract infections, BPH is not considered to be a premalignant lesion.

Adenomatous prostatic growth is believed to begin at approximately age 30 years. An estimated 50% of men have histologic evidence of BPH by age 50 years and 75% by age 80 years. In 40-50% of these patients, BPH becomes clinically significant.

Signs and symptoms

Benign prostatic hyperplasia symptoms are classified as storage or voiding.

Storage symptoms include urinary frequency, urgency (compelling need to void that cannot be deferred), urgency incontinence, and voiding at night (nocturia).

Voiding symptoms include urinary stream, hesitancy (needing to wait for the stream to begin), intermittency (when the stream starts and stops intermittently), straining to void, and dribbling. Pain and dysuria are usually not present. These storage and voiding symptoms are evaluated using the International Prostate Symptom Score (IPSS) questionnaire, designed to assess the severity of BPH.

BPH can be a progressive disease, especially if left untreated. Incomplete voiding results in stasis of bacteria in the bladder residue and an increased risk of urinary tract infection. Urinary bladder stones are formed from the crystallization of salts in the residual urine. Urinary retention, termed acute or chronic, is another form of progression. Acute urinary retention is the inability to void, while in chronic urinary retention the residual urinary volume gradually increases, and the bladder distends. Some patients that suffer from chronic urinary retention may eventually progress to renal failure, a condition termed obstructive uropathy.

Cause

A study published in 2008 in the journal of andrology "Andrologia" reports on a newly discovered venous route by which free (active) testosterone reaches the prostate in extremely high concentrations, promoting the accelerated proliferation of prostate cells,

leading to the gland's enlargement. The study suggests that BPH is caused by malfunction of the valves in the internal Spermatic veins manifesting as varicocele, a phenomenon which has been shown to increase rapidly with age, roughly equal to the 10% per year increasing prevalence of BPH. The 6- to 8-fold elevated hydrostatic pressure then leads to retrograde venous drainage, allowing free communication with the prostatic circulation. Having measured a concentration of free testosterone of some 130-fold above serum level in the internal spermatic vein (the testes being the main source and the blood being undiluted in systemic circulation), the authors conclude that the elevated venous pressure causes hypertrophy and exposure to high concentrations of free testosterone causes hyperplasia in the prostate. The study also proposes a treatment method (Gat–Goren Technique) similar to that used in treating varicocele, which restores normal pressure in the venous drainage system, effectively reducing the volume of the prostate and clinical manifestation of BPH.

Androgens (testosterone and related hormones) are considered to play a permissive role in BPH by most experts. This means that androgens have to be present for BPH to occur, but do not necessarily directly cause the condition. This is supported by the fact that castrated boys do not develop BPH when they age. On the other hand, administering exogenous testosterone is not associated with a significant increase in the risk of BPH symptoms. Dihydrotestosterone (DHT), a metabolite of testosterone, is a critical mediator of prostatic growth. DHT is synthesized in the prostate from circulating testosterone by the action of the enzyme 5α-reductase, type 2. This enzyme is localized principally in the stromal cells; hence, those cells are the main site for the synthesis of DHT.

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. DHT is 10 times more potent than testosterone because it dissociates from the androgen receptor more slowly. The importance of DHT in causing nodular hyperplasia is supported by clinical observations in which an inhibitor of 5α-reductase is given to men with this condition. Therapy with 5α-reductase inhibitor markedly reduces the DHT content of the prostate and, in turn, reduces prostate volume and, in many cases, BPH symptoms.

Testosterone promotes prostate cell proliferation, but relatively low levels of serum testosterone are found in patients with BPH. One small study has shown that that medical castration lowers the serum and prostate hormone levels unevenly, having less effect on testosterone and dihydrotestosterone levels in the prostate.

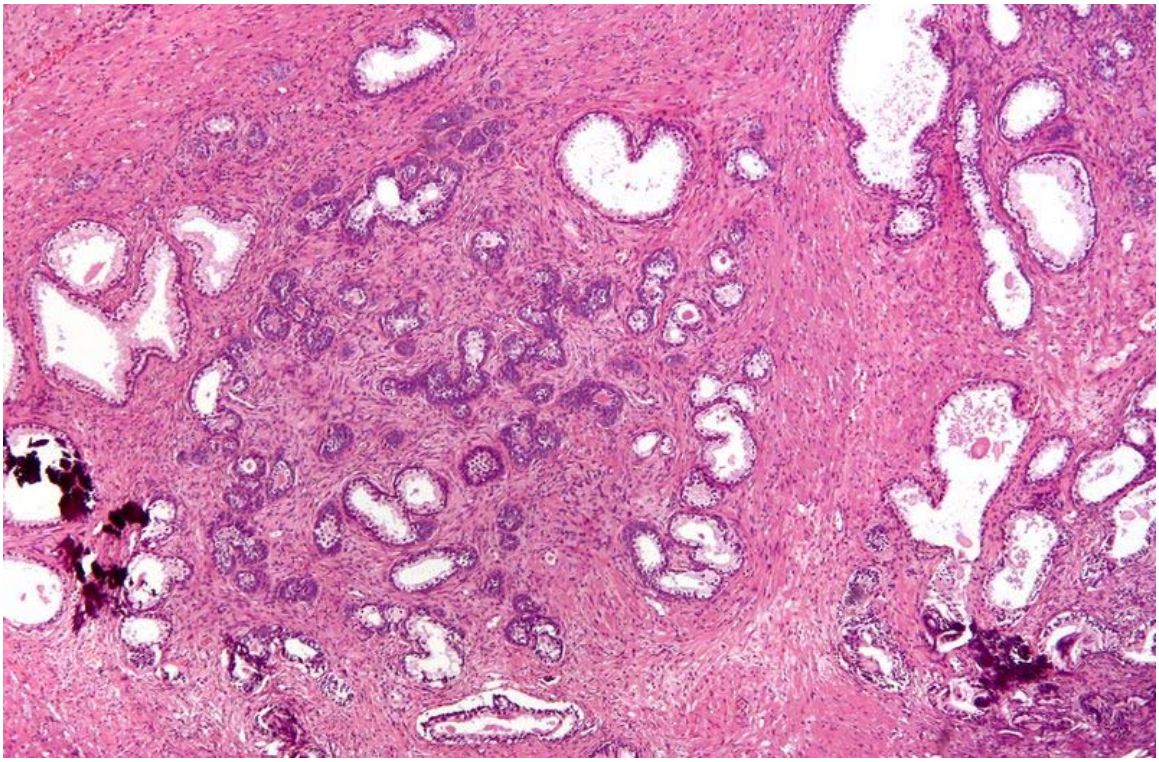
While there is some evidence that estrogen may play a role in the etiology of BPH, this effect appears to be mediated mainly through local conversion of estrogen to androgens in the prostate tissue rather than a direct effect of estrogen itself. In canine *in vivo* studies castration, which significantly reduced androgen levels but left estrogen levels unchanged, caused significant atrophy of the prostate. Studies looking for a correlation between prostatic hyperplasia and serum estrogen levels in humans have generally shown none.

On a microscopic level, BPH can be seen in the vast majority of men as they age, in particular over the age of 70 years, around the world. However, rates of clinically significant, symptomatic BPH vary dramatically depending on lifestyle. Men that lead a western lifestyle have a much higher incidence of symptomatic BPH than men that lead a traditional or rural lifestyle. This is confirmed by research in China showing that men in rural areas have very low rates of clinical BPH, while men living in cities adopting a western lifestyle have a skyrocketing incidence of this condition, though it is still below rates seen in the West.

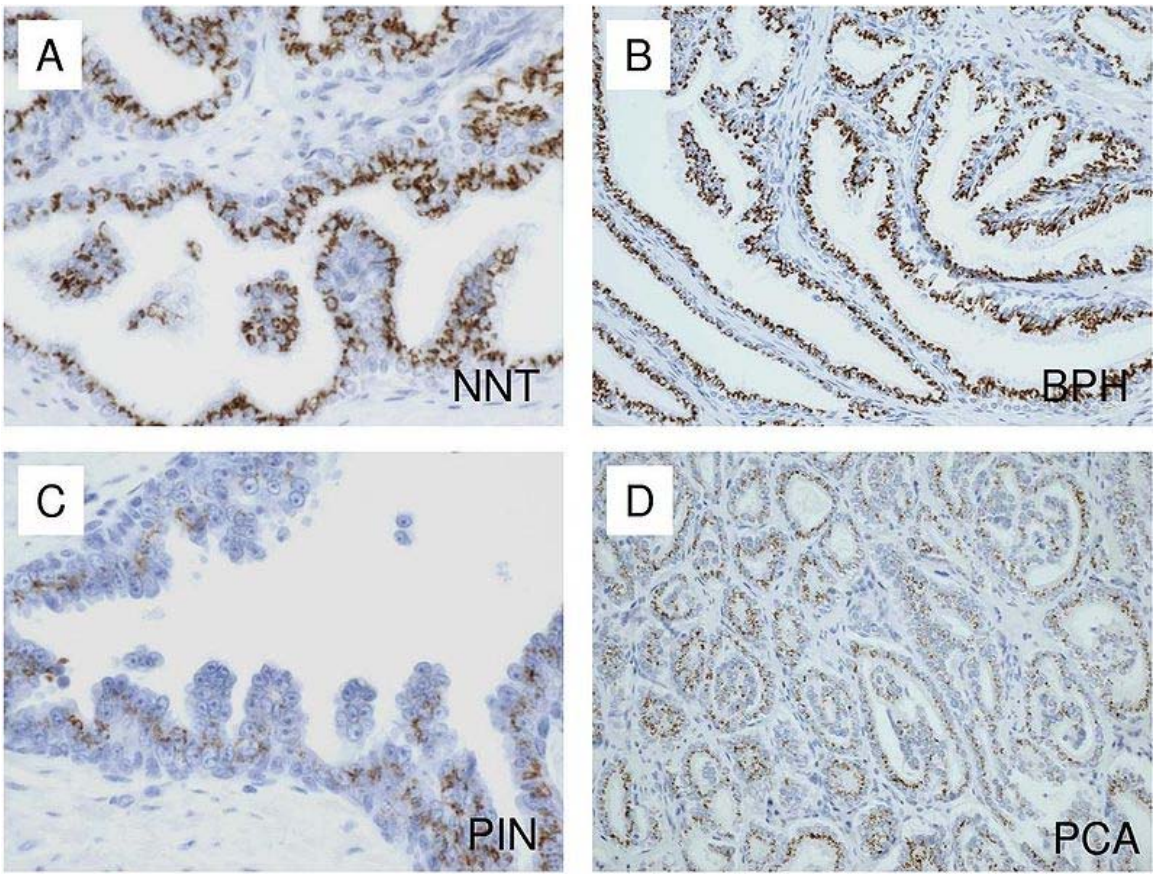
Much work remains to be done to completely clarify the causes of BPH.

Diagnosis

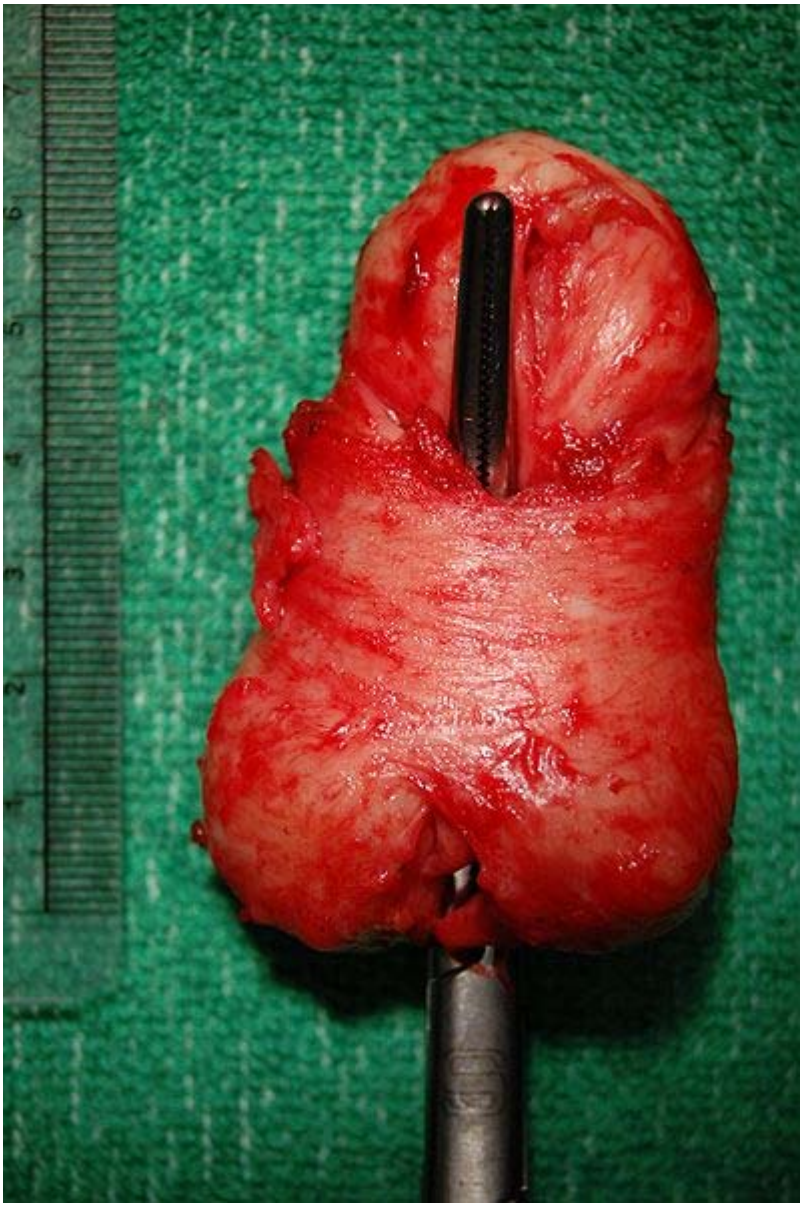
Urinary bladder (black butterfly-like shape) and hyperplastic prostate (BPH) visualized by Medical ultrasonography technique



Micrograph showing nodular hyperplasia (left off center) of the prostate from a transurethral resection of the prostate (TURP). H&E stain.



Microscopic examination of different types of prostate tissues (stained with immunohistochemical techniques): A. Normal (non-neoplastic) prostatic tissue (NNT). B. Benign prostatic hyperplasia. C. High-grade prostatic intraepithelial neoplasia (PIN). D. Prostatic adenocarcinoma (PCA).



Prostate with a large median lobe bulging upwards. A metal instrument is placed in the urethra (which passes through the prostate). This specimen was almost 7 centimeters long with a volume of about 60 cubic centimetres on transrectal ultrasound and was removed during a Hryntschak procedure or transvesical prostatectomy (removal of the prostate through the bladder) for benign prostatic hyperplasia.

Rectal examination (palpation of the prostate through the rectum) may reveal a markedly enlarged prostate, usually affecting the middle lobe.

Often, blood tests are performed to rule out prostatic malignancy: Elevated prostate specific antigen (PSA) levels needs further investigations such as reinterpretation of PSA results, in terms of PSA density and PSA free percentage, rectal examination and

transrectal ultrasonography. These combined measures can provide early cancer detection.

Ultrasound examination of the testicles, prostate, and kidneys is often performed, again to rule out malignancy and hydronephrosis.

Screening and diagnostic procedures for BPH are similar to those used for prostate cancer. Some signs to look for include:

- Weak urinary stream
- Prolonged emptying of the bladder
- Abdominal straining
- Hesitancy
- Irregular need to urinate
- Incomplete bladder emptying
- Post-urination dribble
- Irritation during urination
- Frequent urination
- Nocturia (need to urinate during the night)
- Urgency
- Incontinence (involuntary leakage of urine)
- Bladder pain
- Dysuria (painful urination)
- Problems in ejaculation

Management

Lifestyle

Patients should decrease fluid intake before bedtime, moderate the consumption of alcohol and caffeine-containing products, and follow timed voiding schedules.

Medications

The two main medications for management of BPH are alpha blockers and 5α-reductase inhibitors.

- Alpha blockers (technically α_1-adrenergic receptor antagonists) are the most common choice for initial therapy in the USA and Europe. Alpha blockers used for BPH include doxazosin, terazosin, alfuzosin, tamsulosin, and silodosin. All five are equally effective but have slightly different side effect profiles. The older drugs phenoxybenzamine and prazosin are not recommended. Alpha blockers relax smooth muscle in the prostate and the bladder neck, thus decreasing the blockage of urine flow. Common side effects of alpha blockers include orthostatic hypotension, ejaculation changes, nasal congestion, and weakness.

- The 5α-reductase inhibitors finasteride and dutasteride are another treatment option. These medications inhibit 5a-reductase, which in turn inhibits production of DHT, a hormone responsible for enlarging the prostate. Effects may take longer to appear than alpha blockers, but they persist for many years. When used together with alpha blockers, a reduction of BPH progression to acute urinary retention and surgery has been noted in patients with larger prostates. Side effects include decreased libido and ejaculatory or erectile dysfunction.

Antimuscarinics such as tolterodine may also be used, especially in combination with alpha blockers. They act by decreasing acetylcholine effects on the smooth muscle of the bladder, thus helping control symptoms of an overactive bladder.

Sildenafil citrate shows some symptomatic relief, suggesting a possible common etiology with erectile dysfunction.

Herbal remedies

People often seek herbal remedies for BPH. Several are approved in European countries, but none in the USA. Saw palmetto extract from *Serenoa repens* is one of the most extensively studied. It showed promise in early studies, though later trials of higher methodological quality indicated no difference from placebo.

Other herbal medicines that have research support in systematic reviews include beta-Sitosterol from *Hypoxis rooperi* (African star grass) and pygeum (extracted from the bark of *Prunus africana*), while there is less substantial support for the efficacy of pumpkin seed (*Cucurbita pepo*) and stinging nettle (*Urtica dioica*) root. There is weak evidence that pollen extracts frp, rye grass (*Secale cereale*) may also correlate with modest symptomatic relief.

Minimally invasive therapies

The European Urology Review published in 2009 that two Israeli doctors, Yigal Gat and Menahem Goren, who discovered the main reason for the gland's enlargement, have also developed the Gat-Goren nonsurgical method for BPH. Using an interventional radiological technique that reduces prostate volume and reverses BPH symptoms, the treatment, known as super-selective intra-prostatic androgen deprivation (SPAD) therapy, involves a percutaneus venography and sclerotherapy of the internal spermatic vein network, including associated venous bypasses and retroperitoneal collaterals. The European Urology Review also declared that using the Gat Goren nonsurgical method results in decreased prostate volume, which leads to significantly decreased nocturia, improved urine stream, and also improves emptying of the urinary bladder, and that without the potential side effects and complications of the classic surgery.

While medication is often prescribed as the first treatment option, there are many patients who do not achieve success with this line of treatment. Those patients may not achieve sustained improvement in symptoms or they may stop taking the medication because of

side-effects. There are options for treatment in a urologist's office before proceeding to surgery. The two most common types of office-based therapies are Transurethral microwave thermotherapy (TUMT) and Transurethral Needle Ablation (TUNA). Both of these procedures rely on delivering enough energy to create sufficient heat to cause cell death (necrosis) in the prostate. The goal of the therapies is to cause enough necrosis so that, when the dead tissue is reabsorbed by the body, the prostate shrinks, relieving the obstruction of the urethra. These procedures are typically performed with local anesthesia, and the patient returns home the same day. Some urologists have studied and published long-term data on the outcomes of these procedures, with data out to five years. The most recent American Urological Association (AUA) Guidelines for the Treatment of BPH in 2003 lists minimally invasive therapies including TUMT and TUNA as acceptable alternatives for certain patients with BPH.

Transuretheral microwave therapy (TUMT) was originally approved by the FDA in 1996, with the first generation system by EDAP Technomed. Since 1996, other companies have received FDA approval for TUMT devices, including Urologix, Dornier, Thermatrix, Celsion, and Prostalund. Multiple clinical studies have been published on TUMT. The general principle underlying all the devices is that a microwave antenna that resides in a urethral catheter is placed in the intraprostatic area of the urethra. The catheter is connected to a control box outside of the patient's body and is energized to emit microwave radiation into the prostate to heat the tissue and cause necrosis. It is a one-time treatment that takes approximately 30 minutes to 1 hour, depending on the system used. It takes approximately 4 to 6 weeks for the damaged tissue to be reabsorbed into the patient's body. Some of the devices incorporate circulating coolant through the treatment area with the intent of preserving the urethra while the microwave energy heats the prostatic tissue surrounding the urethra.

Transuretheral needle ablation (TUNA) operates with a different type of energy, radio frequency (RF) energy, but is designed along the same premise as TUMT devices, that the heat the device generates will cause necrosis of the prostatic tissue and shrink the prostate. The TUNA device is inserted into the urethra using a rigid scope much like a cystoscope. The energy is delivered into the prostate using two needles that emerge from the sides of the device, through the urethral wall and into the prostate. The needle-based ablation devices are very effective at heating a localized area to a high enough temperature to cause necrosis. The treatment is typically performed in one session, but may require multiple sticks of the needles depending on the size of the prostate.

Surgery

If medical treatment fails, and the patient elects not to try office-based therapies or the physician determines the patient is a better candidate for transurethral resection of prostate (TURP), surgery may need to be performed. In general, TURP is still considered the gold standard of prostate interventions for patients that require a procedure. This involves removing (part of) the prostate through the urethra. There are also a number of new methods for reducing the size of an enlarged prostate, some of which have not been around long enough to fully establish their safety or side-effects. These include various

methods to destroy or remove part of the excess tissue while trying to avoid damaging what remains. Transurethral electrovaporization of the prostate (TVP), laser TURP, visual laser ablation (VLAP), ethanol injection, and others are studied as alternatives.

Newer techniques involving lasers in urology have emerged in the last 5–10 years, starting with the VLAP technique involving the Nd:YAG laser with contact on the prostatic tissue. A similar technology called Photoselective Vaporization of the Prostate (PVP) with the GreenLight (KTP) laser have emerged very recently. This procedure involves a high-power 80-watt KTP laser with a 550-micrometre laser fiber inserted into the prostate. This fiber has an internal reflection with a 70-degree deflecting angle. It is used to vaporize the tissue to the prostatic capsule. KTP lasers target haemoglobin as the chromophore and typically have a penetration depth of 2.0 mm (four times deeper than holmium).

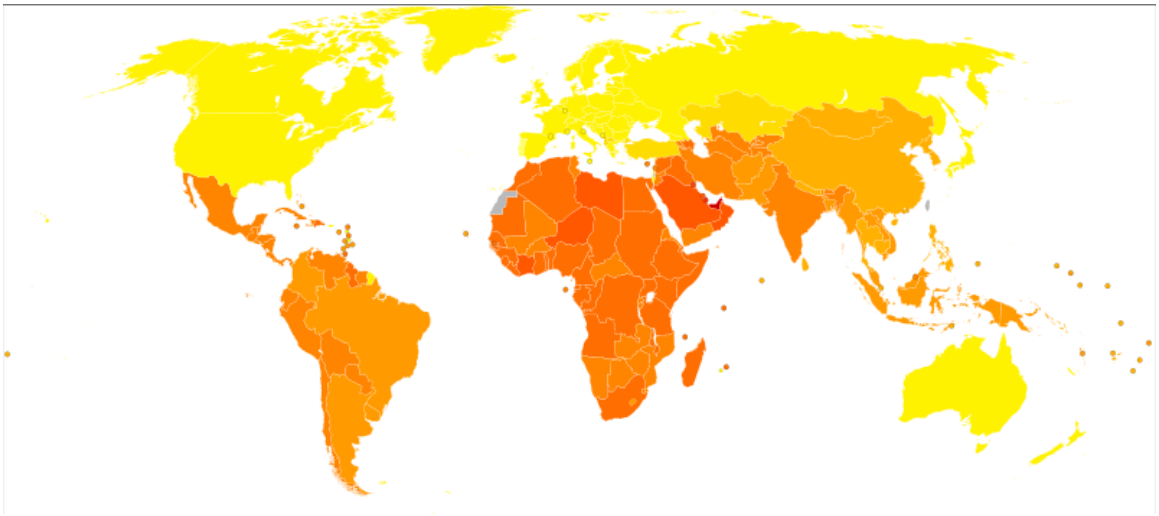
Another procedure termed Holmium Laser Ablation of the Prostate (HoLAP) has also been gaining acceptance around the world. Like KTP, the delivery device for HoLAP procedures is a 550 um disposable side-firing fiber that directs the beam from a high-power 100-watt laser at a 70-degree angle from the fiber axis. The holmium wavelength is 2,140 nm, which falls within the infrared portion of the spectrum and is invisible to the naked eye. Whereas KTP relies on haemoglobin as a chromophore, water within the target tissue is the chromophore for Holmium lasers. The penetration depth of Holmium lasers is <0.5 mm, avoiding complications associated with tissue necrosis often found with the deeper penetration and lower peak powers of KTP.

HoLEP, Holmium Laser Enucleation of the Prostate, is another Holmium laser procedure reported to carry fewer risks compared with either TURP or open prostatectomy. HoLEP is largely similar to the HoLAP procedure; the main difference is that this procedure is typically performed on larger prostates. Instead of ablating the tissue, the laser cuts a portion of the prostate, which is then cut into smaller pieces and flushed with irrigation fluid. As with the HoLAP procedure, there is little bleeding during or after the procedure.

Both wavelengths, KTP and Holmium, ablate approximately one to two grams of tissue per minute.

Post surgery care often involves placement of a Foley Catheter or a temporary Prostatic stent to permit healing and allow urine to drain from the bladder.

Epidemiology



Disability-adjusted life year for benign prostatic hypertrophy per 100,000 inhabitants in 2004.

- no data
- less than 20
- 20-28
- 28-36
- 36-44
- 44-52
- 52-60
- 60-68
- 68-76
- 76-84
- 84-92
- 92-100
- more than 100

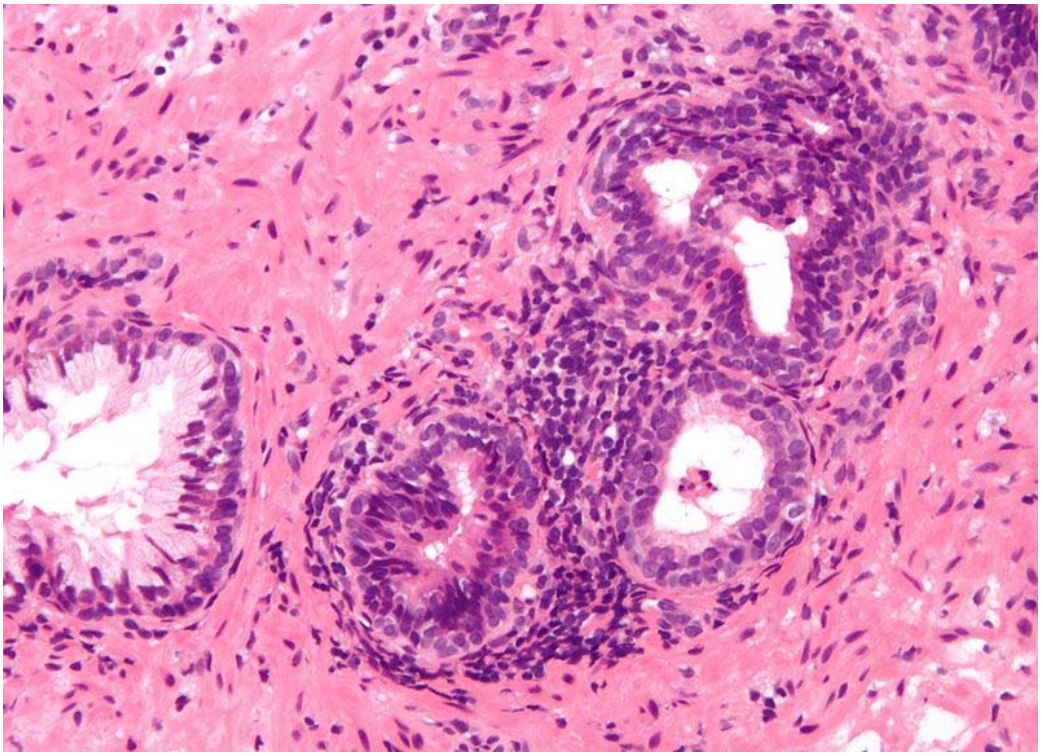
The prostate gets larger in most men as they get older, and, overall, 45% of men over the age of 46 can expect to suffer from the symptoms of BPH if they survive 30 years. Incidence rates increase from 3 cases per 1000 man-years at age 45–49 years, to 38 cases per 1000 man-years by the age of 75–79 years. Whereas the prevalence rate is 2.7% for men aged 45–49, it increases to 24% by the age of 80 years.

Chapter 7

Prostatitis and Acute Prostatitis

Prostatitis

Prostatitis



Micrograph showing an inflamed prostate gland, the histologic correlate of **prostatitis**. A normal non-inflamed prostatic gland is seen on the left of the image. H&E stain.

ICD-10	N41.
ICD-9	601
DiseasesDB	10801

MedlinePlus	000524
eMedicine	emerg/488
MeSH	D011472

Prostatitis is an inflammation of the prostate gland, in men. A prostatitis diagnosis is assigned at 8% of all urologist and 1% of all primary care physician visits in the United States.

Classification

The term *prostatitis* refers, in its strictest sense, to histological (microscopic) inflammation of the tissue of the prostate gland. Like all forms of inflammation, it can be associated with an appropriate response of the body to an infection, but it also occurs in the absence of infection.

in 1999, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) devised a new classification system.

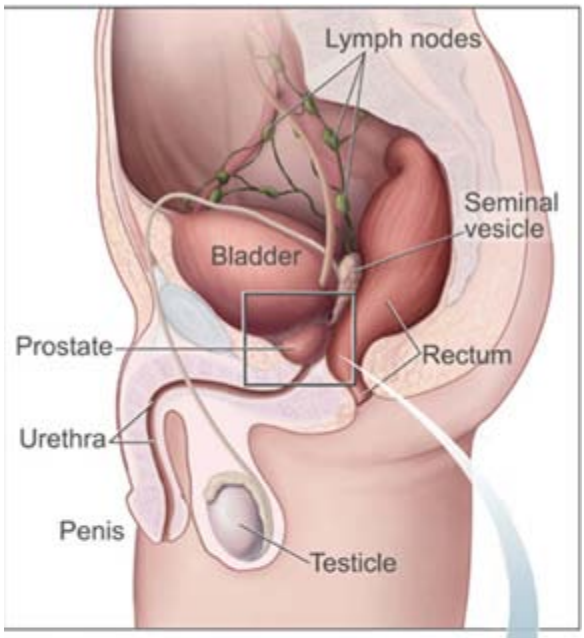
Category	Pain?	Bacteria?	WBCs?	NIDDK (Current)	Description	Meares/Stamey (Old)
I	yes	yes	yes	Acute prostatitis	**Acute prostatitis** is a bacterial infection of the prostate gland that requires urgent medical treatment.	Acute bacterial prostatitis
II	±	yes	yes	Chronic bacterial prostatitis	**Chronic bacterial prostatitis** is a relatively rare condition that usually presents as intermittent urinary tract infections.	Chronic bacterial prostatitis
IIIa	yes	no	yes	Inflammatory CP/CPPS	Chronic prostatitis/chronic pelvic pain syndrome, accounting for 90%-95% of prostatitis diagnoses, used to be known as *chronic nonbacterial prostatitis*.	Nonbacterial prostatitis
IIIb	yes	no	no	Noninflammatory CP/CPPS		Prostatodynia
IV	no	no	yes	Asymptomatic inflammatory prostatitis	**Asymptomatic inflammatory prostatitis** patients have no history of genitourinary pain complaints, but leukocytosis is noted, usually during evaluation for other conditions. Between 6-19% of men have pus cells in their semen but no symptoms.	(none)

In 1968, Meares and Stamey determined a classification technique based upon the culturing of bacteria. This classification is no longer used.

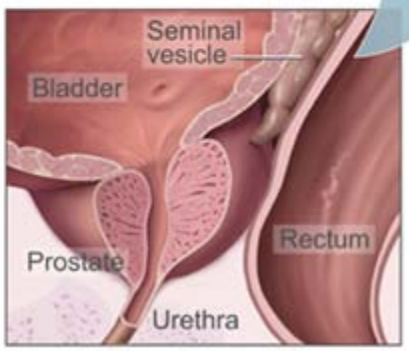
The conditions are distinguished by the different presentation of pain, white blood cells (WBCs) in the urine, duration of symptoms and bacteria cultured from the urine. To help express prostatic secretions that may contain WBCs and bacteria, prostate massage is sometimes used.

Acute prostatitis

Acute Prostatitis



This shows the prostate and nearby organs.



This shows the inside of the prostate, urethra, rectum, and bladder.

ICD-10 N41.0.

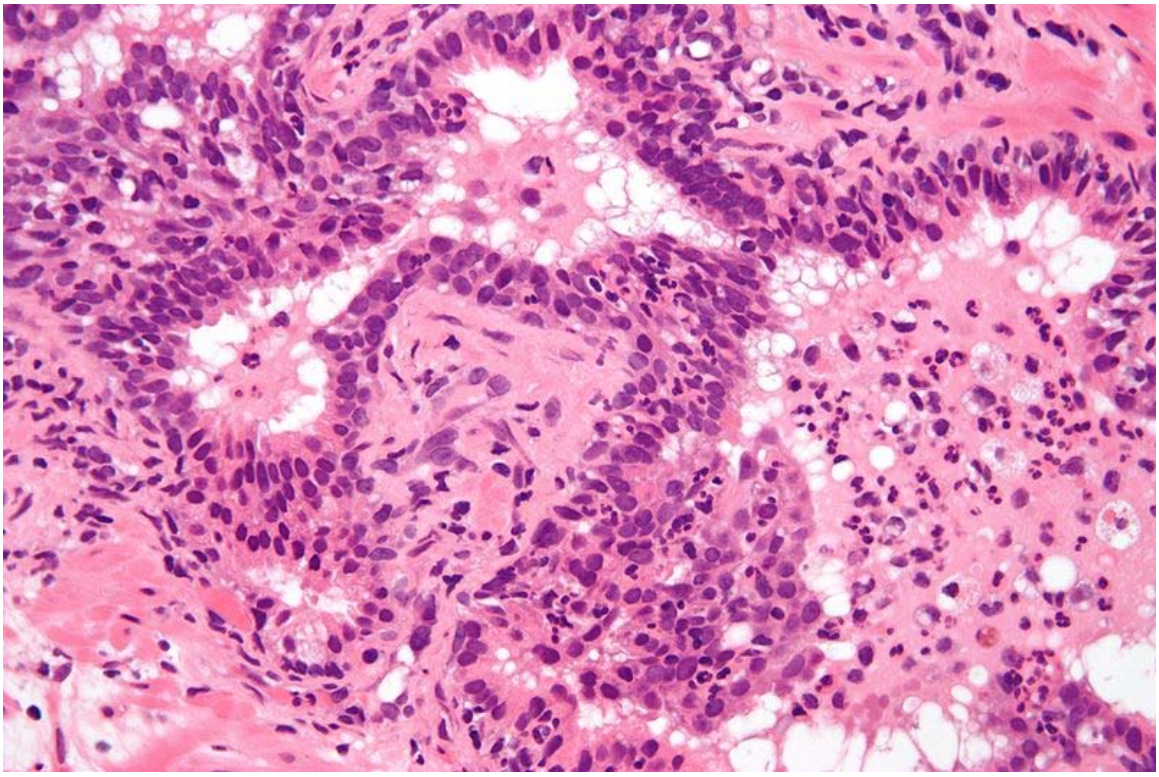
ICD-9	601.0
DiseasesDB	10801
MedlinePlus	000519
eMedicine	med/2845
MeSH	*D011472*

Acute prostatitis is a serious bacterial infection of the prostate gland. This infection is a medical emergency. It should be distinguished from other forms of prostatitis such as chronic bacterial prostatitis and chronic pelvic pain syndrome (CPPS).

Signs and symptoms

Men with this disease often have chills, fever, pain in the lower back and genital area, urinary frequency and urgency often at night, burning or painful urination, body aches, and a demonstrable infection of the urinary tract, as evidenced by white blood cells and bacteria in the urine. Acute prostatitis may be a complication of prostate biopsy.

Diagnosis



Micrograph showing a neutrophilic infiltration of prostatic glands - the histologic correlate of acute prostatitis. H&E stain.

Acute prostatitis is relatively easy to diagnose due to its symptoms that suggest infection. The organism may be found in blood or urine, and sometimes in both. Common bacteria are *Escherichia coli, Klebsiella, Proteus, Pseudomonas, Enterobacter, Enterococcus, Serratia,* and *Staphylococcus aureus.* This can be a medical emergency in some patients and hospitalization with intravenous antibiotics may be required. A complete blood count reveals increased white blood cells. Sepsis from prostatitis is very rare, but may occur in immunocompromised patients; high fever and malaise generally prompt blood cultures, which are often positive in sepsis. A prostate massage should never be done in a patient with suspected acute prostatitis, since it may induce sepsis. Since bacteria causing the prostatitis is easily recoverable from the urine, prostate massage is not required to make the diagnosis. Rectal palpation usually reveals an enlarged, exquisitely tender, swollen prostate gland, which is firm, warm, and, occasionally, irregular to the touch. C-reactive protein is elevated in most cases.

Prostate biopsies are not indicated as the (clinical) features (described above) are diagnostic. The histologic correlate of acute prostatitis is a neutrophilic infiltration of the prostate gland.

Acute prostatitis is associated with a transiently elevated PSA, i.e. the PSA is increased during an episode of acute prostatitis and then decreases again after it has resolved. PSA testing is not indicated in the context of uncomplicated acute prostatitis.

Treatment

Antibiotics are the first line of treatment in acute prostatitis (Cat. I). Antibiotics usually resolve acute prostatitis infections in a very short time. Appropriate antibiotics should be used, based on the microbe causing the infection. Some antibiotics have very poor penetration of the prostatic capsule, others, such as Ciprofloxacin, Co-trimoxazole and tetracyclines such as doxycycline penetrate well. In acute prostatitis, penetration of the prostate is not as important as for category II because the intense inflammation disrupts the prostate-blood barrier. It is more important to choose a bacteriocidal antibiotic (kills bacteria, e.g. quinolone) rather than a bacteriostatic antibiotic (slows bacterial growth, e.g. tetracycline) for acute potentially life threatening infections. Severely ill patients may need hospitalization, while nontoxic patients can be treated at home with bed rest, analgesics, stool softeners, and hydration. Patients in urinary retention are best managed with a suprapubic catheter or intermittent catheterization. Lack of clinical response to antibiotics should raise the suspicion of an abscess and prompt an imaging study such as a transrectal ultrasound (TRUS). E. coli is able to form a biofilm that may allow the pathogen to persist in the prostate.

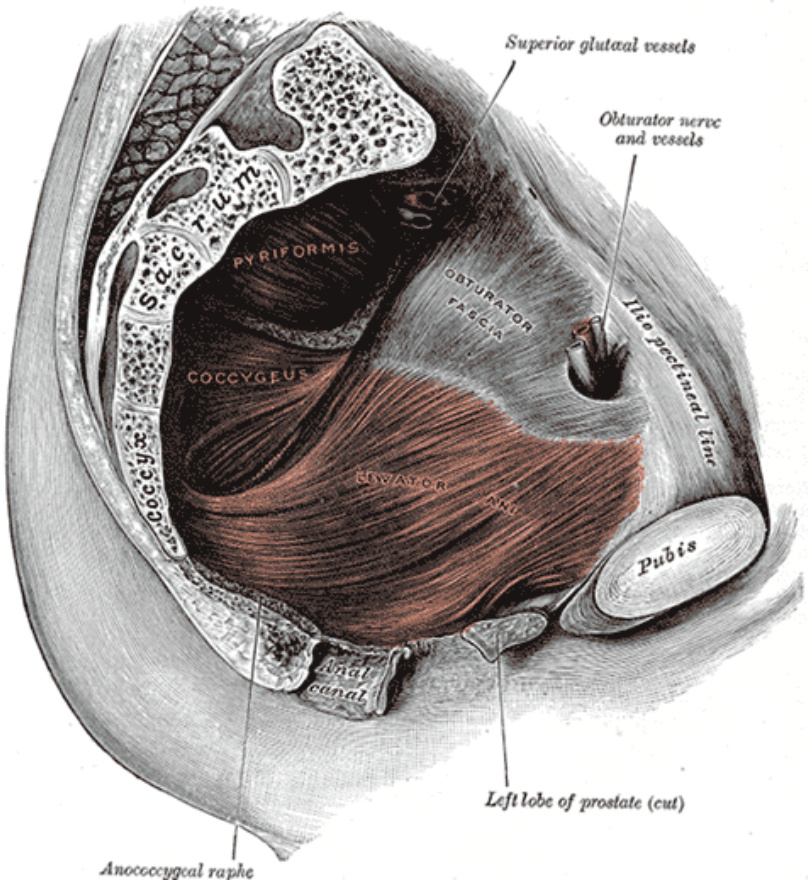
Prognosis

Full recovery without sequelae is usual.

Chapter 8

Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Chronic nonbacterial prostatitis



ICD-10	N41.1
ICD-9	601.1

DiseasesDB	10801
MedlinePlus	000524
eMedicine	med/1922
MeSH	*D011472*

Chronic nonbacterial prostatitis or **chronic prostatitis/chronic pelvic pain syndrome** (**CP/CPPS**) is a pelvic pain condition in men, and should be distinguished from other forms of prostatitis such as chronic bacterial prostatitis and acute bacterial prostatitis. This condition was previously known as prostatodynia (painful prostate).

Nomenclature

A distinction is sometimes made between "IIIa" (Inflammatory) and "IIIb" (Noninflammatory) forms of CP/CPPS, depending on whether pus cells (WBCs) can be found in the expressed prostatic secretions (EPS) of the patient. Some researchers have questioned the usefulness of this categorisation, calling for the Meares-Stamey four-glass test to be abandoned.

In 2007, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) began using the umbrella term **Urologic Chronic Pelvic Pain Syndromes** (UCPPS), for research purposes, to refer to pain syndromes associated with the bladder (i.e. interstitial cystitis/painful bladder syndrome, IC/PBS) and the prostate gland (i.e. chronic prostatitis/chronic pelvic pain syndrome, CP/CPPS).

Older terms for this condition are "prostatodynia" (prostate pain) and non-bacterial chronic prostatitis.

Signs and symptoms

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is characterised by pelvic or perineal pain without evidence of urinary tract infection, lasting longer than 3 months, as the key symptom. Symptoms may wax and wane. Pain can range from mild discomfort to debilitating. Pain may radiate to back and rectum, making sitting difficult. Dysuria, arthralgia, myalgia, unexplained fatigue, abdominal pain, constant burning pain in the penis, and frequency may all be present. Frequent urination and increased urgency may suggest interstitial cystitis (inflammation centred in bladder rather than prostate). Post-ejaculatory pain, mediated by nerves and muscles, is a hallmark of the condition, and serves to distinguish CP/CPPS patients from men with BPH or normal men. Some patients report low libido, sexual dysfunction and erectile difficulties.

Cause

Nerves, stress and hormones

In 2008, a literature review for the years 1966 to 2003 was performed using the MEDLINE database of the United States National Library of Medicine, finding that the symptoms of CP/CPPS appear to result from an interplay between psychological factors and dysfunction in the immune, neurological and endocrine systems.

Theories behind the disease include stress-driven hypothalamic-pituitary-adrenal axis dysfunction and adrenocortical hormone (endocrine) abnormalities, neurogenic inflammation, and myofascial pain syndrome. In the latter two categories, dysregulation of the local nervous system due to past trauma, infection or an anxious disposition and chronic albeit unconscious pelvic tensing lead to inflammation that is mediated by substances released by nerve cells (such as substance P). The prostate (and other areas of the genitourinary tract: bladder, urethra, testicles) can become inflamed by the action of the chronically activated pelvic nerves on the mast cells at the end of the nerve pathways. Similar stress-induced genitourinary inflammation has been shown experimentally in other mammals. However, there is no correlation between inflammation on histological examination of the prostate and the National Institutes of Health Chronic Prostatitis Symptom Index.

The bacterial infection theory that for so long had held sway in this field was shown to be unimportant in a 2003 study from the University of Washington team led by Dr Lee and Professor Richard Berger. The study found that one third of both normal men and patients had equal counts of similar bacteria colonizing their prostates. This view was endorsed by Dr Anthony Schaeffer, Professor and Chairman of the Department of Urology at Northwestern University, in a 2003 editorial of *The Journal of Urology*, in which he stated that *"...these data suggest that bacteria do not have a significant role in the development of the chronic pelvic pain syndrome"*, and a year later with his colleagues he published studies showing that antibiotics are essentially useless for CP/CPPS. Since the publication of these studies, the research focus has shifted from infection to neuromuscular, behavioral, psychological, and genetic etiologies for UCPPS (CP/CPPS and IC/PBS), where the interplay between the lower urinary tract and other physiological systems is stressed. UCPPS is now studied as a systemic disorder. In support of this approach, a 2005 study showed that stress is correlated to Cat III prostatitis.

Overlap with BPS/IC

Some researchers have suggested that CPPS is a form of bladder pain syndrome/interstitial cystitis (BPS/IC). In 2007 the NIDDK began to group IC/PBS and CP/CPPS under the umbrella term **Urologic Chronic Pelvic Pain Syndromes (UCPPS)**. Therapies shown to be effective in treating IC/PBS, such as quercetin, have also shown some efficacy in CP/CPPS. Recent research has focused on genomic and proteomic aspects of the related conditions.

Infection

Additional theories and observations include:

- **Nanobacteria** — In a preliminary 2005 open label study of 16 treatment-recalcitrant CPPS patients, controversial entities known as nanobacteria were proposed as a cause of prostatic calcification and symptoms found in CPPS. Patients were treated with EDTA (to dissolve the calcifications) and 3 months of tetracycline (a calcium-leaching antibiotic with anti-inflammatory effects, used here to kill the "pathogens"), and half had significant improvement in symptoms. Scientists have expressed strong doubts about whether nanobacteria are living organisms. Research in 2008 showed that "nanobacteria" are merely tiny lumps of abiotic limestone. Confirmation of the clinical efficacy of the treatment awaits placebo controlled studies.

- **Viruses** — The evidence supporting a viral cause of prostatitis and chronic pelvic pain syndrome is weak. Single case reports have implicated Herpes simplex virus (HSV) and Cytomegalovirus (CMV) but a study using PCR failed to demonstrate the presence of viral DNA in patients with chronic pelvic pain syndrome undergoing radical prostatectomy for localized prostate cancer. The reports implicating CMV must be interpreted with caution because in *all* cases the patients were immunocompromised. For HSV the evidence is weaker still and there is only one reported case and the causative role of the virus was not proven, and there are no reports of successful treatments using antiviral drugs such as aciclovir.

Climate

The ambient temperature appears to play a role as cold is frequently reported as causing symptom aggravation and heat is often reported to be ameliorating. It appears that cold is one of the factors that can trigger a process resulting in CP/CPPS. Cold also causes aggravation of symptoms and can initiate a relapse. A survey showed that the occurrence of prostatitis symptoms in men living in northern Finland —a cold climate—is higher than that reported in other parts of the world. This could be partly caused by the cold climate.

Diagnosis

There are no definitive diagnostic tests for CP/CPPS. This is a poorly understood disorder, even though it accounts for 90%-95% of prostatitis diagnoses. It is found in men of any age, with the peak incidence in men aged 35–45 years. CP/CPPS may be inflammatory (Category IIIa) or non-inflammatory (Category IIIb), based on levels of pus cells in expressed prostatic secretions (EPS), but these subcategories are of limited use clinically. In the inflammatory form, urine, semen, and other fluids from the prostate contain pus cells (dead white blood cells or WBCs), whereas in the non-inflammatory form no pus cells are present. Recent studies have questioned the distinction between

categories IIIa and IIIb, since both categories show evidence of inflammation if pus cells are ignored and other more subtle signs of inflammation, like cytokines, are measured.

In 2006, Chinese researchers found that men with categories IIIa and IIIb both had significantly and similarly raised levels of anti-inflammatory cytokine TGFβ1 and pro-inflammatory cytokine IFN-γ in their EPS when compared with controls; therefore measurement of these cytokines could be used to diagnose category III prostatitis. A 2010 study found that nerve growth factor could also be used as a biomarker of the condition.

For CP/CPPS patients, analysis of urine and expressed prostatic secretions for leukocytes is debatable, especially due to the fact that the differentiation between patients with inflammatory and non-inflammatory subgroups of CP/CPPS is not useful. Serum PSA tests, routine imaging of the prostate, and tests for Chlamydia trachomatis and Ureaplasma provide no benefit for the patient.

Extraprostatic abdominal/pelvic tenderness is present in >50% of patients with chronic pelvic pain syndrome but only 7% of controls. Healthy men have slightly more bacteria in their semen than men with CPPS. The high prevalence of WBCs and positive bacterial cultures in the asymptomatic control population raises questions about the clinical usefulness of the standard 4-glass test as a diagnostic tool in men with CP/CPPS. The use of the four-glass test by American urologists is now rare, with only 4% using it regularly.

Men with CP/CPPS are more likely than the general population to suffer from Chronic Fatigue Syndrome (CFS), and Irritable Bowel Syndrome (IBS).

Experimental tests that could be useful in the future include tests to measure semen and prostate fluid cytokine levels. Various studies have shown increases in markers for inflammation such as elevated levels of cytokines, myeloperoxidase, and chemokines.

Differential diagnosis

Some conditions have similar symptoms to chronic prostatitis: Bladder neck hypertrophy and urethral stricture may both cause similar symptoms through urinary reflux (*inter alia*), and can be excluded through flexible cytoscopy and urodynamic tests.

Treatment

A 2007 review article by Drs Potts and Payne in the *Cleveland Clinic Journal of Medicine* states:

"Indeed, chronic abacterial prostatitis (also known as chronic pelvic pain syndrome) is both the most prevalent form and also the least understood and the most challenging to evaluate and treat. This form of prostatitis may respond to non-prostate-centered treatment strategies such as physical therapy, myofascial trigger point release, and relaxation techniques."

Nonpharmalogical/noninvasive

Physical and psychological therapy

Category III prostatitis may have no initial trigger other than anxiety, often with an element of OCD, panic disorder, or other anxiety-spectrum problem. This is theorized to leave the pelvic area in a sensitized condition resulting in a loop of muscle tension and heightened neurological feedback (neural pain wind-up). Current protocols largely focus on stretches to release overtensed muscles in the pelvic or anal area (commonly referred to as trigger points), physical therapy to the area, and progressive relaxation therapy to reduce causative stress.

Aerobic exercise can help those sufferers who are not also suffering from Chronic Fatigue Syndrome (CFS) or whose symptoms are not exacerbated by exercise. Acupuncture has reportedly benefited some patients.

For chronic nonbacterial prostatitis (Cat III), also known as CP/CPPS, which makes up the majority of men diagnosed with "prostatitis", a treatment called the "Wise-Anderson Protocol" (aka the "Stanford Protocol"), has recently been published. This is a combination of:

- Medication (using tricyclic antidepressants and benzodiazepines)
- Psychological therapy (paradoxical relaxation, an advancement and adaptation, specifically for pelvic pain, of a type of progressive relaxation technique developed by Edmund Jacobson during the early 20th century)
- Physical therapy (trigger point release therapy on pelvic floor and abdominal muscles, and also yoga-type exercises with the aim of relaxing pelvic floor and abdominal muscles).

Biofeedback

Biofeedback physical therapy to relearn how to control pelvic floor muscles may be useful. According to an article by Yuan Li biofeedback is satisfactory for treatment of chronic prostatitis (with mainly voiding problems) during puberty.

Food allergies

Anecdotal evidence suggests that food allergies and intolerances may have a role in exacerbating CP/CPPS, perhaps through mast cell mediated mechanisms. Specifically patients with gluten intolerance or celiac disease report severe symptom flares after sustained gluten ingestion. Patients may therefore find an elimination diet helpful in lessening symptoms by identifying problem foods. Studies are lacking in this area.

Pharmacological

There is now a substantial list of medications used to treat this disorder. A brief mention of the more common drugs used to treat this condition is:

- Antibiotics: Antibiotics, the old mainstay of treatment, cannot be recommended for men with longstanding, previously treated CP/CPPS. However, even though well-designed clinical trials have failed to demonstrate their efficacy, standard treatment often still consists of prolonged courses of antibiotics. The utility of a trial of antimicrobial treatment is debatable in treatment-naive patients. The use of antibiotics is generally discouraged. Some state improvement on antibiotics is likely to be evanescent, and due to the anti-inflammatory effects of the antibiotic.

- Heparinoids: A large multicenter prospective randomized controlled study showed that Elmiron was slightly better than placebo in treating the symptoms of CPPS, however the primary endpoint did not reach statistical significance.

- Alpha blockers. The effectiveness of alpha blockers (tamsulosin, alfuzosin) is questionable in men with CPPS. A 2006 meta analysis found that they are moderately beneficial when the duration of therapy was at least 3 months. However a 2004 trial found no benefit from alfuzosin during 6 weeks of treatment and a 2008 clinical trial of alfuzosin found it was no better than placebo for treating CPPS in treatment naive recently diagnosed men.

- At least one study suggests that multi-modal therapy (aimed at different pathways such as inflammation and neuromuscular dysfunction simultaneously) is better long term than monotherapy.

- Commonly used therapies that have not been properly evaluated in clinical trials although there is supportive anecdotal evidence gabapentin, benzodiazepines and amitriptyline.

Phytotherapy

- Pollen extract (Cernilton) has also been shown effective in randomized placebo controlled trials.

- Quercetin has shown effective in a randomized, placebo-controlled trial in chronic prostatitis using 500 mg twice a day for 4 weeks Subsequent studies showed that quercetin, a mast cell inhibitor, reduces inflammation and oxidative stress in the prostate.

Surgery

Surgery (including minimally invasive) is recommended only for definitive indications and not generally for CP/CPPS.

Transurethral needle ablation of the prostate (TUNA) has been shown to be ineffective in trials.

Epidemiology

The annual prevalence in the general population of chronic pelvic pain syndrome is 0.5%. 38% of primary care providers, when presented with a vignette of a man with CPPS, indicate that they have never seen such a patient. However, the overall prevalence of symptoms suggestive of CP/CPPS is 6.3%. The role of the prostate was questioned in the etiology of CP/CPPS when both men and women in the general population were tested using the (1) National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) —with the female homolog of each male anatomical term use on questionnaires for female participants— (2) the International Prostate Symptom Score (IPSS), and (3) additional questions on pelvic pain. The prevalence of symptoms suggestive of CPPS in this selected population was 5.7% in women and 2.7% in men, placing in doubt the role of the prostate gland. New evidence suggests that the prevalence of CP/CPPS is much higher in teenage males than once suspected.

Prognosis

In recent years the prognosis for CP/CPPS has improved greatly with the advent of multimodal treatment, phytotherapy, protocols aimed at quieting the pelvic nerves through myofascial trigger point release and anxiety control, and chronic pain therapy.

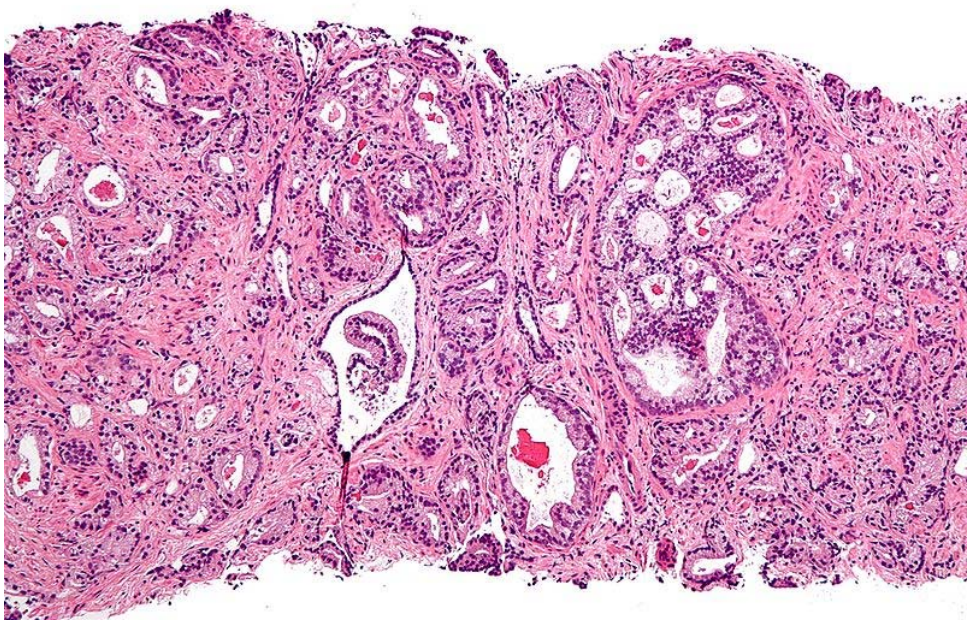
Notable cases

- John Anderson — Deputy Prime Minister of Australia
- James Boswell — author of Life of Samuel Johnson
- John Cleese — British actor
- Vincent Gallo — movie director
- Glenn Gould — pianist
- John F Kennedy — President of the United States of America
- Howard Stern — radio personality
- William Styron — author (Sophie's Choice)

Chapter 9

Prostate Cancer

Prostate cancer



Micrograph of prostate adenocarcinoma, acinar type, the most common type of prostate cancer. Gleason pattern 4. Needle biopsy. H&E stain.

ICD-10	C61.
ICD-9	185
OMIM	176807
DiseasesDB	10780
MedlinePlus	000380

eMedicine	radio/574
MeSH	D011471

Prostate cancer is a form of cancer that develops in the prostate, a gland in the male reproductive system. Most prostate cancers are slow growing; however, there are cases of aggressive prostate cancers. The cancer cells may metastasize (spread) from the prostate to other parts of the body, particularly the bones and lymph nodes. Prostate cancer may cause pain, difficulty in urinating, problems during sexual intercourse, or erectile dysfunction. Other symptoms can potentially develop during later stages of the disease.

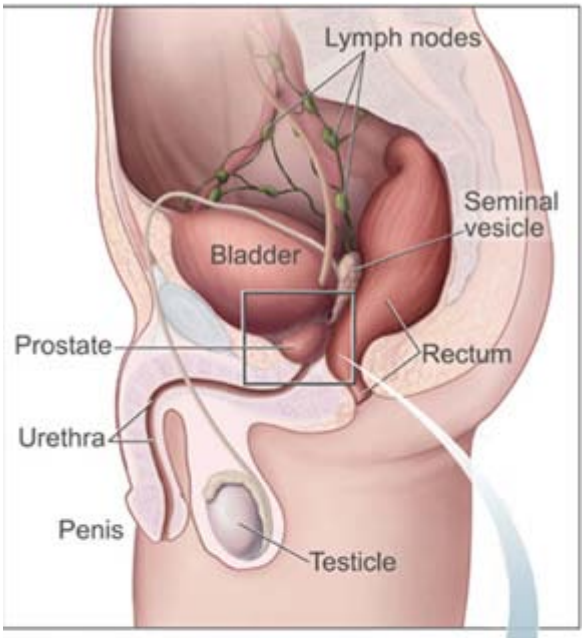
Rates of detection of prostate cancers vary widely across the world, with South and East Asia detecting less frequently than in Europe, and especially the United States. Prostate cancer tends to develop in men over the age of fifty and although it is one of the most prevalent types of cancer in men, many never have symptoms, undergo no therapy, and eventually die of other causes. This is because cancer of the prostate is, in most cases, slow-growing, symptom-free, and since men with the condition are older they often die of causes unrelated to the prostate cancer, such as heart/circulatory disease, pneumonia, other unconnected cancers, or old age. About 2/3 of cases are slow growing, the other third more aggressive and fast developing.

Many factors, including genetics and diet, have been implicated in the development of prostate cancer. The presence of prostate cancer may be indicated by symptoms, physical examination, prostate-specific antigen (PSA), or biopsy. The PSA test increases cancer detection but does not decrease mortality. Suspected prostate cancer is typically confirmed by taking a biopsy of the prostate and examining it under a microscope. Further tests, such as CT scans and bone scans, may be performed to determine whether prostate cancer has spread.

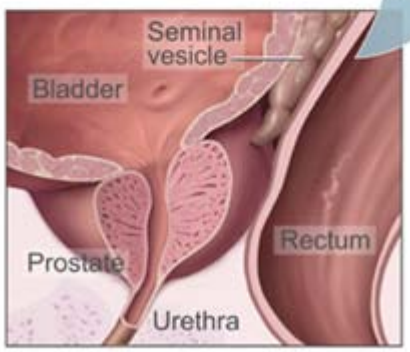
Treatment options for prostate cancer with intent to cure are primarily surgery, radiation therapy, and proton therapy. Other treatments, such as hormonal therapy, chemotherapy, cryosurgery, and high intensity focused ultrasound (HIFU) also exist, depending on the clinical scenario and desired outcome.

The age and underlying health of the man, the extent of metastasis, appearance under the microscope, and response of the cancer to initial treatment are important in determining the outcome of the disease. The decision whether or not to treat localized prostate cancer (a tumor that is contained within the prostate) with curative intent is a patient trade-off between the expected beneficial and harmful effects in terms of patient survival and quality of life.

Overview



This shows the prostate and nearby organs.



This shows the inside of the prostate, urethra, rectum, and bladder.

The prostate is a part of the male reproductive system that helps make and store seminal fluid. In adult men, a typical prostate is about three centimeters long and weighs about twenty grams. It is located in the pelvis, under the urinary bladder and in front of the rectum. The prostate surrounds part of the urethra, the tube that carries urine from the bladder during urination and semen during ejaculation. Because of its location, prostate diseases often affect urination, ejaculation, and rarely defecation. The prostate contains many small glands which make about twenty percent of the fluid constituting semen. In prostate cancer, the cells of these prostate glands mutate into cancer cells. The prostate glands require male hormones, known as androgens, to work properly. Androgens include testosterone, which is made in the testes; dehydroepiandrosterone, made in the adrenal glands; and dihydrotestosterone, which is converted from testosterone within the prostate itself. Androgens are also responsible for secondary sex characteristics such as facial hair and increased muscle mass.

Classification

An important part of evaluating prostate cancer is determining the stage, or how far the cancer has spread. Knowing the stage helps define prognosis and is useful when selecting therapies. The most common system is the four-stage TNM system (abbreviated from Tumor/Nodes/Metastases). Its components include the size of the tumor, the number of involved lymph nodes, and the presence of any other metastases.

The most important distinction made by any staging system is whether or not the cancer is still confined to the prostate. In the TNM system, clinical T1 and T2 cancers are found only in the prostate, while T3 and T4 cancers have spread elsewhere. Several tests can be used to look for evidence of spread. These include computed tomography to evaluate spread within the pelvis, bone scans to look for spread to the bones, and endorectal coil magnetic resonance imaging to closely evaluate the prostatic capsule and the seminal vesicles. Bone scans should reveal osteoblastic appearance due to *increased* bone density in the areas of bone metastasis—opposite to what is found in many other cancers that metastasize.

After a prostate biopsy, a pathologist looks at the samples under a microscope. If cancer is present, the pathologist reports the grade of the tumor. The grade tells how much the tumor tissue differs from normal prostate tissue and suggests how fast the tumor is likely to grow. The Gleason system is used to grade prostate tumors from 2 to 10, where a Gleason score of 10 indicates the most abnormalities. The pathologist assigns a number from 1 to 5 for the most common pattern observed under the microscope, then does the same for the second-most-common pattern. The sum of these two numbers is the Gleason score. The Whitmore-Jewett stage is another method sometimes used.

Signs and symptoms

Early prostate cancer usually causes no symptoms. Often it is diagnosed during the workup for an elevated PSA noticed during a routine checkup.

Sometimes, however, prostate cancer does cause symptoms, often similar to those of diseases such as benign prostatic hyperplasia. These include frequent urination, nocturia (increased urination at night), difficulty starting and maintaining a steady stream of urine, hematuria (blood in the urine), and dysuria (painful urination).

Prostate cancer is associated with urinary dysfunction as the prostate gland surrounds the prostatic urethra. Changes within the gland, therefore, directly affect urinary function. Because the *vas deferens* deposits seminal fluid into the prostatic urethra, and secretions from the prostate gland itself are included in semen content, prostate cancer may also cause problems with sexual function and performance, such as difficulty achieving erection or painful ejaculation.

Advanced prostate cancer can spread to other parts of the body, possibly causing additional symptoms. The most common symptom is bone pain, often in the vertebrae

(bones of the spine), pelvis, or ribs. Spread of cancer into other bones such as the femur is usually to the proximal part of the bone. Prostate cancer in the spine can also compress the spinal cord, causing leg weakness and urinary and fecal incontinence.

Researchers found that men who going bald at 20 of age will have twice the risk of prostate cancer in later life. It is not valid for who lost their hair when they were 30 or 40. Baldness is caused by DHT, a chemical produced by the male hormone testosterone.

Causes

The specific causes of prostate cancer remain unknown. The primary risk factors are age and family history. Prostate cancer is very uncommon in men younger than 45, but becomes more common with advancing age. The average age at the time of diagnosis is 70. However, many men never know they have prostate cancer. Autopsy studies of Chinese, German, Israeli, Jamaican, Swedish, and Ugandan men who died of other causes have found prostate cancer in thirty percent of men in their 50s, and in eighty percent of men in their 70s. Men who have first-degree family members with prostate cancer appear to have double the risk of getting the disease compared to men without prostate cancer in the family. This risk appears to be greater for men with an affected brother than for men with an affected father. In the United States in 2005, there were an estimated 230,000 new cases of prostate cancer and 30,000 deaths due to prostate cancer. Men with high blood pressure are more likely to develop prostate cancer. A 2010 study found that prostate basal cells were the most common site of origin for prostate cancers.

Genetic

Genetic background may contribute to prostate cancer risk, as suggested by associations with race, family, and specific gene variants. Men with one first-degree relative with prostate cancer have a twofold higher risk, and those with two first-degree relatives have a fivefold greater risk of developing prostate cancer compared with men with no family history. In the United States, prostate cancer more commonly affects black men than white or Hispanic men, and is also more deadly in black men. In contrast, the incidence and mortality rates for Hispanic men are one third lower than for non-Hispanic whites. Men who have a brother or father with prostate cancer have twice the risk of developing prostate cancer. Studies of twins in Scandinavia suggest that forty percent of prostate cancer risk can be explained by inherited factors.

No single gene is responsible for prostate cancer; many different genes have been implicated. Mutations in *BRCA1* and *BRCA2*, important risk factors for ovarian cancer and breast cancer in women, have also been implicated in prostate cancer. Other linked genes include the Hereditary Prostate cancer gene 1 (HPC1), the androgen receptor, and the vitamin D receptor. TMPRSS2-ETS gene family fusion, specifically TMPRSS2-ERG or TMPRSS2-ETV1/4 promotes cancer cell growth.

Loss of cancer suppressor genes, early in the prostatic carcinogenesis, have been localized to chromosomes *8p*, *10q*, *13q*,and *16q*. P53 mutations in the primary prostate

cancer are relatively low and are more frequently seen in metastatic settings, hence, p53 mutations are late event in pathology of prostate cancer. Other tumor suppressor genes that are thought to play a role in prostate cancer include PTEN (gene) and KAI1. "Up to 70 percent of men with prostate cancer have lost one copy of the PTEN gene at the time of diagnosis" Relative frequency of loss of E-cadherin and CD44 has also been observed.

Diet

Evidence from epidemiological studies supports a possible protective role in reducing prostate cancer for dietary Vitamin B6, selenium, vitamin E, lycopene, and soy foods. A study in 2007 cast doubt on the effectiveness of lycopene (found in tomatoes) in reducing the risk of prostate cancer. Lower blood levels of vitamin D may increase the risk of developing prostate cancer. This may be linked to lower exposure to ultraviolet (UV) light, since UV light exposure can increase vitamin D in the body.

Studies comparing men who live in areas with high levels of selenium to men in areas with low levels suggest that this mineral protects against prostate cancer. Selenium is believed to reduce the risk of developing prostate cancer because it keeps cells from proliferating or dying off in a rapid or unusual way. An analysis in 2002 of the Nutritional Prevention of Cancer Trial revealed that the men who took selenium supplements daily were half as likely to be diagnosed with prostate cancer. These findings have been confirmed in most observational studies. However, in 2008, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) indicated that neither selenium nor vitamin E, alone or in combination, was effective for the primary prevention of prostate cancer. Whether or not selenium helps prevent prostate cancer, researchers at the Dana-Farber Cancer Institute in Boston found that higher selenium levels in the blood may worsen prostate cancer in many men who already have the disease.

Green tea may be protective (due to its catechins content), although the most comprehensive clinical study indicates that it has no protective effect. Other holistic methods are also studied.

Research published in the Journal of the National Cancer Institute suggests that taking multivitamins more than seven times a week can increase the risks of contracting the disease. This research was unable to highlight the exact vitamins responsible for this increase (almost double), although they suggest that vitamin A, vitamin E and beta-carotene may lie at its heart. It is advised that those taking multivitamins never exceed the stated daily dose on the label.

A 2007 study published in the Journal of the National Cancer Institute found that men eating cauliflower, broccoli, or one of the other cruciferous vegetables, more than once a week were 40% less likely to develop prostate cancer than men who rarely ate those vegetables. The phytochemicals indole-3-carbinol and diindolylmethane, found in cruciferous vegetables, has antiandrogenic and immune modulating properties.

Many doctors prescribe supplements to prostate cancer patients but currently the efficacy of nutrient supplements is still unknown. Supplements may not be as beneficial to prostate health as micronutrients obatined naturally from the diet.

Folic acid supplements have recently been linked to an increase in risk of developing prostate cancer. A ten-year research study led by University of Southern California researchers showed that men who took daily folic acid supplements of 1 mg were three times more likely to be diagnosed with prostate cancer than men who took a placebo. Folate plays a complex role in prostate cancer and folic acid supplements have a different effect on prostate cancer than folate naturally found in foods. The supplement form, folic acid, is more bioavailable in the body compared with dietary sources of folate. Folate hydrolase activity is associated with prostate-specific antigen.

A small Swedish study of 254 subjects, with a median age of 64, and a follow up of 5 years suggested that folate status is not protective against prostate cancer, however, and like folic acid may even result in a 3 fold increase in early prostate cancer development and risk. Supplements and multivitamins, alcohol and drug consumption, GI disorders, and folate bioavailability were not analyzed in this study.

High alcohol intake may increase the risk of prostate cancer and interfere with folate metabolism. Low folate intake and high alcohol intake may increase the risk of prostate cancer to a greater extent than the sole effect of either one by itself. A case control study consisting of 137 veterans addressed this hypothesis and the results were that high folate intake was related to a 79% lower risk of developing prostate cancer and there was no association between alcohol consumption by itself and prostate cancer risk. Folate's effect however was only significant when coupled with low alcohol intake. There is a significant decrease in risk of prostate cancer with increasing dietary folate intake but this association only remains in individuals with low levels of alcohol consumption. There was no association found in this study between folic acid supplements and risk of prostate cancer.

The prostate gland has a high concentration of zinc so zinc may play a role in prostate cancer. Researchers studied the relationship between zinc supplement intake of 100 mg/day and the risk of prostate cancer in 46 974 US men over a 14 year period and reported in 2003 that long term zinc supplement of over 100 mg/day intake seemed to be associated with approximately double the risk of developing prostate cancer. Greater intake of milk, calcium, or dairy calcium has been consistently associated with an elevated risk of prostate cancer in several studies

Medication exposure

There are also some links between prostate cancer and medications, medical procedures, and medical conditions. Use of the cholesterol-lowering drugs known as the statins may also decrease prostate cancer risk.

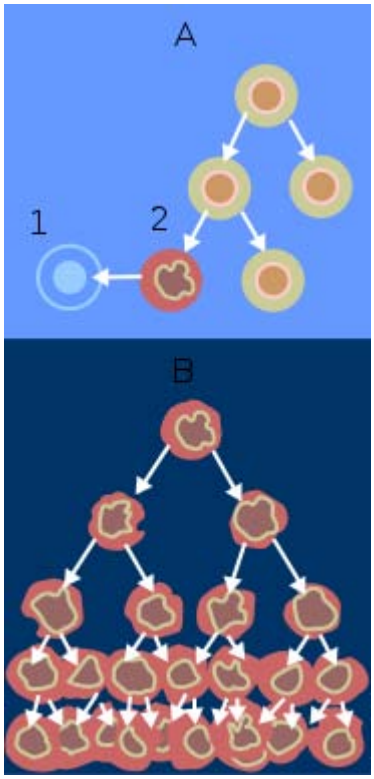
Infection or inflammation of the prostate (prostatitis) may increase the chance for prostate cancer while another study shows infection may help prevent prostate cancer by increasing blood to the area. In particular, infection with the sexually transmitted infections chlamydia, gonorrhea, or syphilis seems to increase risk. Finally, obesity and elevated blood levels of testosterone may increase the risk for prostate cancer. There is an association between vasectomy and prostate cancer however more research is needed to determine if this is a causative relationship.

Research released in May 2007, found that US war veterans who had been exposed to Agent Orange had a 48% increased risk of prostate cancer recurrence following surgery.

Viral

In 2006, researchers associated a previously unknown retrovirus, Xenotropic MuLV-related virus or XMRV, with human prostate tumors. Subsequent reports on the virus have been contradictory. A group of US researchers found XMRV protein expression in human prostate tumors, while German scientists failed to find XMRV-specific antibodies or XMRV-specific nucleic acid sequences in prostate cancer samples.

Pathophysiology



When normal cells are damaged beyond repair, they are eliminated by apoptosis. Cancer cells avoid apoptosis and continue to multiply in an unregulated manner.

Prostate cancer is classified as an adenocarcinoma, or glandular cancer, that begins when normal semen-secreting prostate gland cells mutate into cancer cells. The region of prostate gland where the adenocarcinoma is most common is the peripheral zone. Initially, small clumps of cancer cells remain confined to otherwise normal prostate glands, a condition known as carcinoma in situ or prostatic intraepithelial neoplasia (PIN). Although there is no proof that PIN is a cancer precursor, it is closely associated with cancer. Over time, these cancer cells begin to multiply and spread to the surrounding prostate tissue (the stroma) forming a tumor. Eventually, the tumor may grow large enough to invade nearby organs such as the seminal vesicles or the rectum, or the tumor cells may develop the ability to travel in the bloodstream and lymphatic system. Prostate cancer is considered a malignant tumor because it is a mass of cells that can invade other parts of the body. This invasion of other organs is called metastasis. Prostate cancer most commonly metastasizes to the bones, lymph nodes, and may invade rectum, bladder and lower ureters after local progression.

The prostate is a zinc accumulating, citrate producing organ. The protein ZIP1 is responsible for the active transport of zinc into prostate cells. One of zinc's important roles is to change the metabolism of the cell in order to produce citrate, an important component of semen. The process of zinc accumulation, alteration of metabolism, and citrate production is energy inefficient, and prostate cells sacrifice enormous amounts of energy (ATP) in order to accomplish this task. Prostate cancer cells are generally devoid of zinc. This allows prostate cancer cells to save energy not making citrate, and utilize the new abundance of energy to grow and spread. The absence of zinc is thought to occur via a silencing of the gene that produces the transporter protein ZIP1. ZIP1 is now called a tumor suppressor gene product for the gene SLC39A1. The cause of the epigenetic silencing is unknown. Strategies which transport zinc into transformed prostate cells effectively eliminate these cells in animals. Zinc inhibits NF-κB pathways, is anti-proliferative, and induces apoptosis in abnormal cells. Unfortunately, oral ingestion of zinc is ineffective since high concentrations of zinc into prostate cells is not possible without the active transporter, ZIP1.

RUNX2 is a transcription factor that prevents cancer cells from undergoing apoptosis thereby contributing to the development of prostate cancer.

The PI3k/Akt signaling cascade works with the transforming growth factor beta/SMAD signaling cascade to ensure prostate cancer cell survival and protection against apoptosis. X-linked inhibitor of apoptosis (XIAP) is hypothesized to promote prostate cancer cell survival and growth and is a target of research because if this inhibitor can be shut down then the apoptosis cascade can carry on its function in preventing cancer cell proliferation. Macrophage inhibitory cytokine-1 (MIC-1) stimulates the focal adhesion kinase (FAK) signaling pathway which leads to prostate cancer cell growth and survival.

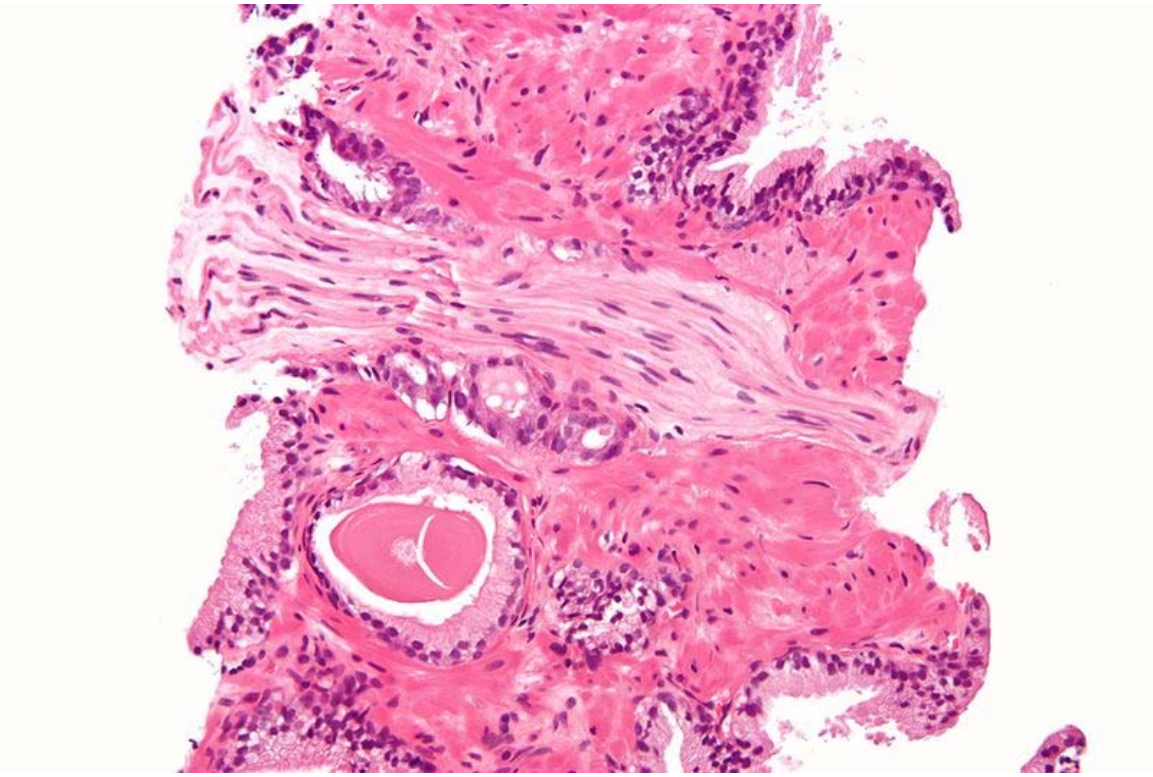
The androgen receptor helps prostate cancer cells to survive and is a target for many anti cancer research studies; so far, inhibiting the androgen receptor has only proven to be effective in mouse studies. Prostate specific membrane antigen (PSMA) stimulates the development of prostate cancer by increasing folate levels for the cancer cells to use to

survive and grow; PSMA increases available folates for use by hydrolyzing glutamated folates.

Diagnosis

The only test that can fully confirm the diagnosis of prostate cancer is a biopsy, the removal of small pieces of the prostate for microscopic examination. However, prior to a biopsy, several other tools may be used to gather more information about the prostate and the urinary tract. Digital rectal examination may allow a doctor to detect prostate abnormalities. Cystoscopy shows the urinary tract from inside the bladder, using a thin, flexible camera tube inserted down the urethra. Transrectal ultrasonography creates a picture of the prostate using sound waves from a probe in the rectum.

Biopsy



Micrograph showing a prostate cancer (conventional adenocarcinoma) with perineural invasion. H&E stain.

If cancer is suspected, a biopsy is offered expediently. During a biopsy a urologist or radiologist obtains tissue samples from the prostate via the rectum. A biopsy gun inserts and removes special hollow-core needles (usually three to six on each side of the prostate) in less than a second. Prostate biopsies are routinely done on an outpatient basis and rarely require hospitalization. Fifty-five percent of men report discomfort during prostate biopsy.

Gleason score

The tissue samples are then examined under a microscope to determine whether cancer cells are present, and to evaluate the microscopic features (or Gleason score) of any cancer found. Prostate specific membrane antigen is a transmembrane carboxypeptidase and exhibits folate hydrolase activity. This protein is overexpressed in prostate cancer tissues and is associated with a higher Gleason score.

Tumor markers

Tissue samples can be stained for the presence of PSA and other tumor markers in order to determine the origin of malignant cells that have metastasized.

Small cell carcinoma is a very rare (1%) type of prostate cancer that cannot be diagnosed using the PSA. As of 2009 researchers are trying to determine the best way to screen for this type of prostate cancer because it is a relatively unknown and rare type of prostate cancer but very serious and quick to spread to other parts of the body. Possible methods include chromatographic separation methods by mass spectrometry, or protein capturing by immunoassays or immunized antibodies. The test method will involve quantifying the amount of the biomarker PCI, with reference to the Gleason Score. Not only is this test quick, it is also sensitive. It can detect patients in the diagnostic grey zone, particularly those with a serum free to total Prostate Specific Antigen ratio of 10-20%.

The oncoprotein BCL-2, has been associated with the development of androgen-independent prostate cancer due to its high levels of expression in androgen-independent tumours in advanced stages of the pathology. The upregulation of BCL-2 after androgen ablation in prostate carcinoma cell lines and in a castrated-male rat model further established a connection between BCL-2 expression and prostate cancer progression.

The expression of Ki-67 by immunohistochemistry may be a significant predictor of patient outcome for men with prostate cancer.

Under investigation

At present, an active area of research involves non-invasive methods of prostate tumor detection. Adenoviruses modified to transfect tumor cells with harmless yet distinct genes (such as luciferase) have proven capable of early detection. So far, however, this area of research has been tested only in animal and LNCaP cell models.

PCA3

Another potential non-invasive method of early prostate tumor detection is through a molecular test that detects the presence of cell-associated PCA3 mRNA in urine. PCA3 mRNA is expressed almost exclusively by prostate cells and has been shown to be highly over-expressed in prostate cancer cells. PCA3 is not a replacement for PSA but an additional tool to help decide whether, in men suspected of having prostate cancer, a

biopsy is really needed. The higher the expression of PCA3 in urine, the greater the likelihood of a positive biopsy, i.e., the presence of cancer cells in the prostate.

Early prostate cancer antigen-2

It was reported in April 2007 that a new blood test for early prostate cancer antigen-2 (EPCA-2) that may alert men if they have prostate cancer and how aggressive it will be is being researched.

Thrombophlebitis is associated with an increased risk of prostate cancer and may be a good way for physicians to remind themselves to screen patients with thrombophlebitis for prostate cancer as well since these two are closely linked.

Prostate mapping

Prostate mapping is a method of diagnosis that may be accurate in determining the precise location and aggressiveness of a tumor. It uses a combination of multi-sequence MRI imaging techniques and a template-guided biopsy system, and involves taking multiple biopsies through the skin that lies in front of the rectum rather than through the rectum itself. The procedure is carried out under general anesthetic.

Prostasomes

Epithelial cells of the prostate secrete prostasomes as well as PSA. Prostasomes are membrane–surrounded, prostate-derived organelles that appear extracellularly, and one of their physiological functions is to protect the sperm from attacks by the female immune system. Cancerous prostate cells continue to synthesize and secrete prostasomes, and may be shielded against immunological attacks by these prostasomes. Research of several aspects of prostasomal involvement in prostate cancer has been performed.

Screening

Prostate cancer screening is an attempt to find unsuspected cancers, and may lead to more specific follow-up tests such as a biopsy, with cell samples taken for closer study. Options include the digital rectal exam (DRE) and the prostate-specific antigen (PSA) blood test. A 2010 analysis concluded that routine screening with either a DRE or PSA is not supported by the evidence as there is no mortality benefit from screening.

Modern screening tests have found cancers that might never have developed into serious disease, and that "the slight reduction of risk by surgically removing the prostate or treating it with radiation may not outweigh the substantial side effects of these treatments," an opinion also shared by the CDC.

Prevention

A comprehensive worldwide report Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective compiled by the World Cancer Research Fund and the American Institute for Cancer Research reports a significant relation between lifestyle (including food consumption) and cancer prevention. Other research also supports this finding. Exercise and diet may help prevent prostate cancer to the same extent as medications such as alpha-blockers and 5-alpha-reductase inhibitors. The potential role of diet in preventing prostate cancer is discussed in greater detail in the diet section.

Two medications which block the conversion of testosterone to dihydrotestosterone, finasteride and dutasteride, have also shown some promise. The use of these medications for primary prevention is still in the testing phase, and they are not widely used for this purpose. A 2008 study found that finasteride reduces the incidence of prostate cancer by 30%, without any increase in the risk of High-Grade prostate cancer. In the original study it turns out that the smaller prostate caused by finasteride means that a doctor is more likely to hit upon cancer nests and more likely to find aggressive-looking cells.

Compared to placebo treatment, taking 5-alpha-reductase inhibitors (5-ARIs) can reduce a man’s risk of being diagnosed with prostate cancer from around 5–9% to around 4-6% during up to 7 years of treatment, according to a Cochrane Review of studies.

Ejaculation frequency

More frequent ejaculation also may decrease a man's risk of prostate cancer. One study showed that men who ejaculated 3-5 times a week at the age of 15-19 had a decreased rate of prostate cancer when they are old, though other studies have shown no benefit. The results contradict those of previous studies, which have suggested that having had many sexual partners, or a high frequency of sexual activity, increases the risk of prostate cancer by up to 40 percent. A key difference may be that these earlier studies defined sexual activity as sexual intercourse, whereas this study focused on the number of ejaculations, whether or not intercourse was involved. Another study completed in 2004 reported that "Most categories of ejaculation frequency were unrelated to risk of prostate cancer. However, high ejaculation frequency was related to decreased risk of total prostate cancer." The report abstract concluded, "Our results suggest that ejaculation frequency is not related to increased risk of prostate cancer."

Diet

Oils and fatty acids

polyunsaturated fatty acids (PUFAs) increased prostate tumor growth,and has sped up histopathological progression, and decreased survival, while the omega-3 fatty acids, in the same situation, had the opposite, beneficial effect.

Men with high serum linoleic acid, but not palmitic, can reduce the risk of prostate cancer by taking tocopherol supplementation.

Men with elevated levels of long-chain omega-3 fatty acids (EPA and DHA) had lowered incidence.

A long-term study reports that "blood levels of trans fatty acids, in particular trans fats resulting from the hydrogenation of vegetable oils, are associated with an increased prostate cancer risk."

Some researchers have indicated that serum myristic acid and palmitic acid and dietary myristic and palmitic saturated fatty acids and serum palmitic combined with alpha-tocopherol supplementation are associated with increased risk of prostate cancer in a dose-dependent manner. These associations may, however, reflect differences in intake or metabolism of these fatty acids between the precancer cases and controls, rather than being an actual cause.

Other

The American Dietetic Association and Dieticians of Canada report a decreased incidence of prostate cancer for those following a vegetarian diet.

In lab tests on mice, prostate tumors grow slower with a no-carbohydrate diet.

A preliminary study found a correlation between coffee consumption and a lower risk of aggressive prostate cancer.

Management

Treatment for prostate cancer may involve active surveillance (monitoring for tumor progress or symptoms), surgery (i.e. radical prostatectomy), radiation therapy including brachytherapy (prostate brachytherapy) and external beam radiation therapy, High-intensity focused ultrasound (HIFU), chemotherapy, oral chemotherapeutic drugs (Temozolomide/TMZ), cryosurgery, hormonal therapy, or some combination. William J. Catalona, MD: regarding Active Surveillance, "Watchful Waiting or for some patients, Wishful Waiting: Can delay prompt treatment of life-threatening tumors, it would require repeated biopsies that often make subsequent nerve-sparing surgery more difficult and it causes many patients anxiety about living with untreated cancer, thus diminishing their quality of life." These men may have already been chemically castrated and impotent.

Which option is best depends on the stage of the disease, the Gleason score, and the PSA level. Other important factors are the man's age, his general health, and his feelings about potential treatments and their possible side-effects. Because all treatments can have significant side-effects, such as erectile dysfunction and urinary incontinence, treatment discussions often focus on balancing the goals of therapy with the risks of lifestyle alterations. Prostate cancer patients are strongly recommended to work closely with their

physicians and use a combination of the treatment options when managing their prostate cancer.

The selection of treatment options may be a complex decision involving many factors. For example, radical prostatectomy after primary radiation failure is a very technically challenging surgery and may not be an option, while salvage radiation therapy after surgical failure may have many complications. This may enter into the treatment decision.

If the cancer has spread beyond the prostate, treatment options significantly change, so most doctors that treat prostate cancer use a variety of nomograms to predict the probability of spread. Treatment by watchful waiting/active surveillance, external beam radiation therapy, brachytherapy, cryosurgery, HIFU, and surgery are, in general, offered to men whose cancer remains within the prostate. Hormonal therapy and chemotherapy are often reserved for disease that has spread beyond the prostate. However, there are exceptions: radiation therapy may be used for some advanced tumors, and hormonal therapy is used for some early stage tumors. Cryotherapy (the process of freezing the tumor), hormonal therapy, and chemotherapy may also be offered if initial treatment fails and the cancer progresses.

Hormone-refractory prostate cancer

Most hormone dependent cancers become refractory (independent) after one to three years and resume growth despite hormone therapy.

Docetaxel has been used for HRPC with a median survival benefit of 2 to 3 months.

A combination of bevacizumab(Avastin), taxotere, thalidomide and prednisone appears effective in the treatment of hormone-refractory prostate cancer.

Provenge is also effective (better than placebo) in the treatment of hormone-refractory prostate cancer, as is Cabazitaxel.

MDV3100 is in phase III trials for HRPC (chemo-naive and post-chemo patient populations).

Abiraterone completed a phase 3 trial for HRPC patients who have failed chemotherapy in 2010. Results were overwhelmingly positive. Johnson & Johnson has filed an application with the FDA to have abiraterone approved for use in this patient population. Approval is expected sometime in 2011.

Prognosis

Prostate cancer rates are higher and prognosis poorer in developed countries than the rest of the world. Many of the risk factors for prostate cancer are more prevalent in the developed world, including longer life expectancy and diets high in red meat (People that

consume larger amounts of meat and dairy also tend to consume fewer portions of fruits and vegetables. It is not currently clear whether both of these factors, or just one of them, contribute to the occurrence of prostate cancer.) Also, where there is more access to screening programs, there is a higher detection rate. Prostate cancer is the ninth-most-common cancer in the world, but is the number-one non-skin cancer in United States men. Prostate cancer affected eighteen percent of American men and caused death in three percent in 2005. In Japan, death from prostate cancer was one-fifth to one-half the rates in the United States and Europe in the 1990s. In India in the 1990s, half of the people with prostate cancer confined to the prostate died within ten years. African-American men have 50–60 times more prostate cancer and prostate cancer deaths than men in Shanghai, China. In Nigeria, two percent of men develop prostate cancer and 64% of them are dead after two years.

In patients that undergo treatment, the most important clinical prognostic indicators of disease outcome are stage, pre-therapy PSA level and Gleason score. In general, the higher the grade and the stage the poorer the prognosis. Nomograms can be used to calculate the estimated risk of the individual patient. The predictions are based on the experience of large groups of patients suffering from cancers at various stages.

In 1941, Charles Huggins reported that androgen ablation therapy causes regression of primary and metastatic androgen-dependent prostate cancer. Androgen ablation therapy causes remission in 80-90% of patients undergoing therapy, resulting in a median progression-free survival of 12 to 33 months. After remission, an androgen-independent phenotype typically emerges, wherein the median overall survival is 23–37 months from the time of initiation of androgen ablation therapy. The actual mechanism contributes to the progression of prostate cancer is not clear and may vary between individual patient. A few possible mechanisms have been proposed.

Classification systems

Many prostate cancers are not destined to be lethal, and most men will ultimately die from causes other than of the disease. Decisions about treatment type and timing may, therefore, be informed by an estimation of the risk that the tumor will ultimately recur after treatment and/or progress to metastases and mortality. Several tools are available to help predict outcomes such as pathologic stage and recurrence after surgery or radiation therapy. Most combine stage, grade, and PSA level, and some also add the number or percent of biopsy cores positive, age, and/or other information.

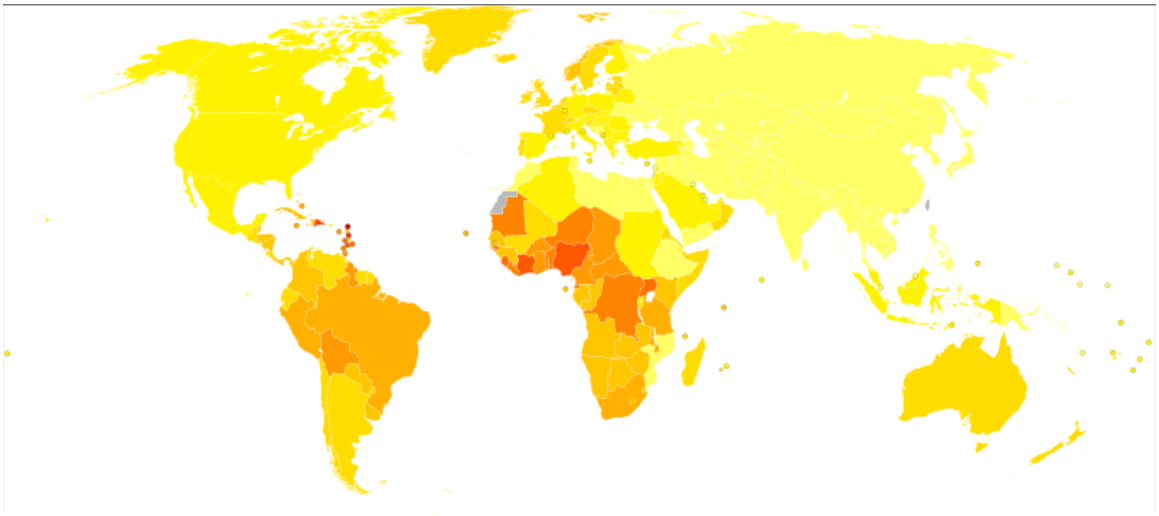
- The *D'Amico classification* stratifies men by low, intermediate, or high risk based on stage, grade, and PSA. It is used widely in clinical practice and research settings. The major downside to the 3-level system is that it does not account for multiple adverse parameters (e.g., high Gleason score *and* high PSA) in stratifying patients.

- The Partin tables predict pathologic outcomes (margin status, extraprostatic extension, and seminal vesicle invasion) based on the same 3 variables, and are published as lookup tables.

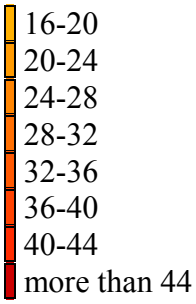
- The *Kattan nomograms* predict recurrence after surgery and/or radiation therapy, based on data available either at time of diagnosis or after surgery. The nomograms can be calculated using paper graphs, or using software available on a website or for handheld computers. The Kattan score represents the likelihood of remaining free of disease at a given time interval following treatment.

- The UCSF *Cancer of the Prostate Risk Assessment (CAPRA) score* predicts both pathologic status and recurrence after surgery. It offers comparable accuracy as the Kattan preoperative nomogram, and can be calculated without paper tables or a calculator. Points are assigned based on PSA, Grade, stage, age, and percent of cores positive; the sum yields a 0–10 score, with every 2 points representing roughly a doubling of risk of recurrence. The CAPRA score was derived from community-based data in the CaPSURE database. It has been validated among over 10,000 prostatectomy patients, including patients from CaPSURE; the SEARCH registry, representing data from several Veterans Administration and active military medical centers; a multi-institutional cohort in Germany; and the prostatectomy cohort at Johns Hopkins University. More recently, it has been shown to predict metastasis and mortality following prostatectomy, radiation therapy, watchful waiting, or androgen deprivation therapy.

Epidemiology



Age-standardized death from prostate cancer per 100,000 inhabitants in 2004.
no data
less than 4
4-8
8-12
12-16



Rates of prostate cancer vary widely across the world. Although the rates vary widely between countries, it is least common in South and East Asia, more common in Europe, and most common in the United States. The average annual incidence rate of prostate cancer between 1988 and 1992 among Chinese men in the United States was 15 times higher than that of their counterparts living in Shanghai and Tianjin. However, these high rates may be affected by increasing rates of detection. Many suggest that prostate cancer may be under reported, yet BPH incidence in China and Japan is similar to rates in Western countries.

Prostate cancer develops primarily in men over fifty. It is the most common type of cancer in men in the United States, with 186,000 new cases in 2008 and 28,600 deaths. It is the second leading cause of cancer death in U.S. men after lung cancer. In the United Kingdom it is also the second most common cause of cancer death after lung cancer, where around 35,000 cases are diagnosed every year and of which around 10,000 die of it. Many factors, including genetics and diet, have been implicated in the development of prostate cancer. The Prostate Cancer Prevention Trial found that finasteride reduces the incidence of prostate cancer rate by 30%. There had been a controversy about this also increasing the risk of more aggressive cancers, but more recent research showed this may not be the case.

History

Although the prostate was first described by Venetian anatomist Niccolò Massa in 1536, and illustrated by Flemish anatomist Andreas Vesalius in 1538, prostate cancer was not identified until 1853. Prostate cancer was initially considered a rare disease, probably because of shorter life expectancies and poorer detection methods in the 19th century. The first treatments of prostate cancer were surgeries to relieve urinary obstruction. Removal of the entire gland (radical perineal prostatectomy) was first performed in 1904 by Hugh H. Young at Johns Hopkins Hospital. Surgical removal of the testes (orchiectomy) to treat prostate cancer was first performed in the 1890s, but with limited success. Transurethral resection of the prostate (TURP) replaced radical prostatectomy for symptomatic relief of obstruction in the middle of the 20th century because it could better preserve penile erectile function. Radical retropubic prostatectomy was developed in 1983 by Patrick Walsh. This surgical approach allowed for removal of the prostate and lymph nodes with maintenance of penile function.

In 1941, Charles B. Huggins published studies in which he used estrogen to oppose testosterone production in men with metastatic prostate cancer. This discovery of "chemical castration" won Huggins the 1966 Nobel Prize in Physiology or Medicine. The role of the hormone GnRH in reproduction was determined by Andrzej W. Schally and Roger Guillemin, who both won the 1977 Nobel Prize in Physiology or Medicine for this work.

Receptor agonists, such as leuprolide and goserelin, were subsequently developed and used to treat prostate cancer.

Radiation therapy for prostate cancer was first developed in the early 20th century and initially consisted of intraprostatic radium implants. External beam radiation became more popular as stronger radiation sources became available in the middle of the 20th century. Brachytherapy with implanted seeds was first described in 1983.

Systemic chemotherapy for prostate cancer was first studied in the 1970s. The initial regimen of cyclophosphamide and 5-fluorouracil was quickly joined by multiple regimens using a host of other systemic chemotherapy drugs.

On 30 July 2010 Owen Witte M.D. et al. of UCLA published a series of studies in *Science* during which they had introduced viruses known to cause cancerous mutation in prostate cells: AKT, ERG, and AR into isolated samples of basal and luminal cells and grafted the treated tissue into mice. After 16 weeks, none of the luminal samples had undergone malignant mutation, while the basal samples had mutated into prostate-like tubules which had then developed malignancy and formed cancerous tumors, which appeared identical to human samples under magnification. This led to the conclusion that the prostate basal cell may be the most likely "site of origin" of prostate cancer.

Research

Androgen at a concentration of 10-fold higher than the physiological concentration has also been shown to cause growth suppression and reversion of androgen-independent prostate cancer xenografts or androgen-independent prostate tumors derived in vivo model to an androgen-stimulated phenotype in athymic mice. These observation suggest the possibility to use androgen to treat the development of relapsed androgen-independent prostate tumors in patients.

Oral infusion of green tea catechins, a potential alternative therapy for prostate cancer by natural compounds, has been shown to inhibit the development, progression, and metastasis as well in autochthonous transgenic adenocarcinoma of the mouse prostate (TRAMP) model, which spontaneously develops prostate cancer.

The insulin-like growth factor signaling axis is thought to play a key role in the progression of prostate carcinoma. It consists of two ligands (IGF-1 and IGF-2), two receptors (IGF-IR and IGF-IIR) and six related high-affinity IGF-binding proteins

(IGFBP 1-6). Altered expression of IGF axis members has been implicated in the development of many different types of cancers, including prostate.

A genistein derivative KBU2046 is under investigation for prostate cancer.

The Color of Prostate Cancer Awareness is Light Blue.

Prostate cancer models

Scientists have established a few prostate cancer cell lines to investigate the mechanism involved in the progression of prostate cancer. LNCaP, PC-3 (PC3), and DU-145 (DU145) are commonly used prostate cancer cell lines. The LNCaP cancer cell line was established from a human lymph node metastatic lesion of prostatic adenocarcinoma. PC-3 and DU-145 cells were established from human prostatic adenocarcinoma metastatic to bone and to brain, respectively. LNCaP cells express androgen receptor (AR); however, PC-3 and DU-145 cells express very little or no AR. AR, an androgen-activated transcription factor, belongs to the steroid nuclear receptor family. Development of the prostate is dependent on androgen signaling mediated through AR, and AR is also important during the development of prostate cancer. The proliferation of LNCaP cells is androgen-dependent but the proliferation of PC-3 and DU-145 cells is androgen-insensitive. Elevation of AR expression is often observed in advanced prostate tumors in patients. Some androgen-independent LNCaP sublines have been developed from the ATCC androgen-dependent LNCaP cells after androgen deprivation for study of prostate cancer progression. These androgen-independent LNCaP cells have elevated AR expression and express prostate specific antigen upon androgen treatment. The paradox is that androgens inhibit the proliferation of these androgen-independent prostate cancer cells.

Chapter 10

Prostate Cancer Staging and Prostate Cancer Screening

Prostate cancer staging

Prostate cancer staging is the process by which physicians categorize the risk of cancer having spread beyond the prostate, or equivalently, the probability of being cured with local therapies such as surgery or radiation. Once patients are placed in prognostic categories, this information can contribute to the selection of an optimal approach to treatment. The information considered in such a prognostic classification can be based on physical examination, imaging studies and blood tests (so-called "clinical stage"), or based on the extent of disease as revealed in a surgical specimen (so-called "pathologic stage").

There are two schemes commonly used to stage prostate cancer. The most common is promulgated by the American Joint Committee on Cancer, and is known as the TNM system, which evaluates the size of the tumor, the extent of involved lymph nodes, and any metastasis (distant spread) and also takes into account cancer grade. As with many other cancers, these are often grouped into four stages (I–IV). Another scheme, now used less commonly for research, but often still used by clinicians, is the Whitmore-Jewett stage.

Briefly, Stage I disease is cancer that is found incidentally in a small part of the sample when prostate tissue was removed for other reasons, such as benign prostatic hypertrophy, and the cells closely resemble normal cells and the gland feels normal to the examining finger. In Stage II more of the prostate is involved and a lump can be felt within the gland. In Stage III, the tumor has spread through the prostatic capsule and the lump can be felt on the surface of the gland. In Stage IV disease, the tumor has invaded nearby structures, or has spread to lymph nodes or other organs. The Gleason Grading System is based on cellular content and tissue architecture from biopsies, which provides an estimate of the destructive potential and ultimate prognosis of the disease.

TNM staging

From the AJCC 6th edition (2002) and UICC 6th edition.

Evaluation of the (primary) tumor ('T')

- **TX**: cannot evaluate the primary tumor
- **T0**: no evidence of tumor
- **T1**: tumor present, but not detectable clinically or with imaging
    - **T1a**: tumor was incidentally found in less than 5% of prostate tissue resected (for other reasons)
    - **T1b**: tumor was incidentally found in greater than 5% of prostate tissue resected
    - **T1c**: tumor was found in a needle biopsy performed due to an elevated serum PSA
- **T2**: the tumor can be felt (palpated) on examination, but has not spread outside the prostate
    - **T2a**: the tumor is in half or less than half of one of the prostate gland's two lobes
    - **T2b**: the tumor is in more than half of one lobe, but not both
    - **T2c**: the tumor is in both lobes
- **T3**: the tumor has spread through the prostatic capsule (if it is only part-way through, it is still **T2**)
    - **T3a**: the tumor has spread through the capsule on one or both sides
    - **T3b**: the tumor has invaded one or both seminal vesicles
- **T4**: the tumor has invaded other nearby structures

It should be stressed that the designation "T2c" implies a tumor which is *palpable* in both lobes of the prostate. Tumors which are found to be bilateral on biopsy only but which are not palpable bilaterally should not be staged as T2c.

Evaluation of the regional lymph nodes ('N')

- **NX**: cannot evaluate the regional lymph nodes
- **N0**: there has been no spread to the regional lymph nodes
- **N1**: there has been spread to the regional lymph nodes

Evaluation of distant metastasis ('M')

- **MX**: cannot evaluate distant metastasis
- **M0**: there is no distant metastasis
- **M1**: there is distant metastasis
    - **M1a**: the cancer has spread to lymph nodes beyond the regional ones
    - **M1b**: the cancer has spread to bone
    - **M1c**: the cancer has spread to other sites (regardless of bone involvement)

Evaluation of the histologic grade ('G')

Usually, the grade of the cancer (how different the tissue is from normal tissue) is evaluated separately from the stage; however, for prostate cancer, grade information is used in conjunction with TNM status to group cases into four overall stages.

- **GX**: cannot assess grade
- **G1**: the tumor closely resembles normal tissue (Gleason 2–4)
- **G2**: the tumor somewhat resembles normal tissue (Gleason 5–6)
- **G3–4**: the tumor resembles normal tissue barely or not at all (Gleason 7–10)

Of note, this system of describing tumors as "well-", "moderately-", and "poorly-" differentiated based on Gleason score of 2-4, 5-6, and 7-10, respectively, persists in SEER and other databases but is generally outdated. In recent years pathologists rarely assign a tumor a grade less than 3, particularly in biopsy tissue. A more contemporary consideration of Gleason grade is:

- Gleason 3+3: tumor is low grade (favorable prognosis)
- Gleason 3+4 / 3+5: tumor is mostly low grade with some high grade
- Gleason 4+3 / 5+3: tumor is mostly high grade with some low grade
- Gleason 4+4 / 4+5 / 5+4 / 5+5: tumor is all high grade

Overall staging

The tumor, lymph node, metastasis, and grade status can be combined into four stages of worsening severity.

Stage	Tumor	Nodes	Metastasis	Grade
Stage I	T1a	N0	M0	G1
	T1a	N0	M0	G2–4
	T1b	N0	M0	Any G
Stage II	T1c	N0	M0	Any G
	T1	N0	M0	Any G
	T2	N0	M0	Any G
Stage III	T3	N0	M0	Any G
	T4	N0	M0	Any G
Stage IV	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

Whitmore-Jewett staging

The Whitmore-Jewett system is similar to the TNM system, with approximately equivalent stages. Roman numerals are sometimes used instead of Latin letters for the overall stages (for example, Stage I for Stage A, Stage II for Stage B, and so on).

- **A**: tumor is present, but not detectable clinically; found incidentally
  - **A1**: tissue resembles normal cells; found in a few chips from one lobe
  - **A2**: more extensive involvement
- **B**: the tumor can be felt on physical examination but has not spread outside the prostatic capsule
  - **BIN**: the tumor can be felt, it does not occupy a whole lobe, and is surrounded by normal tissue
  - **B1**: the tumor can be felt and it does not occupy a whole lobe
  - **B2**: the tumor can be felt and it occupies a whole lobe or both lobes
- **C**: the tumor has extended through the capsule
  - **C1**: the tumor has extended through the capsule but does not involve the seminal vesicles
  - **C2**: the tumor involves the seminal vesicles
- **D**: the tumor has spread to other organs

Risk groups

While TNM staging is important, systems based just on anatomic features are not well suited for deciding what treatment is best for a patient with prostate cancer, as there is still considerable heterogeneity of prognosis within the stage categories. A more refined prognosis can be established by consideration of prostate specific antigen, and grade (i.e. Gleason score). For example, it is now common to classify patients into high, intermediate and low risk groups on the basis of these three factors (TNM stage, PSA and Gleason score). Currently, there is no clear division between stage, which is historically a statement of anatomic extent of disease at diagnosis, and prognostic models that may include many features that contribute to clinical outcome.

If treated, patients with low risk disease are usually treated with prostatectomy or radiotherapy alone. Patients with intermediate risk disease are usually treated with radiotherapy and a short duration (less than 6 months) of hormonal ablation (medical castration using a gonadotropin-releasing hormone analog) although the role of surgery in these patients remains uncertain, and those with high risk disease are usually treated with radiotherapy and a long duration of hormonal ablation. Many high risk patients are not cured by this treatment, and the search for better treatments in this group is a particularly pressing concern in prostate cancer research.

Prostate cancer screening

Prostate cancer screening is an attempt to identify individuals with prostate cancer in a broad segment of the population—those for whom there is no reason to suspect prostate cancer. There are currently two methods used: One is the digital rectal examination (DRE), in which the examiner inserts a gloved, lubricated finger into the rectum to examine the adjoining prostate. The other is the prostate-specific antigen (PSA) blood test, which measures the concentration of this molecule in the blood.

Screening is controversial. Prostate cancer can develop into a fatal, painful disease, but it can also develop so slowly that it will never cause problems during the man's lifetime. It is difficult for a physician to determine how the cancer will proceed based on the two major types of screening tests currently available. A major consideration for any screening protocol is to weigh up the possibility someone will have needless treatment against saving lives. A 2010 analysis concluded that routine screening with either a DRE or PSA is not supported by the evidence as there is no mortality benefit from screening.

Many doctors argue against PSA testing for men who are in their 70s or older, because even if prostate cancer were detected, most men would be dead of something else before the cancer progressed. Others argue against PSA testing for men who are too young, because too many men would have to be screened to find one cancer, and too many men would have treatment for cancer that would not progress.

Interpreting screening tests

Two clinical prediction rules help predict the probability of cancer based on the level of the prostate-specific antigen and other clinical findings.

Clinical practice guidelines

Clinical practice guidelines for prostate cancer screening are controversial because the benefits of screening may not outweigh the risks of follow-up diagnostic tests and cancer treatments:

- U.S. Preventive Services Task Force (USPSTF):

  "the evidence is insufficient to recommend for or against routine screening for prostate cancer using prostate-specific antigen (PSA) testing or digital rectal examination (DRE). This is a grade I recommendation". In 2008, the guidelines were updated to recommend *against* the routine screening of prostate cancer in men age 75 years or older (Grade D recommendation).

- American Cancer Society, in its cancer screening guidelines says that it does not support routine screening for prostate cancer. This is because the benefits are unclear or unproven. Instead it recommends that doctors discuss the pros and cons of testing and that men should be offered the possibility of a DRE and a PSA test if they are over 50 with a life expectancy of more than 10 years (or over 40 if they are in a high risk group). It recommends that men should sit down with their physician and weigh the benefits and risks of the test before a decision is made. Men at high risk for prostate cancer such as African-American men should discuss this with their doctor at age 45. Men who have a first-degree relative (father, brother, or son) diagnosed with prostate cancer at an early age (younger than age 65) and men with several first-degree relatives diagnosed at an early age should begin the discussion at age 40.

Other racial and ethnic groups, such as Asian- and Hispanic-Americans have a lower risk of prostate cancer, and may not benefit from screening. Screening is likely not useful for men over age 70 or with other significant medical problems and a life expectancy of fewer than 10 years.

In the European Randomized Study of Screening for Prostate Cancer initiated in the early 1990s, the intention was to evaluate the effect of screening with prostate-specific antigen (PSA) testing on death rates from prostate cancer. The trial involved 182,000 men between the ages of 50 and 74 years in seven European countries randomly assigned to a group that was offered PSA screening at an average of once every 4 years or to a control group that did not receive such screening. During a median follow-up of almost 9 years, the cumulative detected incidence of prostate cancer was 820 per 10,000 in the screening group and 480 per 10,000 in the control group. Deaths from these cancers in this time was much lower. There were 214 prostate cancer deaths in the screening group and 326 in the control group, a difference of 7.1 men per 10,000 in the tested group compared to the control. The researchers concluded that PSA-based screening did reduce the rate of death from prostate cancer by 20%, but that this was associated with a high risk of overdiagnosis, which means that 1410 men would need to be screened and 48 additional cases of prostate cancer would need to be treated to prevent just one death from prostate cancer.

In addition to the 20 percent reduction in prostate cancer mortality shown by the ERSPC study, a more recent study has shown greater effectiveness in how screening has reduced the prostate cancer death rate. A study published in the *European Journal of Cancer* (October 2009) documented that prostate cancer screening reduced prostate cancer mortality by 37 percent. By utilizing a control group of men from Northern Ireland, where PSA screening is infrequent, the research showed this substantial reduction in prostate cancer deaths when compared to men who were PSA tested as part of the ERSPC study.

A US study, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, looked at the general effectiveness of a screening program involving both PSA and DRE methods. This was conducted between 1993 through 2001, in which 76,693 men at 10 U.S. study centers were enrolled and 38,343 subjects received screening (an annual PSA testing for 6 years and DRE for 4 years), with subjects and healthcare providers receiving the results and deciding on the type of follow-up evaluation, while a control group of 38,350 subjects received 'usual care'. 'Usual care' means that the subjects received routine care from their personal care providers and so some in this group would have received some screening, as some organizations have recommended. After 7 years of follow-up, the incidence of prostate cancer per 10,000 person-years was 116 (2,820 cancers) in the screening group and 95 (2,322 cancers) in the control group. The incidence of death attributed to prostate cancer per 10,000 person-years was 2.0 (50 deaths) in the screening group and 1.7 (44 deaths) in the control group (rate ratio, 1.13; 95% CI, 0.75 to 1.70). The data at 10 years were 67% complete and consistent with these overall findings. The

researchers concluded that, after 7 to 10 years of follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the two study groups.

Commenting on the findings, the Chief Medical Officer of the American Cancer Society, Otis W. Brawley, MD, said

many experts had anticipated these studies would show a small number of men will benefit from prostate screening, but a large number of men will be treated unnecessarily. And that's what these studies show. However, the question is not as simple as: 'does prostate cancer screening work?' What we need to know is: what are benefits of prostate cancer screening and are they large enough to outweigh the harms associated with it? And, despite the release of this early data, we still cannot say whether the benefits outweigh the risk."

His Deputy chief medical officer, Len Lichtenfeld, MD, MACP said

"When one considers all of the problems associated with treatment for prostate cancer -- urine incontinence, impotence, pain and bleeding among others -- that is a lot of men left with a lot of symptoms to save one life."

The American Urological Association said that "The decision to screen is one that a man should make in conjunction with his physician, and should incorporate known prostate cancer risk factors, such as family history of prostate cancer, age, ethnicity/race, and whether or not a man has had a previous negative prostate biopsy. These factors are different for every man and, therefore, the benefits of screening should be considered in the broader perspective." The organization will review its best practice guidelines later this year.

- The 2008 recommendations of the U.S. Preventive Services Task Force (USPSTF) concluded that routine screening for prostate cancer using PSA testing or digital rectal examination (DRE) was not recommended for men over 75 and that the evidence was insufficient to recommend for or against screening for men under 75 years old. The previous 1995 USPSTF recommendation was against routine screening.
- The American Cancer Society (ACS) has recently updated its guidelines making clear that it does not recommend routine prostate cancer screening for all men.. It recommends that the risks and benefits of screening need to be weighed, and discussions should start early for those in high risk groups. Screening should take place only wíth informed consent of the patient in full knowledge of both benefits and risks. The revised guidelines reflect the concerns about the potentially down-played risks and over-blown claims for the success of prostate cancer screening.

  The American Cancer Society (ACS) does not support routine testing for prostate cancer at this time. ACS does believe that health care professionals should discuss the potential benefits and limitations of prostate cancer early detection

testing with men before any testing begins. This discussion should include an offer for testing with the prostate-specific antigen (PSA) blood test and digital rectal exam (DRE) yearly, beginning at age 50, to men who are at average risk of prostate cancer and have at least a 10-year life expectancy. Following this discussion, those men who favor testing should be tested. Men should actively take part in this decision by learning about prostate cancer and the pros and cons of early detection and treatment of prostate cancer. This discussion should take place starting at age 45 for men at high risk of developing prostate cancer. This includes African American men and men who have a first-degree relative (father, brother, or son) diagnosed with prostate cancer at an early age (younger than age 65). This discussion should take place at age 40 for men at even higher risk (those with several first-degree relatives who had prostate cancer at an early age). If, after this discussion, a man asks his health care professional to make the decision for him, he should be tested (unless there is a specific reason not to test).

- The 2007 National Comprehensive Cancer Network (NCCN) guideline recommends *offering* a baseline PSA test and DRE at ages 40 and 45 and annual PSA testing and DRE beginning at age 50 (with annual PSA testing and DRE beginning at age 40 for African-American men, men with a family history of prostate cancer, and men with a PSA $\geq$ 0.6 ng/mL at age 40 or PSA > 0.6 ng/mL at age 45) through age 80, along with information on the risks and benefits of screening. Biopsy is recommended if DRE is positive or PSA $\geq$ 4 ng/mL, and biopsy considered if PSA > 2.5 ng/mL or PSA velocity $\geq$ 0.35 ng/mL/year when PSA $\leq$ 2.5 ng/mL.
- Some U.S. radiation oncologists and medical oncologists who specialize in treating prostate cancer recommend obtaining a baseline PSA in all men at age 35 or beginning annual PSA testing in high risk men at age 35.
- The American Urological Association Patient Guide to Prostate Cancer.

Since there is no general agreement that the benefits of PSA screening outweigh the harms, the consensus is that clinicians use a process of shared decision-making that includes discussing with patients the risks of prostate cancer, the potential benefits and harms of screening, and involving the patients in the decision.

However, PSA screening is widespread in the United States, and at least one doctor lost a malpractice suit even though he was following the recommendations of major scientific and medical organizations by letting his patient decide. In 2003, a Virginia jury found a family practice residency program guilty of malpractice and liable for $1 million for following national guidelines and using shared decision-making, thereby allowing a patient (subsequently found to have a high PSA and incurable advanced prostate cancer) to decline a screening PSA test, instead of routinely ordering without discussion PSA tests in all men $\geq$ 50 years of age as four local physicians testified was their practice, and was accepted by the jury as the local standard of care.

An estimated 20 million PSA tests are done per year in North America and possibly 20 million more outside of North America.

- In 2000, 34.1% of all U.S. men age ≥ 50 had a *screening* PSA test within the past year and 56.8% reported ever having a PSA test.
- In 2000, 33.6% of all U.S. men age 50–64 and 51.3% of men age ≥ 65 had a PSA test within the past year.
- In 2005, 33.5% of all U.S. men age 50–64 had a PSA test in the past year.
    - 37.5% of men with private health insurance, 20.8% of men with Medicaid insurance, 14.0% of currently uninsured men, and 11.5% of men uninsured for > 12 months.
- In 2000–2001, 34.1% of all Canadian men age ≥ 50 had a *screening* PSA test within the past year and 47.5% reported ever having a *screening* PSA test.
- Canadian men in Ontario were most likely to have had a PSA test within the past year and men in Alberta were least likely to have had a PSA test with the past year or ever.

Digital rectal examination

Digital rectal examination (DRE) is a procedure where the examiner inserts a gloved, lubricated finger into the rectum to check the size, shape, and texture of the prostate. Areas that are irregular, hard, or lumpy need further evaluation, since they may contain cancer. Although the DRE evaluates only the back of the prostate, 85% of prostate cancers arise in this part of the prostate. Prostate cancer that can be felt on DRE is, in general, more advanced. The use of DRE has never been shown to prevent prostate cancer deaths when used as the only screening test.

Prostate specific antigen

The PSA test measures the blood level of prostate-specific antigen, an enzyme produced by the prostate. To be specific, PSA is a serine protease similar to kallikrein. Its normal function is to liquify gelatinous semen after ejaculation, allowing spermatozoa to more easily navigate through the uterine cervix.

PSA testing is controversial. Since the test was introduced PSA screening in the U.S. more than 1 million additional men there have being diagnosed and treated for prostate cancer but it has been estimated that the vast majority (more than 95%) of these men receive no benefit from their positive diagnosis. Even if one makes the most optimistic assumption about the benefit of screening (i.e. that the entire decline in prostate cancer mortality observed since the introduction of PSA testing is due to introduction of the test) less than 5% (or one in twenty) of those getting a positive diganosis received any benefit at all from it.

Other research studies, however, point to the success of the PSA test in reducing death due to prostate cancer. The European Randomized Study of Screening for Prostate Cancer (ERSPC) study, published in the *New England Journal of Medicine* (March 2009), documented that screening resulted in a 20 percent reduction in prostate cancer mortality.

More recent studies have shown greater effectiveness in how screening has reduced the prostate cancer death rate. A study published in the *European Journal of Cancer* (October 2009) documented that prostate cancer screening reduced prostate cancer mortality by 37 percent. By utilizing a control group of men from Northern Ireland, where PSA screening is infrequent, the research showed this substantial reduction in prostate cancer deaths when compared to men who were PSA tested as part of the ERSPC study.

The risk of prostate cancer increases with increasing PSA levels. 4 ng/mL was chosen arbitrarily as a decision level for biopsies in the clinical trial upon which the U.S. Food and Drug Administration (FDA) in 1994 based adding prostate cancer detection in men age 50 and over as an approved indication for the first commercially available PSA test. 4 ng/mL was used as the biopsy decision level in the PLCO trial, 3 ng/mL was used in the ERSPC and ProtecT trials, and 2.5 ng/mL is used in the 2007 NCCN guideline.

PSA levels can change for many reasons other than cancer. Two common causes of high PSA levels are enlargement of the prostate (benign prostatic hypertrophy (BPH)) and infection in the prostate (prostatitis). It can also be raised for 24 hours after ejaculation and several days after catheterization.

PSA levels are lowered in men that use finasteride (Proscar or Propecia) or dutasteride (Avodart) to treat BPH. After a year, finasteride was shown to lower PSA levels by 50% or more. Finasteride is also marketed as Propecia (1 mg.) for baldness, and the lower dose was shown in a further clinical trial to also lower PSA readings by 50% after a year. As a result, reference ranges and calculations of the rate of change in PSA levels per year must be adjusted accordingly in men taking such drugs.

Several other ways of evaluating the PSA have been developed to avoid the shortcomings of simple PSA screening. The use of age-specific reference ranges improves the sensitivity and specificity of the test. The rate of rise of the PSA over time, called the PSA velocity, has been used to evaluate men with PSA levels between 4 and 10 ng/ml, but it has not proven to be an effective screening test. Comparing the PSA level with the size of the prostate, as measured by ultrasound or magnetic resonance imaging, has also been studied. This comparison, called PSA density, is both costly and has not proven to be an effective screening test. PSA in the blood may either be free or bound to other proteins. Measuring the amount of PSA which is free or bound may provide additional screening information, but questions regarding the usefulness of these measurements limit their widespread use.

Controversy

Screening for prostate cancer is controversial because of cost and uncertain long-term benefits to patients. Testing may lead to overdiagnosis and additional, but often unnecessary, testing and treatment. Follow-up tests can include painful biopsies which can result in excessive bleeding and infection. The discoverer of PSA, Dr. Richard J. Ablin, concludes that the test's popularity "has led to a hugely expensive public health

disaster," as only 16 percent of men will ever receive a diagnosis of prostate cancer, but only a 3 percent chance of dying from it. He states that "the test is hardly more effective than a coin toss." Dr. Horan echos that sentiment in his book.

According to the American Urological Association, the controversy over prostate cancer should not surround the test, but rather how test results influence the decision to treat:

"The decision to proceed to prostate biopsy should be based not only on elevated PSA and/or abnormal DRE results, but should take into account multiple factors including free and total PSA, patient age, PSA velocity, PSA density, family history, ethnicity, prior biopsy history and comorbidities.
"A cancer cannot be treated if it is not detected. Not all prostate cancers require immediate treatment; active surveillance, in lieu of immediate treatment, is an option that should be considered for some men. Testing empowers patients and their urologists with the information to make an informed decision."

In 2002, the U.S. Preventive Services Task Force concluded that "evidence was insufficient to recommend for or against screening." Currently, the American Centers for Disease Control and Prevention (CDC), answers the question, "Should I Get Screened for Prostate Cancer?" with a statement:

"Not all medical experts agree that screening for prostate cancer will save lives. Currently, there is not enough evidence to decide if the potential benefits of prostate cancer screening outweigh the potential risks."

Private medical institutes, such as the Mayo Clinic, likewise acknowledge that "organizations vary in their recommendations about who should — and who shouldn't — get a PSA screening test." They conclude: "Ultimately, whether you should have a PSA test is something you'll have to decide after discussing it with your doctor, considering your risk factors and weighing your personal preferences."

Expense

The annual cost of PSA screening in the U.S. totals at least $3 billion, with much of it paid for by Medicare and the Veterans Administration. A study in Europe resulted in only a small decline in death rates and concluded that 48 men would need to be treated to save one life. But of the 47 men who were treated, most would be unable to ever again function sexually and require more frequent trips to the bathroom.

A study by the New England Journal of Medicine found that over a 7 to 10 year period, "screening did not reduce the death rate in men 55 and over." Former screening proponents, including some from Stanford University, have come out against routine testing. In February 2010, the American Cancer Society urged "more caution in using the test." And the American College of Preventive Medicine concluded that "there was insufficient evidence to recommend routine screening."

According to Ablin, "testing should absolutely not be deployed to screen the entire population of men over the age of 50 . . ." He concludes that the primary promoters of tests are drug companies, which "continue peddling the tests," along with advocacy groups including the American Urological Association, all of which "stand to profit" by pushing continual tests. He states:

"I never dreamed that my discovery four decades ago would lead to such a profit-driven public health disaster. The medical community must confront reality and stop the inappropriate use of P.S.A. screening. Doing so would save billions of dollars and rescue millions of men from unnecessary, debilitating treatments."

Research

The results from two of the largest randomized trials have now been published.

In the European Randomized Study of Screening for Prostate Cancer (ERSPC) study initiated in the early 1990s, the intention was to evaluate the effect of screening with prostate-specific antigen (PSA) testing on death rates from prostate cancer. The trial involved 182,000 men between the ages of 50 and 74 years in seven European countries randomly assigned to a group that was offered PSA screening at an average of once every 4 years or to a control group that did not receive such screening. During a median follow-up of almost 9 years, the cumulative detected incidence of prostate cancer was 820 per 10,000 in the screening group and 480 per 10,000 in the control group. Deaths from these cancers in this time was much lower. There were 214 prostate cancer deaths in the screening group and 326 in the control group, a difference of 7.1 men per 10,000 in the tested group compared to the control. The researchers concluded that PSA-based screening did reduce the rate of death from prostate cancer by 20% but that this was associated with a high risk of overdiagnosis. Statistically, it means that 1410 men would need to be screened and 48 additional cases of prostate cancer would need to be treated to prevent just one death from prostate cancer.

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A further study, the NHS *Comparison Arm for ProtecT (**CAP**)* and *Prostate testing for cancer and Treatment (**ProtecT**)* studies randomized GP practices with 460,000 men aged 50–69 at centers in 9 cities in Britain from 2001-2005 to usual care or prostate cancer screening with PSA (biopsy if PSA $\geq$ 3), has yet to report.

This study and its Protocols need to be reviewed by independent professionals before its results considered. It has been running for many years and should include the views of the patient in feedback about the treatments and options made available by the consultants. However this is not being considered because it is outside the original specification.

Chapter 11

Management of Prostate Cancer

Treatment for prostate cancer may involve active surveillance, surgery, radiation therapy including brachytherapy (prostate brachytherapy) and external beam radiation therapy, High-intensity focused ultrasound (HIFU), chemotherapy, cryosurgery, hormonal therapy, or some combination. Which option is best depends on the stage of the disease, the Gleason score, and the PSA level. Other important factors are the man's age, his general health, and his feelings about potential treatments and their possible side effects. Because all treatments can have significant side effects, such as erectile dysfunction and urinary incontinence, treatment discussions often focus on balancing the goals of therapy with the risks of lifestyle alterations.

The selection of treatment options may be a complex decision involving many factors. For example, radical prostatectomy after primary radiation failure is a very technically challenging surgery and may not be an option. This may enter into the treatment decision.

If the cancer has spread beyond the prostate, treatment options significantly change, so most doctors that treat prostate cancer use a variety of nomograms to predict the probability of spread. Treatment by watchful waiting/active surveillance, HIFU, external beam radiation therapy, brachytherapy, cryosurgery, and surgery are, in general, offered to men whose cancer remains within the prostate. Hormonal therapy and chemotherapy are often reserved for disease that has spread beyond the prostate. However, there are exceptions: Radiation therapy may be used for some advanced tumors, and hormonal therapy is used for some early stage tumors. Cryotherapy (the process of freezing the tumor), hormonal therapy, and chemotherapy may also be offered if initial treatment fails and the cancer progresses.

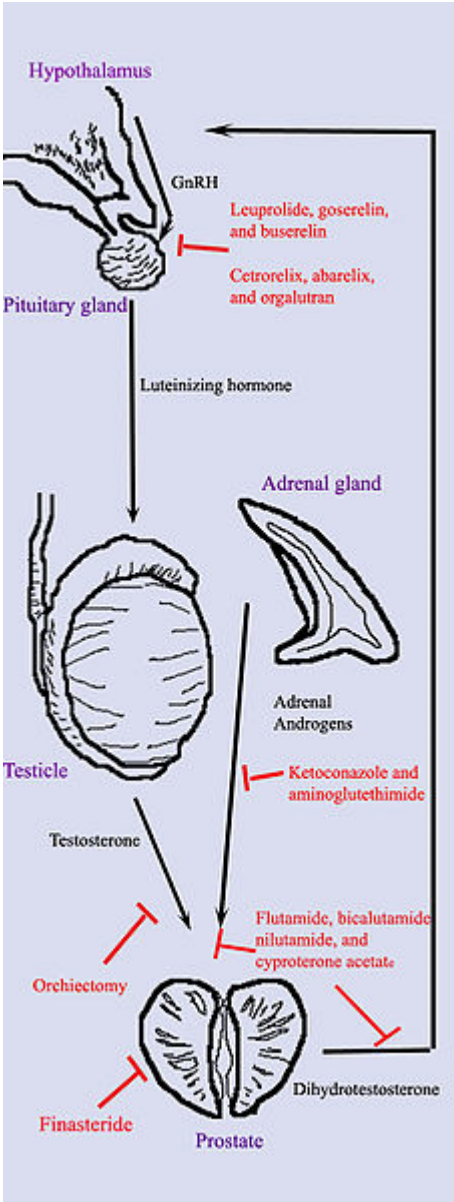
Active surveillance

Active surveillance refers to observation and regular monitoring without invasive treatment. Active surveillance is often used when an early stage, slow-growing prostate cancer is suspected. However, watchful waiting may also be suggested when the risks of surgery, radiation therapy, or hormonal therapy outweigh the possible benefits. Other treatments can be started if symptoms develop, or if there are signs that the cancer growth

is accelerating (e.g., rapidly-rising PSA, increase in Gleason score on repeat biopsy, etc.). Approximately one-third of men that choose active surveillance for early stage tumors eventually have signs of tumor progression, and they may need to begin treatment within three years. Men that choose active surveillance avoid the risks of surgery, radiation, and other treatments. The risk of disease progression and metastasis (spread of the cancer) may be increased, but this increase risk appears to be small if the program of surveillance is followed closely, generally including serial PSA assessments and repeat prostate biopsies every 1–2 years depending on the PSA trends.

For younger men, a trial of active surveillance may not mean avoiding treatment altogether, but may reasonably allow a delay of a few years or more, during which time the quality of life impact of active treatment can be avoided. Published data to date suggest that carefully selected men will not miss a window for cure with this approach. Additional health problems that develop with advancing age during the observation period can also make it harder to undergo surgery and radiation therapy.

Hormonal therapy



Hormonal therapy in prostate cancer. Diagram shows the different organs (*purple text*), hormones (*black text and arrows*), and treatments (*red text and arrows*) important in hormonal therapy.

Hormonal therapy uses medications or surgery to block prostate cancer cells from getting dihydrotestosterone (DHT), a hormone produced in the prostate and required for the growth and spread of most prostate cancer cells. Blocking DHT often causes prostate cancer to stop growing and even shrink. However, hormonal therapy rarely cures prostate cancer because cancers that initially respond to hormonal therapy typically become resistant after one to two years. Hormonal therapy is, therefore, usually used when cancer

has spread from the prostate. It may also be given to certain men undergoing radiation therapy or surgery to help prevent return of their cancer.

Hormonal therapy for prostate cancer targets the pathways the body uses to produce DHT. A feedback loop involving the testicles, the hypothalamus, and the pituitary, adrenal, and prostate glands controls the blood levels of DHT. First, low blood levels of DHT stimulate the hypothalamus to produce gonadotropin-releasing hormone (GnRH). GnRH then stimulates the pituitary gland to produce luteinizing hormone (LH), and LH stimulates the testicles to produce testosterone. Finally, testosterone from the testicles and dehydroepiandrosterone from the adrenal glands stimulate the prostate to produce more DHT. Hormonal therapy can decrease levels of DHT by interrupting this pathway at any point. There are several forms of hormonal therapy:

- Orchiectomy, also called "castration," is surgery to remove the testicles. Because the testicles make most of the body's testosterone, after orchiectomy testosterone levels drop. Now the prostate not only lacks the testosterone stimulus to produce DHT but also does not have enough testosterone to transform into DHT. Orchiectomy is considered the gold standard of treatment.
- Antiandrogens are medications such as flutamide, bicalutamide, nilutamide, and cyproterone acetate that directly block the actions of testosterone and DHT within prostate cancer cells.
- Medications that block the production of adrenal androgens such as DHEA include ketoconazole and aminoglutethimide. Because the adrenal glands make only about 5% of the body's androgens, these medications are, in general, used only in combination with other methods that can block the 95% of androgens made by the testicles. These combined methods are called total androgen blockade (TAB). TAB can also be achieved using antiandrogens.
- GnRH action can be interrupted in one of two ways. GnRH antagonists such as abarelix and degarelix suppress the production of LH directly by acting on the anterior pituitary. GnRH agonists such as leuprolide and goserelin acetate suppress LH through the process of downregulation after an initial stimulation effect which can cause initial tumor flare. Abarelix and degarelix are examples of GnRH antagonists, whereas the GnRH agonists include leuprolide, goserelin, triptorelin, and buserelin. Initially, GnRH agonists *increase* the production of LH. However, because the constant supply of the medication does not match the body's natural production rhythm, production of both LH and GnRH decreases after a few weeks.
- A very recent Trial I study (N=21) found that abiraterone acetate caused dramatic reduction in PSA levels and tumor sizes in aggressive end-stage prostate cancer for 70% of patients. This is prostate cancer that resists all other treatments (e.g., castration, other hormones, etc.). Officially the impacts on life-span are not yet known because subjects have not been taking the drug very long. Larger Trial III Clinical Studies are in the works. If successful an approved treatment is hoped for around 2011.

The most successful hormonal treatments are orchiectomy and GnRH agonists. Despite their higher cost, GnRH agonists are often chosen over orchiectomy for cosmetic and emotional reasons. Eventually, total androgen blockade may prove to be better than orchiectomy or GnRH agonists used alone.

Each treatment has disadvantages that limit its use in certain circumstances. Although orchiectomy is a low-risk surgery, the psychological impact of removing the testicles can be significant, and sterility is certain. The loss of testosterone can cause hot flashes, weight gain, loss of libido, enlargement of the breasts (gynecomastia), impotence, testicular atrophy, penile atrophy, and osteoporosis. GnRH agonists eventually cause the same side effects as orchiectomy but may cause worse symptoms at the beginning of treatment. When GnRH agonists are first used, testosterone surges can lead to increased bone pain from metastatic cancer, so antiandrogens or abarelix is often added to blunt these side effects. Estrogens are not commonly used because they increase the risk for cardiovascular disease and blood clots. In general, the antiandrogens do not cause impotence, and usually cause less loss of bone and muscle mass. Ketoconazole can cause liver damage with prolonged use, and aminoglutethimide can cause skin rashes.

Surgery

Surgical removal of the prostate, or prostatectomy, is a common treatment either for early stage prostate cancer or for cancer that has failed to respond to radiation therapy. The most common type is radical retropubic prostatectomy, when the surgeon removes the prostate through an abdominal incision. Another type is radical perineal prostatectomy, when the surgeon removes the prostate through an incision in the perineum, the skin between the scrotum and anus. Radical prostatectomy can also be performed laparoscopically, through a series of small (1 cm) incisions in the abdomen, with or without the assistance of a surgical robot.

Radical prostatectomy

Radical prostatectomy is effective for tumors that have not spread beyond the prostate; cure rates depend on risk factors such as PSA level and Gleason grade. However, it may cause nerve damage that may significantly alter the quality of life of the prostate cancer survivor.

Radical prostatectomy has traditionally been used alone when the cancer is localized to the prostate. In the event of positive margins or locally advanced disease found on pathology, adjuvant radiation therapy may offer improved survival. Surgery may also be offered when a cancer is not responding to radiation therapy. However, because radiation therapy causes tissue changes, prostatectomy after radiation has higher risks of complications.

Laparoscopic radical prostatectomy, LRP, is a new way to approach the prostate surgically with intent to cure. Contrasted with the open surgical form of prostate cancer surgery, laparoscopic radical prostatectomy requires a smaller incision. Relying on

modern technology, such as miniaturization, fiber optics, and the like, laparoscopic radical prostatectomy is a minimally invasive prostate cancer treatment but is technically demanding and seldom done in the USA.

Some believe that in the hands of an experienced surgeon, robotic-assisted laparoscopic prostatectomy (RALP) may reduce positive surgical margins when compared to radical retropubic prostatectomy (RRP) among patients with prostate cancer according to a retrospective study. The relative risk reduction was 57.7%. For patients at similar risk to those in this study (35.5% of patients had positive surgical margins following RRP), this leads to an absolute risk reduction of 20.5%. 4.9 patients must be treated for one to benefit (number needed to treat = 4.9). Other recent studies have shown RALP to result in a significantly higher rate of positive margins. Other studies showed no difference of robotic to open surgery. A recent French study comparing standard laparoscopic to robotic to open prostatectomy showed no difference in margin status or biochemical recurrence at 5 years. The relative merits of RALP and potential benefit versus open radical prostatectomy is currently an area of intense research and debate in urology. The only proven and accepted advantage to RALP is less intraoperative blood loss. Other suggested advantages beyond this lack definitive data and have not been widely accepted by the broader urological community.

Transurethral resection of the prostate

Transurethral resection of the prostate, commonly called a "TURP," is a surgical procedure performed when the tube from the bladder to the penis (urethra) is blocked by prostate enlargement. In general, TURP is for benign disease and is not meant as definitive treatment for prostate cancer. During a TURP, a small instrument (cystoscope) is placed into the penis and the blocking prostate is cut away.

Orchiectomy

In metastatic disease, where cancer has spread beyond the prostate, removal of the testicles (called orchiectomy) may be done to decrease testosterone levels and control cancer growth.

Cryosurgery

Cryosurgery is another method of treating prostate cancer in which the prostate gland is exposed to freezing temperatures. It is less invasive than radical prostatectomy, and general anesthesia is less commonly used. Under ultrasound guidance, a method invented by Dr. Gary Onik, metal rods are inserted through the skin of the perineum into the prostate. Highly-purified argon gas is used to cool the rods, freezing the surrounding tissue at −186 °C (−302 °F). As the water within the prostate cells freezes, the cells die. The urethra is protected from freezing by a catheter filled with warm liquid. In general, cryosurgery causes fewer problems with urinary control than other treatments, but impotence occurs up to ninety percent of the time. When used as the initial treatment for prostate cancer and in the hands of an experienced cryosurgeon, cryosurgery has a 10-

year biochemical disease-free rate superior to all other treatments including radical prostatectomy and any form of radiation. Cryosurgery has also been demonstrated to be superior to radical prostatectomy for recurrent cancer following radiation therapy.

Brachytherapy

Brachytherapy for prostate cancer involves the surgical placement of radioactive 'seeds' or implants directly into the cancerous portions of the prostate, where the radiation kills the surrounding cancerous cells. It is therefore usually classified as a radiation treatment, rather than as a surgical treatment, because the actual treatment of the disease is by radiation, not surgery. See: Brachytherapy, below

Complications of surgery

The most common serious complications of surgery are loss of urinary control and impotence. Reported rates of both complications vary widely depending on how they are assessed, by whom, and how long after surgery, as well as the setting (e.g., academic series vs. community-based or population-based data). Although penile sensation and the ability to achieve orgasm usually remain intact, erection and ejaculation are often impaired. Medications such as sildenafil (Viagra), tadalafil (Cialis), or vardenafil (Levitra) may restore some degree of potency. For most men with organ-confined disease, a more limited "nerve-sparing" technique may help reduce urinary incontinence and impotence.

Radiation therapy

Overview

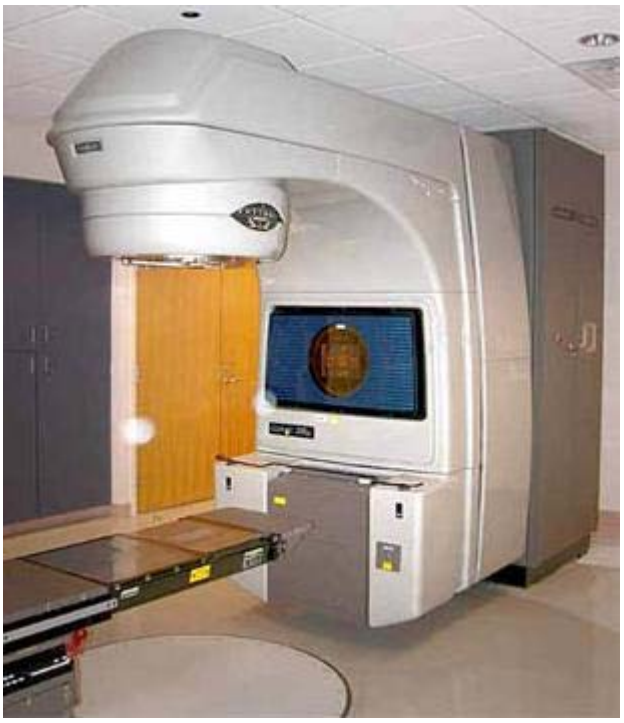
Brachytherapy for prostate cancer is administered using "seeds," small radioactive pellets or ribbons implanted directly into the tumor.

Radiation therapy, also known as radiotherapy, is often used to treat all stages of prostate cancer. It is also often used after surgery if the surgery was not successful at curing the cancer. Radiotherapy uses ionizing radiation to kill prostate cancer cells. When absorbed in tissue, Ionizing radiation such as gamma and x-rays damage the DNA in cancer cells, which increases the probability of apoptosis (cell death). Normal cells are able to repair radiation damage, while cancer cells are not. Radiation therapy exploits this fact to treat cancer. Two different kinds of radiation therapy are used in prostate cancer treatment: external beam radiation therapy and brachytherapy (specifically prostate brachytherapy).

External beam radiation therapy

External beam radiation therapy uses a linear accelerator to produce high-energy x-rays that are directed in a beam towards the prostate. A technique called Intensity Modulated Radiation Therapy (IMRT) may be used to adjust the radiation beam to conform with the

shape of the tumor, allowing higher doses to be given to the prostate and seminal vesicles with less damage to the bladder and rectum. External beam radiation therapy is generally given over several weeks, with daily visits to a radiation therapy center. New types of radiation therapy such as IMRT have fewer side effects than traditional treatment. Doctors are also studying proton therapy for prostate cancer, which uses protons rather than X-rays to kill the cancer cells. They are also studying types of stereotactic body radiotherapy (SBRT) to treat prostate cancer.



External beam radiation therapyfor prostate cancer is delivered by a linear accelerator, such as this one.

Brachytherapy

Permanent implant brachytherapy is a popular treatment choice for patients with low to intermediate risk features, can be performed on an outpatient basis, and is associated with good 10-year outcomes with relatively low morbidity It involves the placement of about 100 small "seeds" containing radioactive material (such as iodine-125 orpalladium-103) with a needle through the skin of the perineum directly into the tumor while under spinal or general anesthetic. These seeds emit lower-energy X-rays which are only able to travel a short distance. Although the seeds eventually become inert, they remain in the prostate permanently. The risk of exposure to others from men with implanted seeds is generally accepted to be insignificant. However, men are encouraged to talk to their doctors about any special temporary precautions around small children and pregnant women.

Uses

Radiation therapy is commonly used in prostate cancer treatment. It may be used instead of surgery or after surgery in early stage prostate cancer (adjuvant radiotherapy). Radiation treatments also can be combined with hormonal therapy for intermediate risk disease, when surgery or radiation therapy alone is less likely to cure the cancer. Some radiation oncologists combine external beam radiation and brachytherapy for intermediate to high-risk situations. Radiation therapy is often used in conjunction with hormone therapy for high-risk patients. Others use a "triple modality" combination of external beam radiation therapy, brachytherapy, and hormonal therapy. In advanced stages of prostate cancer, radiation is used to treat painful bone metastases or reduce spinal cord compression.

Radiation therapy is also used after radical prostatectomy either for cancer recurrence or if multiple risk factors are found during surgery. Radiation therapy delivered immediately after surgery when risk factors are present (positive surgical margin, extracapsular extension, seminal vessicle involvement) has been demonstrated to reduce cancer recurrence, decrease distant metastasis, and increase overall survival in two separate randomized trials.

Side effects

Side effects of radiation therapy might occur after a few weeks into treatment. Both types of radiation therapy may cause diarrhea and mild rectal bleeding due to radiation proctitis, as well as potential urinary incontinence and impotence. Symptoms tend to improve over time except erections which typically worsen as time progresses.

Comparison to surgery

Multiple retrospective analyses have demonstrated that overall survival and disease-free survival outcomes are similar between radical prostatectomy, external beam radiation therapy, and brachytherapy. Rates for impotence when comparing radiation to nerve-sparing surgery are similar. Radiation has lower rates of incontinence compared with surgery, but has higher rates of occasional mild rectal bleeding. Men who have undergone external beam radiation therapy may have a slightly higher risk of later developing colon cancer and bladder cancer.

High intensity focused ultrasound (HIFU)

HIFU for prostate cancer utilizes high-intensity focused ultrasound to ablate/destroy the tissue of the prostate. During the HIFU procedure, sound waves are used to heat the prostate tissue, thus destroying the cancerous cells. In essence, ultrasonic waves are precisely focused on specific areas of the prostate to eliminate the prostate cancer, with minimal risks of affecting other tissue or organs. Temperatures at the focal point of the sound waves can exceed 100 °C (212 °F). The ability to focus the ultrasonic waves leads to a relatively low occurrence of both incontinence and impotence. (0.6% and 0-20%,

respectively) According to preliminary international studies, HIFU has a high success rate with a reduced risk of side effects. Studies using HIFU machine have shown that 94% of patients with a pretreatment PSA (Prostate Specific Antigen) of less than 10 ng/mL were cancer-free after three years. However, many studies of HIFU were performed by manufacturers of HIFU devices, or members of manufacturers' advisory panels.

HIFU was first used in the 1940s and 1950s in efforts to destroy tumors in the central nervous system. Since then, HIFU has been shown to be effective at destroying malignant tissue in the brain, prostate, spleen, liver, kidney, breast, and bone. Today, the HIFU procedure for prostate cancer is performed using a transrectal probe. This procedure has been performed for over ten years and is currently approved for use in Japan, Europe, Canada, and parts of Central and South America.

Contraindications to HIFU for prostate cancer include a prostate volume larger than 40 grams, which can prevent targeted HIFU waves from reaching the anterior and anterobasal regions of the prostate, anatomic or pathologic conditions that may interfere with the introduction or displacement of the HIFU probe into the rectum, and high-volume calcification within the prostate, which can lead to HIFU scattering and transmission impairment.

HIFU is currently not approved for medical use in the United States. Current NCCN guidelines for the treatment of prostate cancer do not include HIFU as part of standard of care, though many promising clinical trials exist. Many patients have received the HIFU procedure at facilities in Canada, and Central, and South America.

Palliative care

Palliative care for advanced stage prostate cancer focuses on extending life and relieving the symptoms of metastatic disease. As noted above, Abiraterone Acetate is showing some promise in treating advance-stage prostate cancer. It causes a dramatic reduction in PSA levels and Tumor sizes in aggressive advanced-stage prostate cancer for 70% of patients. Chemotherapy may be offered to slow disease progression and postpone symptoms. The most commonly-used regimen combines the chemotherapeutic drug docetaxel with a corticosteroid such as prednisone.one study showed that treatment with docetaxel with prednisone prolonged life from 16.5 months for those taking mitoxantrone and prednisone to 18.9 months for those taking docetaxel + prednisone. Bisphosphonates such as zoledronic acid have been shown to delay skeletal complications such as fractures or the need for radiation therapy in patients with hormone-refractory metastatic prostate cancer. Alpharadin is a new alpha emitting pharmaceutical targeting bone metastasis. The phase II testing shows prolonged patient survival times, reduced pain, and improved quality of life.

Bone pain due to metastatic disease is treated with opioid pain relievers such as morphine and oxycodone. External beam radiation therapy directed at bone metastases may provide

pain relief. Injections of certain radioisotopes, such as strontium-89, phosphorus-32, or samarium-153, also target bone metastases and may help relieve pain.

Alternative therapies

As an alternative to active surveillance or definitive treatments, other therapies are also under investigation for the management of prostate cancer. PSA has been shown to be lowered in men with apparent localized prostate cancer using a vegan diet (fish allowed), regular exercise, and stress reduction. These results have so far proven durable after two-years' treatment. However, this study did not compare the vegan diet to either active surveillance or definitive treatment, and thus cannot comment on the comparative efficacy of the vegan diet in treating prostate cancer.

Many other single agents have been shown to reduce PSA, slow PSA doubling times, or have similar effects on secondary markers in men with localized cancer in short term trials, such as pomegranate juice or genistein, an isoflavone found in various legumes.

The potential of using multiple such agents in concert, let alone combining them with lifestyle changes, has not yet been studied. A more thorough review of natural approaches to prostate cancer has been published.

Neutrons have been shown to be superior to X-rays in a the treatment of prostatic cancer. The rationale is that tumours containing hypoxic cells (cells with enough oxygen concentration to be viable, yet not enough to be X-ray-radiosensitive) and cells deficient in oxygen are resistant to killing by X-rays. Thus, the lower Oxygen Enhancement Ratio (OER) of neutrons confers an advantage. Also, neutrons have a higher relative biological effectiveness (RBE) for slow-growing tumours than X-rays, allowing for an advantage in tumour cell killing.