

Part 1

Tumors of the Prostate Gland

Tumors of the Prostate Gland, Seminal Vesicles, Penis, and Scrotum

1

THE NORMAL PROSTATE GLAND

ANATOMY

The adult prostate gland surrounds the urethra immediately below the base of the urinary bladder and is located posterior to the inferior symphysis pubis, superior to the urogenital diaphragm, and anterior to the rectum (fig. 1-1) (1,2). It has a shape like a truncated cone or a top lying on its side, with the base in direct continuity with the urinary bladder neck (fig. 1-2). The seminal vesicles lie posterolateral to the base of the bladder and join with the ampulla of the vasa deferentia to form paired intraprostatic ejaculatory ducts. These ejaculatory ducts course through the base of the prostate to their exit at the posterior urethral protuberance, known as the verumontanum (or

colliculus seminalis) (figs. 1-3, 1-4). The utricle, a vestigial müllerian structure, is a central depression in the verumontanum.

The prostatic urethra is formed at the bladder neck, turns anteriorly 35 degrees at its midpoint (the urethral angle), and exits the prostate at its apex, where it is continuous with the membranous urethra. The urethral angle divides the urethra into proximal (so-called preprostatic) and distal (so-called prostatic) segments. The apex of the prostate is attached to the urogenital diaphragm. A patch of nonglandular tissue, called the anterior fibromuscular stroma, is present anteriorly over the prostate and extends from the bladder neck to the apex of the gland.

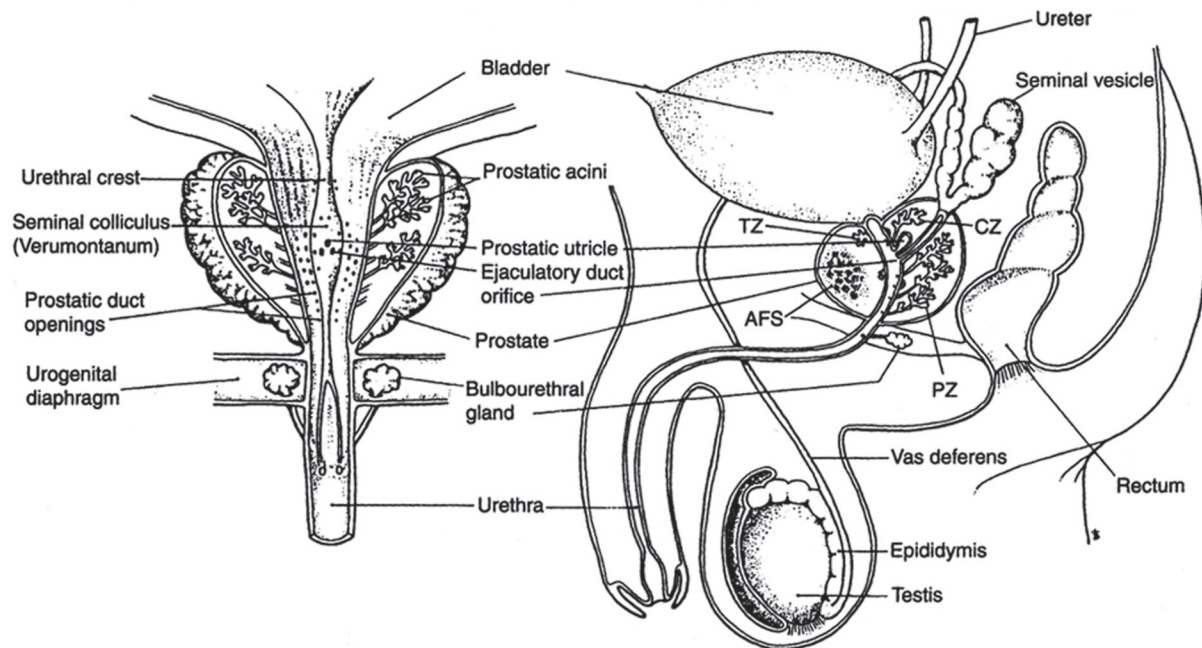


Figure 1-1

ANATOMY OF PROSTATE IN FRONTAL (LEFT) AND SAGITTAL (RIGHT) VIEWS

Abbreviations: TZ = transition zone, CZ = central zone, PZ = peripheral zone, AFS = anterior fibromuscular stroma. (Fig. 4-4 from Timms BG. Anatomical perspectives of prostate development. In: Naz RK, ed. Prostate: basic and clinical aspects. New York: CRC Press; 1997:36.)

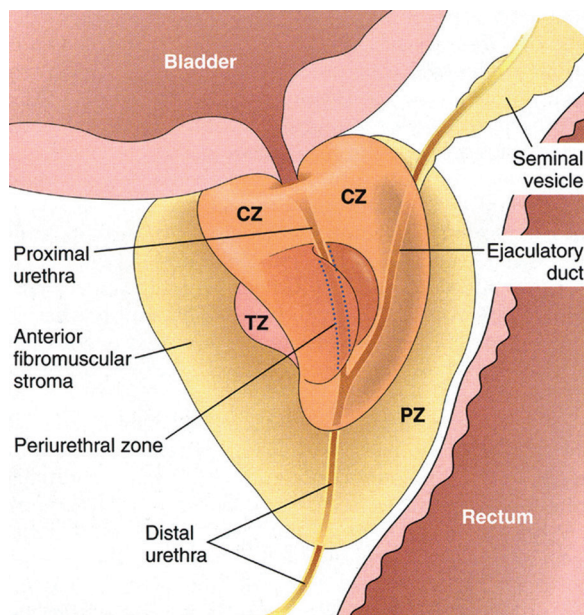


Figure 1-2

ANATOMY OF ADULT PROSTATE

The prostate has three zones: central zone (CZ, through which the ejaculatory ducts course), transition zone (TZ, site of benign prostatic hyperplasia [BPH] nodules), and the peripheral zone (PZ), where most carcinomas arise. (Fig. 21-30 from Kumar V, Abbas AK, Fausto N, eds. Robbins and Cotran pathologic basis of disease, 7th ed. Philadelphia: Elsevier; 2005:1047.)

The prostate gland measures 5 x 4 x 3 cm. It weighs 20 g from ages 20 to 50 years, with an increase to 30 g from ages 60 to 80 years (2,3-5).

Anatomic Models

Over the past century, anatomic models of the prostate have emphasized the concept of lobes or zones (fig. 1-5) (2,4,6-11). The prostate was thought to possess from two to six lobes. In the first half of the twentieth century, the five-lobe model (7) dominated, but this was based on embryonic and fetal prostates, not adult glands. In 1954, Franks (8) put forth the idea of an outer gland (where carcinomas arose) and a periurethral inner gland. Further evolution of this concept occurred when McNeal developed the zonal model that is currently widely used (2,4,5,9). This model defines three zones: a central zone, a transition zone, and a peripheral zone (figs. 1-2, 1-4, 1-6). It may be difficult to grossly and microscopically recognize a sharp demarcation between these zones (12,13),

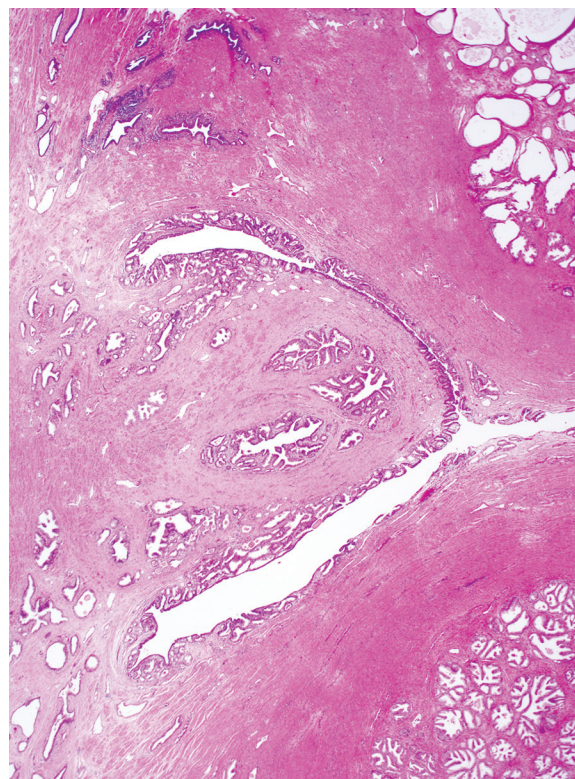


Figure 1-3

VERUMONTANUM

This is a mound of tissue projecting into the urethral lumen, which is here compressed into an angular slit-like space.



Figure 1-4

NORMAL PROSTATE GLAND

Cross section of prostate gland from a young adult male at the level of the verumontanum. (Courtesy of Dr. W. A. Sakr, Detroit, MI.)

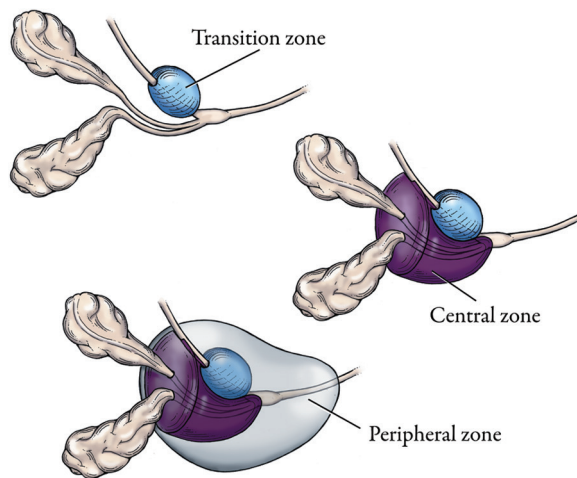


Figure 1-5
ADULT PROSTATE: ZONAL ANATOMY

although occasionally, a fibrous band separates the transition zone from the peripheral zone at the macroscopic level. These zones do appear to have structural differences and diseases differentially affect these zones.

Carcinoma of the prostate tends to arise in the peripheral zone, while benign prostatic hyperplasia (BPH) is typically a transition zone process. Ten to 20 percent of carcinomas do arise in the transition zone (14,15), while the central zone is remarkably resistant to disease, with only about 3 percent of carcinomas arising there (16).

The transition zone, which normally makes up 5 percent of prostate gland volume, wraps around the proximal urethra (fig. 1-2). The main ducts of this zone drain into posterolateral recesses of the urethra at a point just proximal to the urethral angle. Some of the more medial ducts penetrate through the thick smooth muscle bundles of the preprostatic sphincter. Also found in the smooth muscle of the preprostatic sphincter are minute ducts and abortive acinar arrangements of periurethral glands, which constitute only about 1 percent of the total glandular volume of the prostate.

The central zone makes up about 25 percent of the entire prostate gland and is a posteriorly situated cone-like structure with the base of the cone projecting toward the base of the bladder. The paired ejaculatory ducts run through the

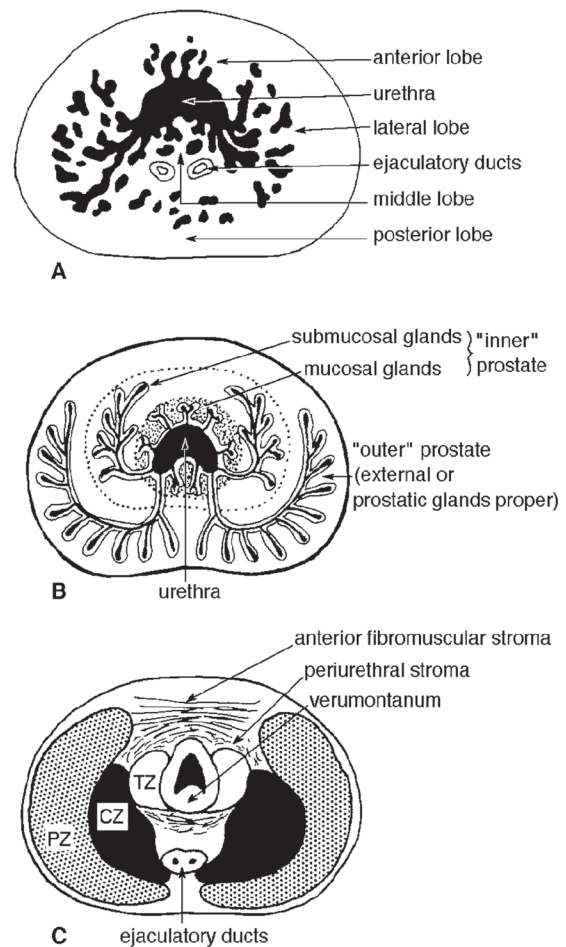


Figure 1-6

ANATOMIC MODELS OF PROSTATE GLAND

A: Lowsley lobar model: note location of anterior, posterior, lateral, and middle lobes.

B: Frank concentric zone model: mucosal and submucosal glands comprise the "outer" prostate.

C: McNeal zonal model: periurethral transition zone (TZ), central zone (CZ) closely related to ejaculatory ducts, and peripheral zone (PZ) wrapping around the CZ. In the anterior aspect, stroma predominates and is referred to as the anterior fibromuscular stroma.

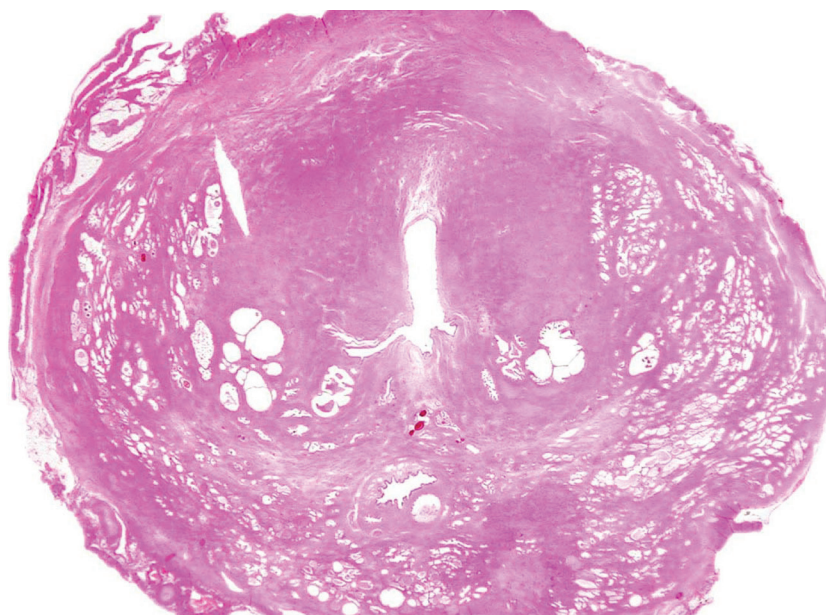
central zone. The ducts from the central zone drain into the urethra via orifices positioned next to the ejaculatory duct orifices on the verumontanum.

The peripheral zone of the prostate gland is the bulk of the posterior, lateral, and apical portions of the gland, with a small portion wrapping anteriorly, known as the anterior horn of the peripheral zone. The peripheral zone accounts for

Figure 1-7

**ANTERIOR
FIBROMUSCULAR STROMA**

Anterior fibromuscular stroma is located anterior to the urethra (top). (Courtesy of Dr. S. Fine, New York, NY.)



70 percent of the total gland volume. The ducts of this zone empty into the posterior urethral recesses or grooves in a double row from the verumontanum to the prostatic apex.

The designation of prostatic lobes has been advanced by some in clinical medicine so that pathologists may receive needle biopsies from the “right lobe” or “left lobe,” although the designation of “right side” or “left side,” respectively, is preferable.

A patch of nonglandular tissue, the anterior fibromuscular stroma, is located anteriorly over the prostate and extends from the bladder neck to the apex of the prostate (figs. 1-2, 1-7) (17). The anterior fibromuscular stroma is composed of fibrous tissue and compact smooth muscle bundles that fuse with the smooth muscle tissue of the bladder neck at the prostate base, and interdigitate with skeletal muscle of the urogenital diaphragm at the apex. The external surface of the anterior fibromuscular stroma is in continuity with adipose tissue in the space of Retzius (2).

Additional nonglandular tissues are the preprostatic sphincter and the striated sphincter (2). The preprostatic sphincter is a cylinder of smooth muscle that encircles the proximal segment of the prostatic urethra. It functions to prevent retrograde flow of seminal fluid and also perhaps to maintain closure of the proximal urethra via its resting tone. The striated

sphincter is composed of skeletal muscle fibers around the distal prostatic urethra, between the verumontanum and the prostatic apex. It is incomplete posterolaterally, and is contiguous with the external urethral sphincter distal to the prostatic apex.

“Capsule”

Although the term “prostatic capsule” has been used in the past, and is still less frequently used, there is no well-defined fibromuscular band surrounding the prostate gland. There is Denonvilliers fascia, which is a sheath between the rectum and prostate that covers the posterior aspect of the prostate and seminal vesicles.

Despite the absence of a distinct capsule surrounding the prostate, there are well-defined edges posteriorly, posterolaterally, and laterally, except at the most apical and basal portions of the gland. The best method of determining the outer boundary of the prostate gland in these areas is where the condensed smooth muscle of the prostate ends. Exterior to the prostate, there is either adipose tissue or loose connective tissue containing small wisps of smooth muscle, vessels, and nerves (figs. 1-8, 1-9). Anteriorly and anterolaterally, the muscle of the prostate continues out to the pubic bone, and only the presence of adipose tissue denotes extraprostatic tissue. At the apex, there is a jumble of smooth muscle, skeletal muscle, and fibroelastic fibers.

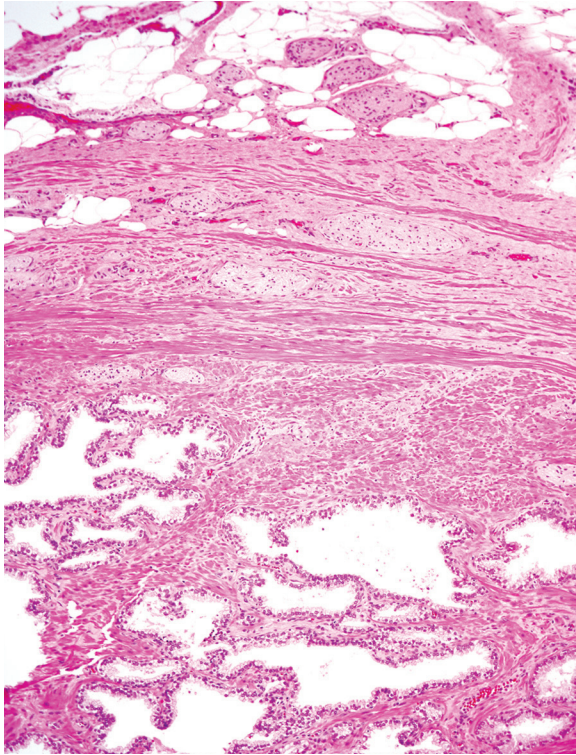


Figure 1-8

FIBROMUSCULAR BAND, OR "PROSTATIC CAPSULE"

This separates prostatic glands (bottom) from peri-prostatic adipose tissue (top).

The urethral striated sphincter (rhabdosphincter) is in direct continuity with the prostate, and skeletal muscle fibers are normally found at an anterior and apical location within the substance of the gland itself (fig. 1-10) (21). At the bladder neck, there is no clear separation of bladder and prostate, and the compact irregular smooth muscle of the prostate stroma gradually transitions into discrete smooth muscle bundles of the bladder neck. However, prostate tissue also is seen in these discrete smooth muscle bundles at the prostate interface, blurring the edge between prostate and bladder (fig. 1-11).

Since there is no true histologically distinct prostatic "capsule," it is preferable not to refer to "capsular penetration" when noting tumor that has spread beyond the gland. Rather, a more appropriate designation is to state whether tumor is organ-confined or shows extraprostatic extension.

The term capsule has also been used by urologists in referring to a "surgical capsule," which is a surgical plane of dissection when enucleating

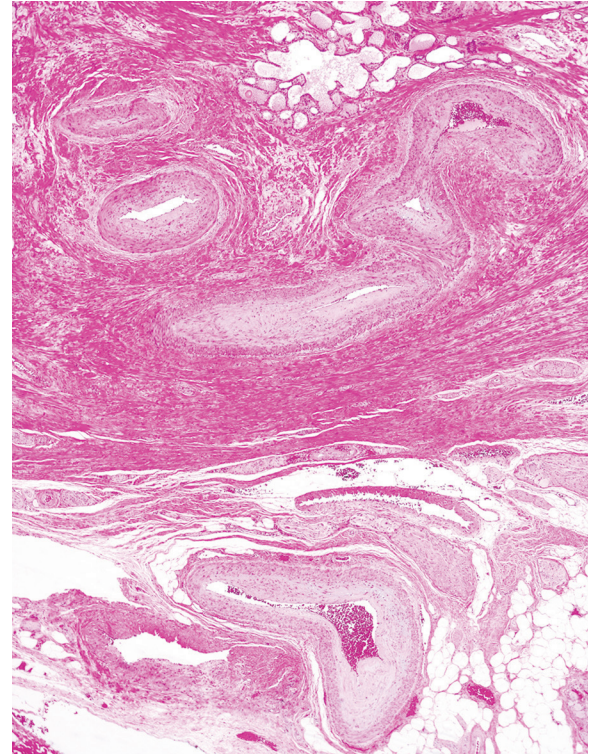


Figure 1-9

LARGE BLOOD VESSELS IN PROSTATE

These are present in prostate and in extraprostatic locations.

nodules of BPH by blunt dissection between the nodules and the peripheral zone. However, histologically, a true capsule (a discrete fibrous or fibromuscular band of tissue) does not separate the BPH nodules from the peripheral zone.

Blood Supply

The blood supply to the prostate gland is from the inferior vesical artery, which branches off the internal iliac artery (22) and terminates in capsular and urethral arterial groups (fig. 1-12). Venous drainage is into the plexus of Santorini.

Lymphatic Drainage

There is a network of intraprostatic lymphatics that drain principally into obturator and then internal iliac lymph nodes. A minor amount of drainage occurs through the presacral group and external iliac nodes. An uncommon site of flow is through periprostatic or periseminal vesicle lymph nodes (fig. 1-13), which are found in about 4 percent of radical prostatectomy specimens (24).

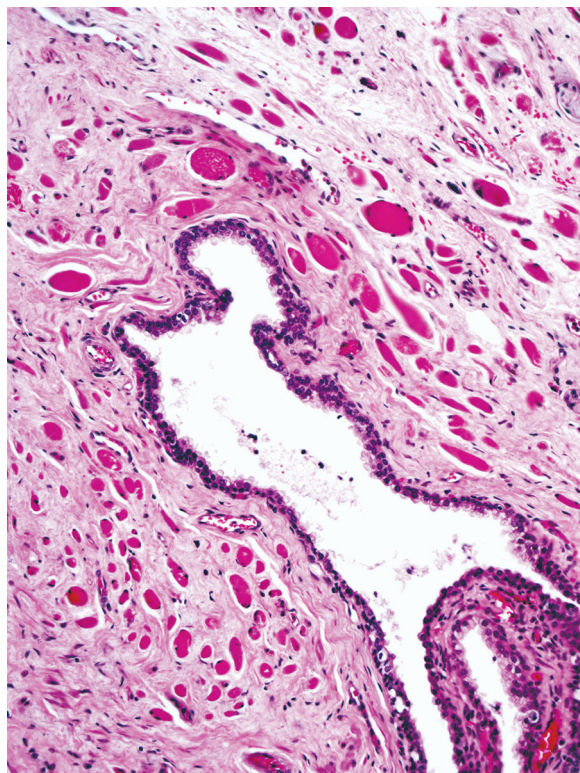


Figure 1-10

SKELETAL MUSCLE IN PROSTATE

Benign prostatic gland surrounded by skeletal muscle fibers at the apex.

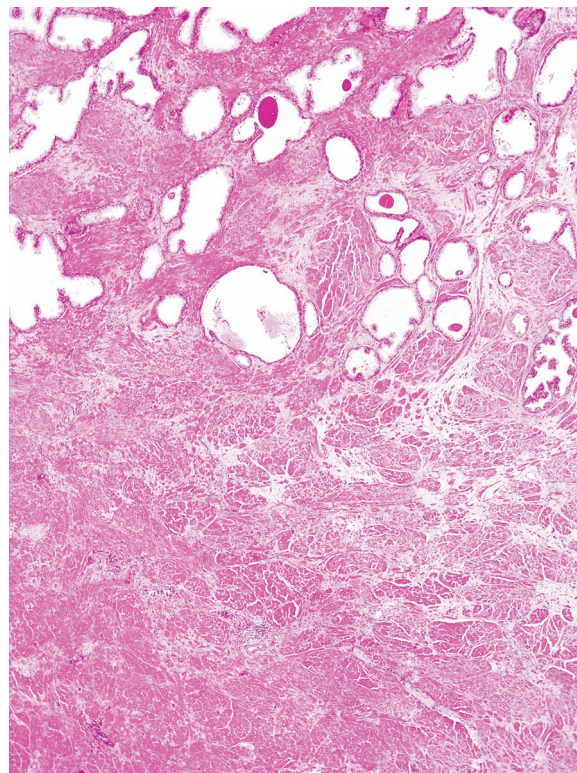


Figure 1-11

PROSTATIC INTERFACE WITH BLADDER

Junction between prostate gland (top) and urinary bladder neck (bottom). The smooth muscle stroma is continuous.

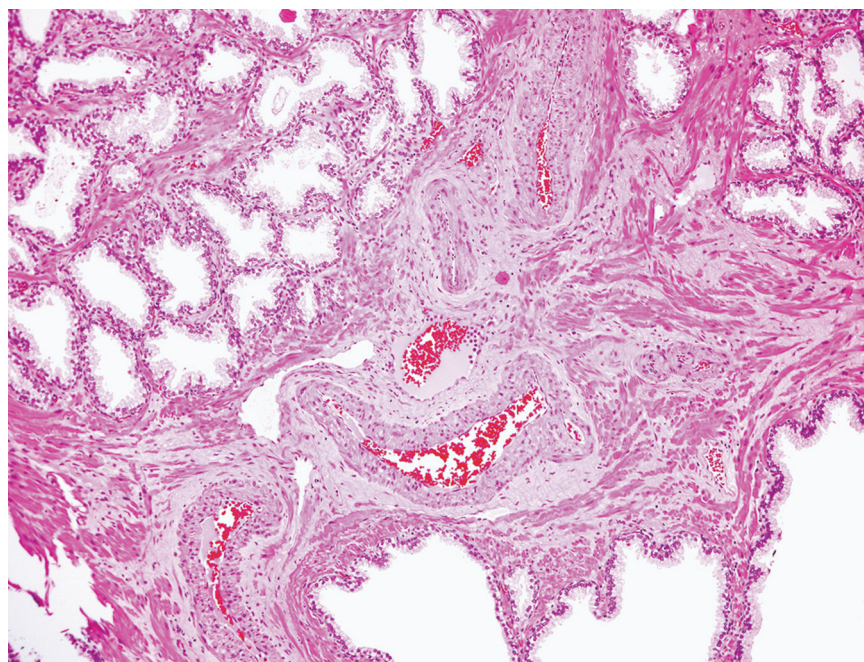


Figure 1-12

BLOOD VESSELS IN PROSTATIC STROMA

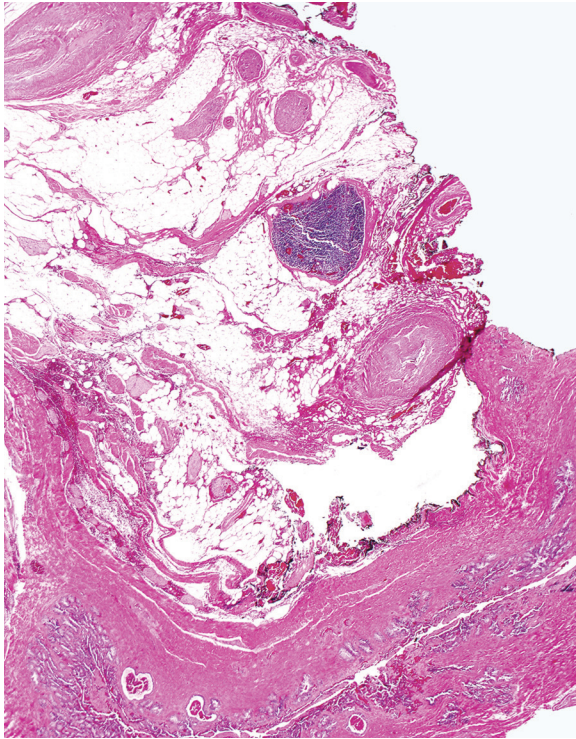


Figure 1-13

PERISEMINAL VESICLE LYMPH NODE

The small size (1 mm) is typical for periprostatic and periseminal vesicle lymph nodes.

These tend to be small lymph nodes, averaging about 2 mm in greatest dimension.

Nerve Supply

The prostate gland has a rich nerve supply, with sympathetic and parasympathetic innervation arising from the pelvic plexus (25,26). These nerves run with branches of the capsular artery and penetrate the prostate: parasympathetic fibers course to acini and stimulate secretion and sympathetic fibers cause contraction of outer band "capsular" and intraprostatic smooth muscle. There is greater innervation of the peripheral zone than the transition zone (27).

Histologically, nerves are seen in the periprostatic neurovascular bundle (fig. 1-14), in the outer fibromuscular band, and in the prostate itself. Ganglia (fig. 1-15) and paraganglia (fig. 1-16) are usually found outside the gland but may also be found within it. Paraganglia are most often located in or adjacent to the lateral neurovascular bundles (28). Because ganglia and paraganglia

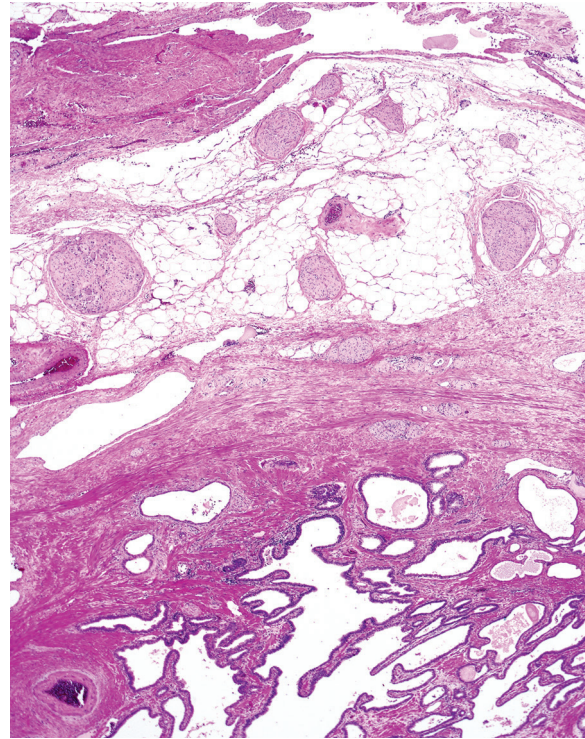


Figure 1-14

PERIPROSTATIC NERVES IN ADIPOSE TISSUE

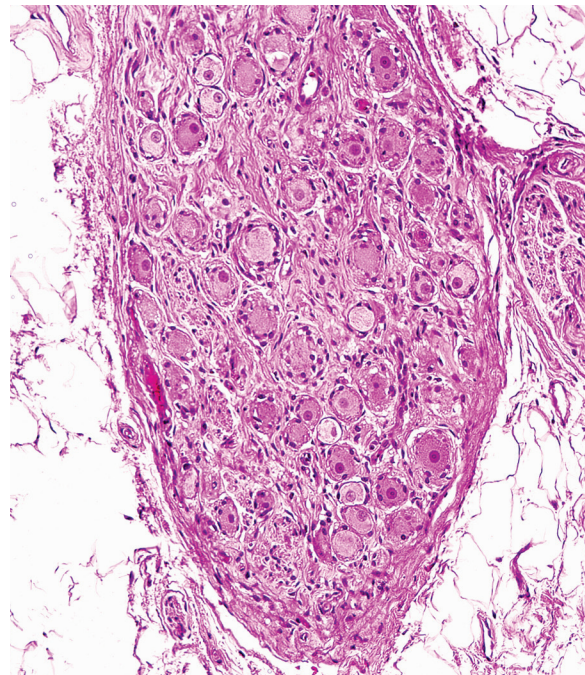


Figure 1-15

PERIPROSTATIC GANGLION

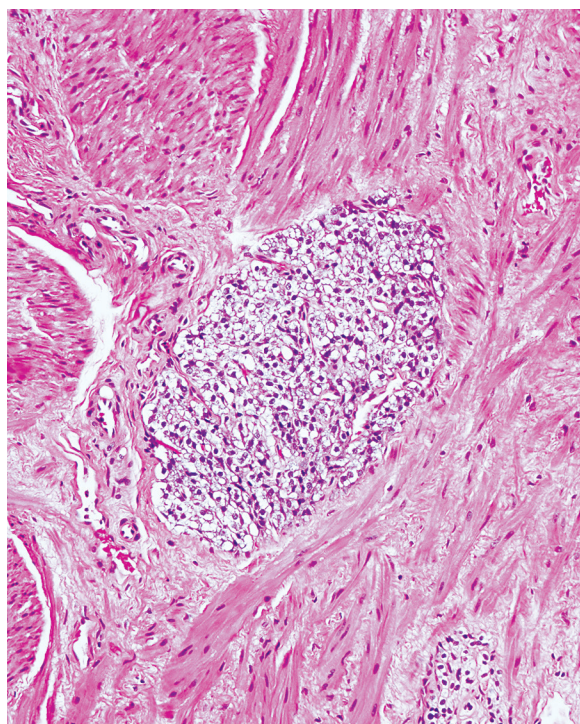


Figure 1-16

PERIPROSTATIC PARAGANGLION

Paraganglion in periprostatic bladder neck tissue (top) and in periprostatic soft tissue (bottom). The paraganglion in the bladder neck is nodular, while there is dispersion of variably sized nests in the periprostatic soft tissue, with a few single paraganglionic cells also present.

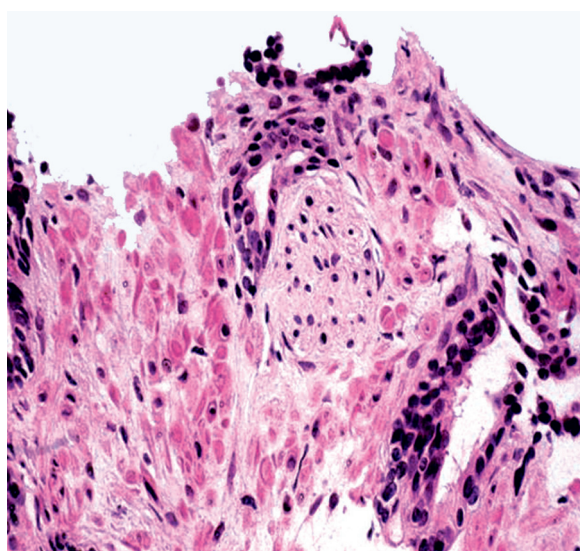


Figure 1-17

BENIGN PROSTATIC GLAND ABUTTING NERVE

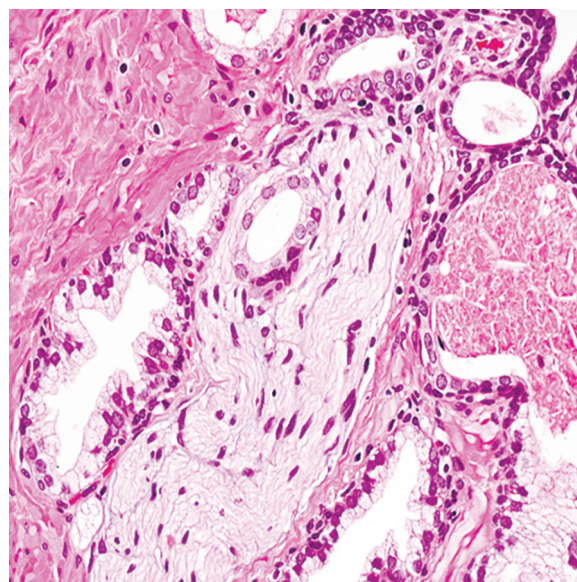


Figure 1-18

INTRANEURAL BENIGN PROSTATIC GLAND

are found inside the prostate and in the outer fibromuscular band, carcinoma invading around these structures should not necessarily be equated with extraprostatic extension.

Another diagnostic pitfall is the relationship of normal and benign prostatic glands to intraprostatic nerves. Benign prostatic glands can abut nerves (fig. 1-17) (29–31) and can even be found within nerves (fig. 1-18) (31,32). Such glands should not automatically be considered malignant, and a constellation of histomorphologic traits should be used in diagnosis, not solely the physical proximity of prostatic glands and nerves.

EMBRYOLOGY AND DEVELOPMENTAL ANATOMY

The prostate is derived from the urogenital sinus, and is first recognizable at 9 to 10 weeks of development (2). Testosterone from the embryonic testis stimulates ingrowth of endodermal buds into urogenital sinus mesenchyme. It is thought that there is a reciprocal interaction of epithelium and mesenchyme during development, by which, under the influence of androgens, urogenital sinus mesenchyme induces urogenital sinus epithelium to undergo prostatic ductal morphogenesis and differentiation (33,34). The differentiating prostatic epithelium, in turn, signals the

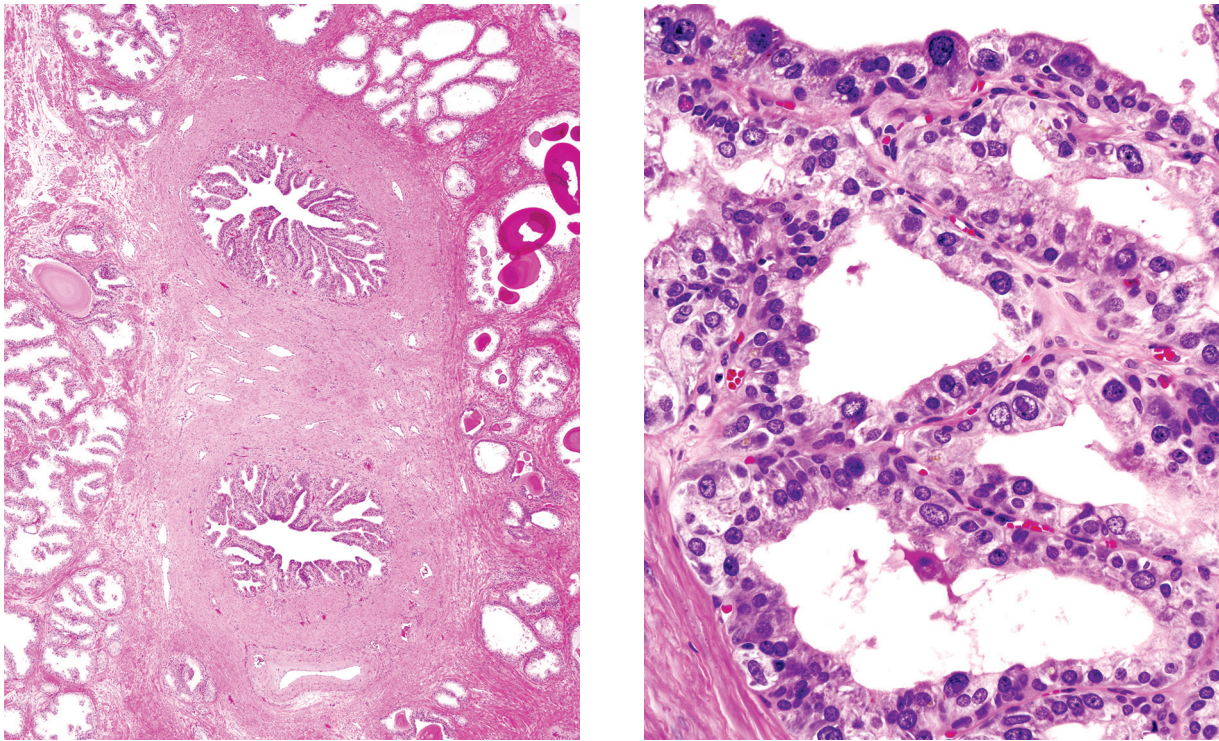


Figure 1-19

PAIRED EJACULATORY DUCTS

The paired ejaculatory duct epithelium (left) is identical to seminal vesicle epithelium, with nuclear atypia often observed (right).

urogenital mesenchyme to differentiate into smooth muscle cells that closely surround the epithelial ducts. This dynamic dance of tissue remodeling entails coordinated temporal and spatial processes of ductal budding, branching morphogenesis, cellular proliferation, and secretory function (35). By 13 weeks, some 70 primary ducts are present.

Three stages of development from 20 weeks' gestation to 1 month of age have been delineated (36). The bud stage at 20 to 30 weeks exhibits solid cellular buds at the end of ducts, with spindled cells in the center and columnar cells at the periphery. The bud-tubule stage at 31 to 36 weeks shows small collections of cellular buds and acinar structures. The third stage is characterized by more distinct lobular organization of acinotubular clusters. Squamous metaplasia of prostatic ducts and urethra is a common finding in the fetal prostate. This metaplasia is gradually lost after birth. The immunophenotype of fetal prostatic epithelial cells is similar to the rare adult transiently amplifying epithelial cells, which show coexpression of basal

and luminal cytokeratins, high proliferation, and lack of p27 expression (37).

Molecular pathways thought to be important in prostate organogenesis and morphogenesis include those regulated by androgens, hedgehog, p63, NKX3.1, SOX9, Noggin, fibroblast growth factor receptor, forkhead transcription factor, Notch, and BMP7. Most of this research, with a few exceptions (38), has been done in rodent model systems. Some of these molecules have been implicated in human prostate cancer biologic behavior (39). The definitive identification of prostatic epithelial stem cells involved in prostate gland development has not yet been realized, but cell populations enriched for cells exhibiting stem cell characteristics express the stem cell markers CD133 (positive), alpha2beta1 (high), CD44, and SCA-1 along with embryonic stem cell factors including OCT-1, NANOG, SOX2, and nestin (40).

The seminal vesicles, epididymis, vas deferens, and ejaculatory ducts (fig. 1-19) are formed from wolffian (mesonephric) ducts under the influence

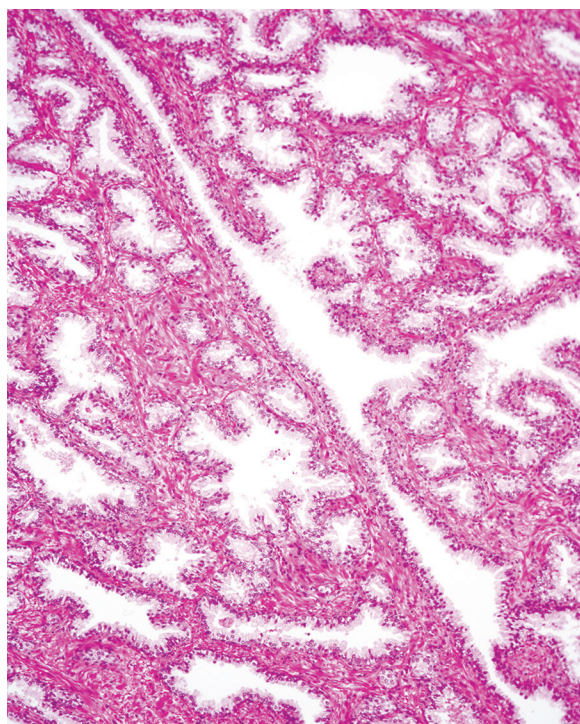


Figure 1-20

NORMAL PERIPHERAL ZONE

Branching glands in a fibromuscular stroma.

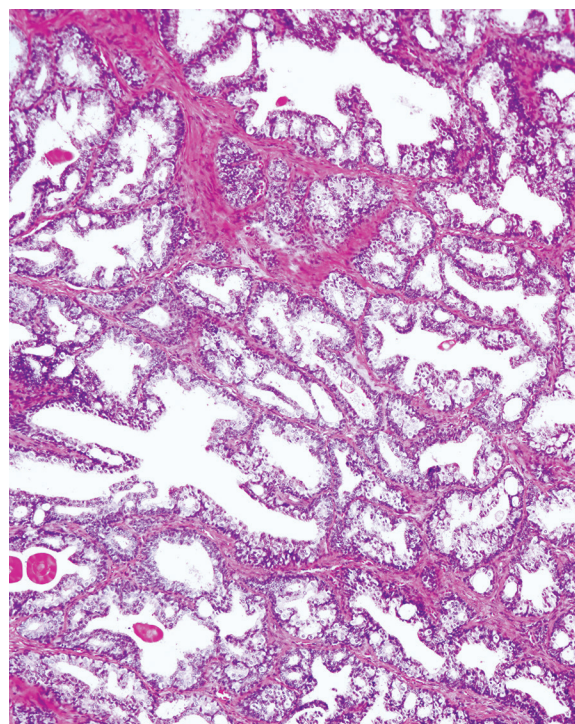


Figure 1-21

NORMAL CENTRAL ZONE GLANDS

There is crowding of complex glands with Roman bridge formation.

of testosterone. It has been proposed that the central zone of the prostate is also of mesodermal wolffian duct origin (2). In this model the prostate gland is of dual embryonic derivation.

After birth, there is an infantile resting period until 10 to 12 years of age, and then a pubertal maturation period until age 18. In the resting period, the size of the prostate gland remains stable but duct formation, solid budding at the periphery, and branching morphogenesis continue (35). The pubertal period is marked by a substantial androgen-driven increase in gland size, further branching, and differentiation of epithelium into adult-type basal and secretory cells.

HISTOLOGY

Microscopically, the normal adult prostate is a branching duct-acinar glandular system embedded in a dense fibromuscular stroma (fig. 1-20). Zonal architectural differences are appreciated (2). Normally, the peripheral zone ducts and acini are evenly distributed but are irregular in size and shape. Normal transition zone glands are

similar to those of the peripheral zone. Central zone glands are more densely arranged than peripheral and transition zone glands (fig. 1-21). The epithelial-stromal ratio in the central zone is 2 to 1, compared to 1 to 1 for the peripheral and transition zones. Also, central zone glands are larger and display intraluminal projections with fibrovascular cores. Central zone epithelium displays tall columnar cells with eosinophilic cytoplasm, a prominent basal cell layer, and on occasion, complex intraluminal architecture such as Roman bridge and cribriform formations (fig. 1-22). These findings can be misdiagnosed as prostatic intraepithelial neoplasia (PIN) (41). Central zone epithelium is distinctive in selective expression of pepsinogen II, lactoferrin, and lectin-binding sites (2). Central zone epithelium also differs from epithelium in other zones in proteomic profile (42).

The normal adult prostate is classically defined as having two epithelial cell layers: a luminal or secretory cell layer and a basal cell layer (fig. 1-23). A third cell type in normal

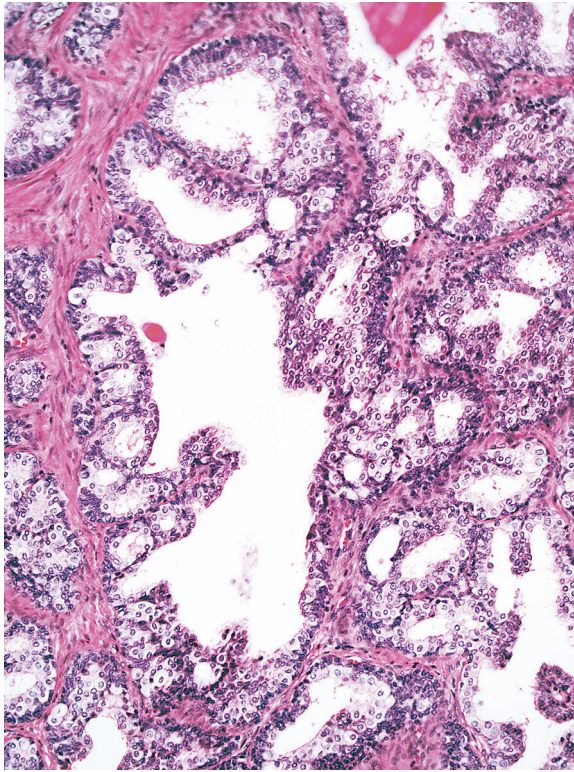


Figure 1-22

NORMAL CENTRAL ZONE GLAND COMPLEXITY

There are cribriform structures and arcades, and a prominent basal cell layer.

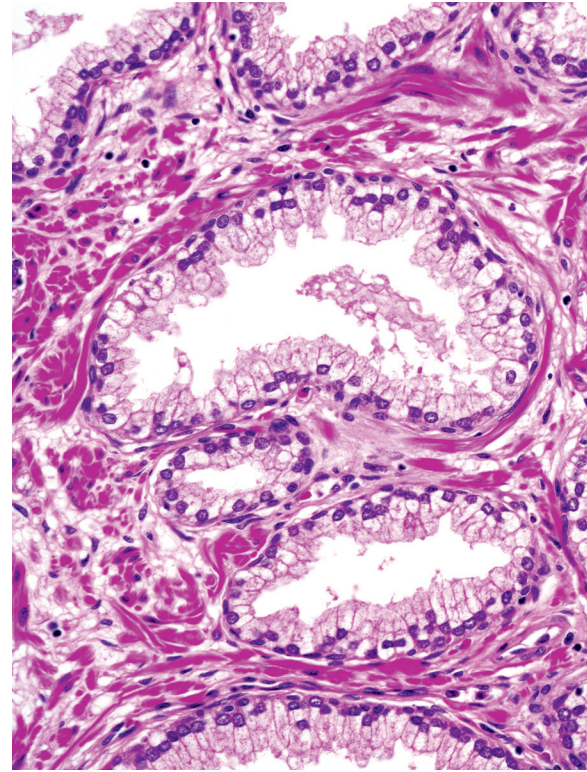


Figure 1-23

NORMAL GLANDULAR EPITHELIUM

Two cell layers are seen: an inner luminal secretory cell layer and an outer basal cell layer. Basal cells may be difficult to detect on hematoxylin and eosin (H&E)-stained sections.

prostatic epithelium is the neuroendocrine cell, which is less common. The secretory or luminal cells of the normal prostate glandular epithelium make up the bulk (about three quarters) of the epithelial volume. The secretory cells are cuboidal to columnar, with nuclei positioned in the basal to midportion of the cell. Cleared or lightly eosinophilic cytoplasm is a hallmark of normal prostatic secretory cells due to the presence of a large number of small clear secretory vacuoles. The central zone secretory cell cytoplasm is somewhat denser because it contains a smaller number of these vacuoles (2). Pigment is common in the cytoplasm of normal prostatic secretory epithelial cells (fig. 1-24). These granules are 1 to 3 μm in diameter, are apical or subnuclear, and are yellow-brown to gray-brown to blue by hematoxylin and eosin (H&E) staining (43). This lipofuscin pigment can also be found in the cytoplasm of seminal

vesicle and ejaculatory duct epithelium, where it is more abundant, coarser, and more refractile.

The nuclei of normal prostatic secretory epithelial cells are small and round, with fine, evenly dispersed chromatin. Nucleoli usually are not evident or are pinpoint in size. Nuclei in the central zone usually are larger than those in the peripheral zone and also appear crowded. This results in a pseudostratified nuclear appearance in the central zone, and along with the aforementioned denser cytoplasm, may yield a false impression of PIN (41).

The basal cell layer separates the secretory cells from the basement membrane and is nearly continuous (fig. 1-25). Basal cells in the prostatic epithelium often appear as rounded or oblong cells, but can also be flattened, spindled, cuboidal, and triangular (44). Basal cells have a scant amount of dense cytoplasm and small, hyperchromatic nuclei. The precise function of basal

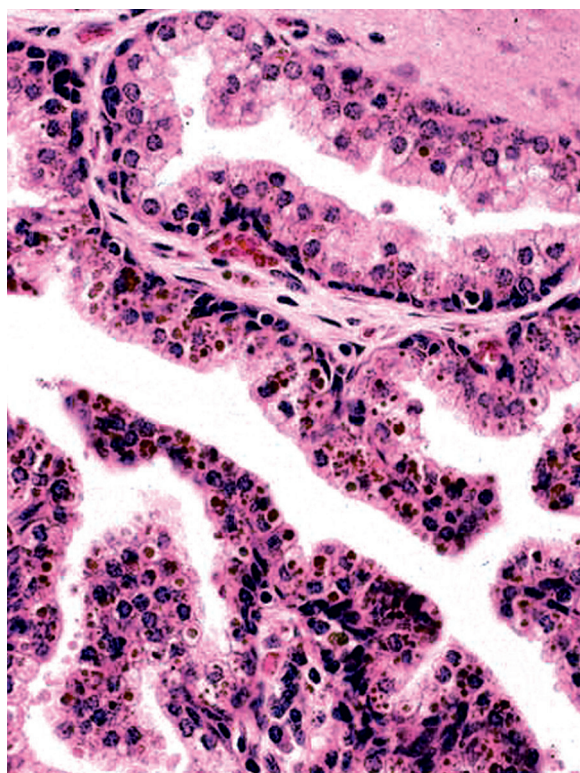


Figure 1-24

LIPOFUSCIN PIGMENT IN PROSTATIC EPITHELIUM

cells is unsettled, but they represent the proliferative component of prostatic epithelium. Stem cells may reside within the basal cell population.

Neuroendocrine (endocrine-paracrine) cells constitute a third population of cells in normal prostatic epithelium (45). These cells form about 0.4 percent of the total adult prostatic epithelial cell population. This is a terminally differentiated, postmitotic cell population. Neuroendocrine cells are usually recognizable only by histochemical (Fontana-Masson argentaffin and Churukian-Schenk argyrophil) or immunohistochemical staining (see Immunohistochemical Findings below). Neurosecretory granules of varying size are found in these cells by electron microscopy. The functional significance of neuroendocrine cells in the normal prostate is not clear, but it seems likely that the neuroendocrine products of these cells influence neighboring cells through the elaborate dendritic processes via a paracrine effect. Autocrine and endocrine influences may also be in operation.

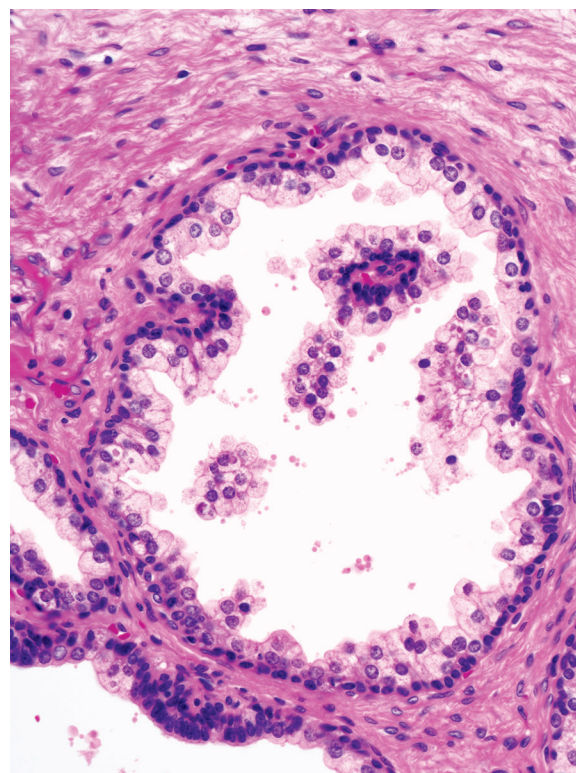


Figure 1-25

DARK BASAL CELLS

Normal prostate gland with prominent rim of dark basal cells.

Urothelium is another type of epithelial cell normally found in the prostate. In addition to lining the prostatic urethra, urothelium also normally lines major prostatic ducts (fig. 1-26). This ductal lining is variable in extent from one man to the next. The urothelium in the prostatic ducts differs from such lining elsewhere in the urinary tract in that an umbrella layer of cap cells is lacking and is replaced by secretory cells. Recognition of urothelium usually is straightforward: this is a multilayered epithelium with rounded to elongated nuclei, some of which possess nuclear grooves. A degree of cytoplasmic clearing usually is evident. When urothelium involves acini in the peripheral aspects of the prostate gland, the designation *urothelial metaplasia* is applied (46).

Intraluminal contents of normal prostate glands include shed and degenerating epithelial cells, corpora amylacea, and calculi. Corpora amylacea are extremely common in the normal prostate (seen in 78 percent of benign glands) (47). They

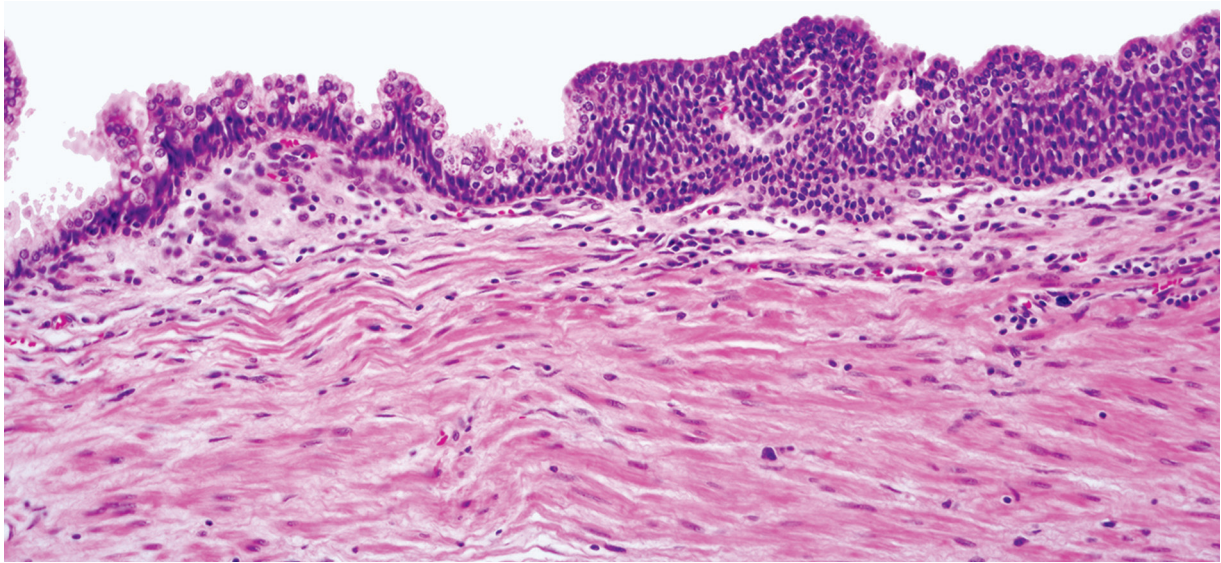


Figure 1-26

UROTHELIAL LINING OF A LARGE PROSTATIC DUCT

There is a preserved prostatic secretory cell layer, seen best on the left.

are inspissated secretions that often assume a concentrically lamellated appearance (48), like rings in a tree (fig. 1-27). They are mainly rounded and may vary widely in size and shape.

Corpora amylacea usually are pink to purple but may be yellow-gold to orange, particularly in verumontanum glands. Sometimes corpora can be seen in atrophic glands, with only a thin atrophic epithelial lining surrounding them, in spaces without an obvious epithelial lining, or in stroma, with or without associated giant cells. They often calcify and probably contribute to the formation of prostatic calculi. Prostatic corpora possess many cellular constituents, including RNA, DNA, lipid, mucopolysaccharide, and protein (49,50); by electron microscopy they show interwoven fibrils arranged in rings (51).

Prostatic calculi are also extremely common, and are detectable in 75 to 100 percent of men by ultrasonography (52). They are typically found in central, large prostatic ducts. These stones vary in size from microscopic to 4 cm, and grossly are usually multiple, round or ovoid, and brown, with variable white or gray areas (48). Prostatic stones mainly contain calcium phosphate, but calcium oxalate, carbonate-apatite, and hydroxyapatite may also be present. Prostatic calculi are most often seen

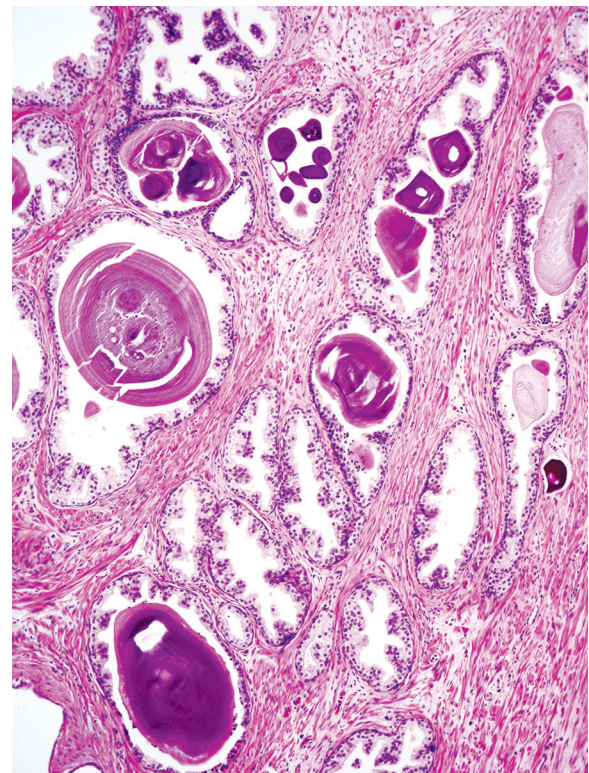


Figure 1-27

INTRALUMINAL CORPORA AMYLACEA

These are of varying sizes and shapes.

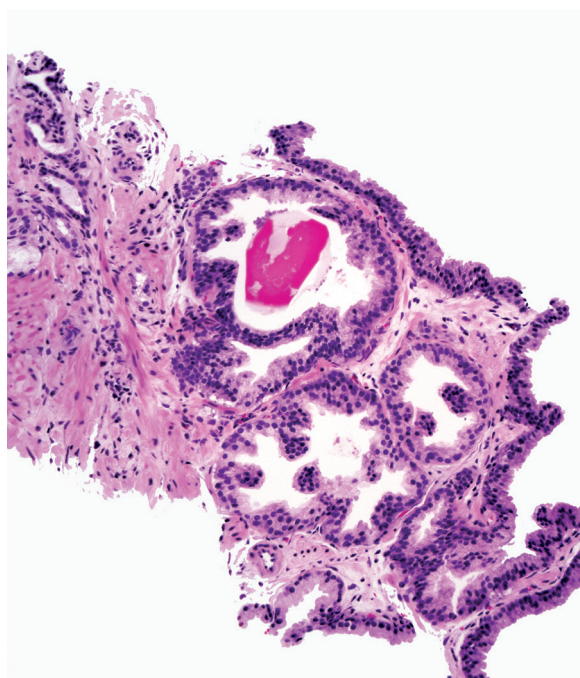


Figure 1-28

INTRALUMINAL CRYSTALLOID IN BENIGN GLAND

as incidental findings in the setting of inflammation and BPH.

The diagnostic impact of corpora, microcalcifications, and calculi is that they are all more common in benign glands, but their presence does not rule out malignancy. Corpora amylacea have been reported in 13 percent of carcinomas (53), and calculi are found in 6 percent of prostate cancers (54).

Other intraluminal materials are, conversely, rare in normal gland lumens but are more common in neoplastic processes. These intraluminal materials include pink amorphous acellular secretions, intraluminal wispy blue mucin (also known as blue-tinged mucinous secretions), and crystalloids. Identification of these secretions, mucin, or crystalloids (55) in benign prostatic tissue in a needle biopsy specimen (fig. 1-28) is not an indication for rebiopsy.

The stroma in the prostate gland consists chiefly of smooth muscle cells and fibroblasts, with ramifications of blood and lymph vessels as well as nerve bundles and axons (2). The stroma of the transition zone is more compact than that of the peripheral zone, with more

densely concentrated smooth muscle bundles. Skeletal muscle fibers can be found admixed with smooth muscle stroma and normal prostate glands at the distal apex of the prostate (21). Normal and benign glands in this skeletal muscle tissue (see fig. 1-9) should not be mistaken as neoplastic. The extracellular stromal matrix of the prostate consists primarily of collagen of types I and III, complex polysaccharides, and glycosaminoglycans such as dermatan sulfate, heparin, chondroitin, and hyaluronic acid (1). Fibronectin and tenascin polypeptides are also found in prostatic stroma (56).

Abutting the prostatic gland is a thick, delicate basement membrane, that, at 100 nm in thickness, is too small to be seen in H&E-stained sections. Uncommonly, a few adipocytes can be seen in the prostate (57–59).

IMMUNOHISTOCHEMICAL FINDINGS

The identification of cell type-specific markers by immunohistochemistry is of significant diagnostic value in the prostate gland. The immunophenotype of basal cells is distinctive, is different from luminal secretory cells, and can be of diagnostic use. The most commonly used basal cell-specific antibodies are those that react with p63 (fig. 1-29) and high molecular weight cytokeratins, especially 1, 5, 10, and 14, which are detected by mouse monoclonal antibody 34 β E12 (also known as CK903) (fig. 1-30) (60). p63 immunostains appear to be slightly more sensitive (61) and specific (62) than 34 β E12 immunostains. P40, an isoform of p63, is diagnostically interchangeable with p63, and has no advantage in distinguishing prostate adenocarcinoma from benign prostate glands (63). P63 immunostaining is substantially better in labeling basal cells in the transition zone than 34 β E12 (64). A cocktail comprised of 34 β E12 and p63 antibodies slightly improves the detection of basal cells compared to each antibody alone (65). Immunostaining of basal cells is also achieved using antibodies directed against cytokeratins (CK) 5/6 (66).

Basal cell antibodies are commonly used in cocktails with antibodies directed against α -methylacyl-coenzyme A racemase (AMACR) for diagnostic assessment of prostatic carcinoma (see below) (60). Discontinuity or even focal lack of basal cell staining may be seen in a minority

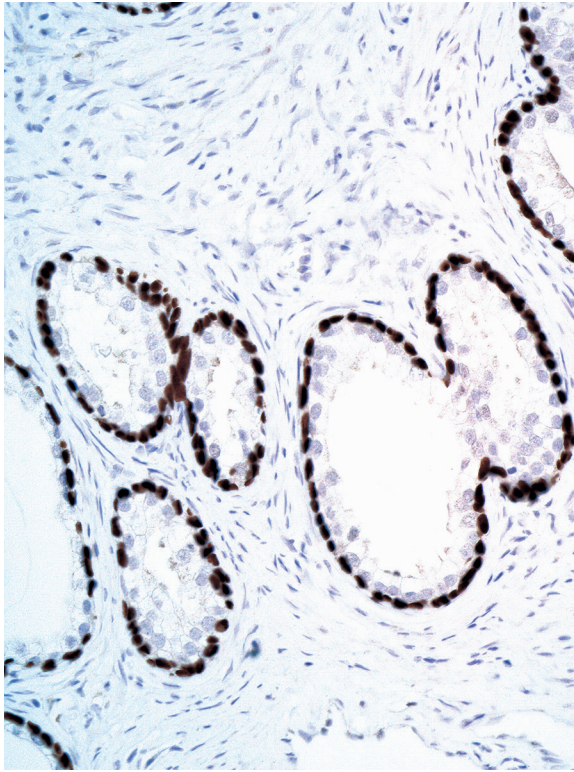


Figure 1-29

P63 IN BASAL CELL NUCLEI IN NORMAL GLAND

Detected by immunohistochemical staining.

of entirely normal glands (67,68). Prostatic basal cells are not myoepithelial cells and they are negative with smooth muscle actin and S-100 protein immunostains (44).

Normal secretory cells are immunoreactive for pancytokeratins, CK8, CK18, prostate-specific antigen (PSA) (fig. 1-31), prostatic specific acid phosphatase (PSAP), and the androgen receptor. Of diagnostic significance, immunostains for AMACR, also known as P504S, a marker for prostatic neoplasia, can be focally positive in secretory cells in normal glands, but this staining should be weak and noncircumferential in normal and benign glands (60). The specificity of AMACR for prostate cancer varies significantly between laboratories, with some institutions having more nonspecific labeling of benign prostate glands.

Additional prostate markers that have been tested in diagnostic immunohistochemistry include prostate-specific membrane antigen (PSMA), prostein (P501S), proPSA, and NKX3.1.

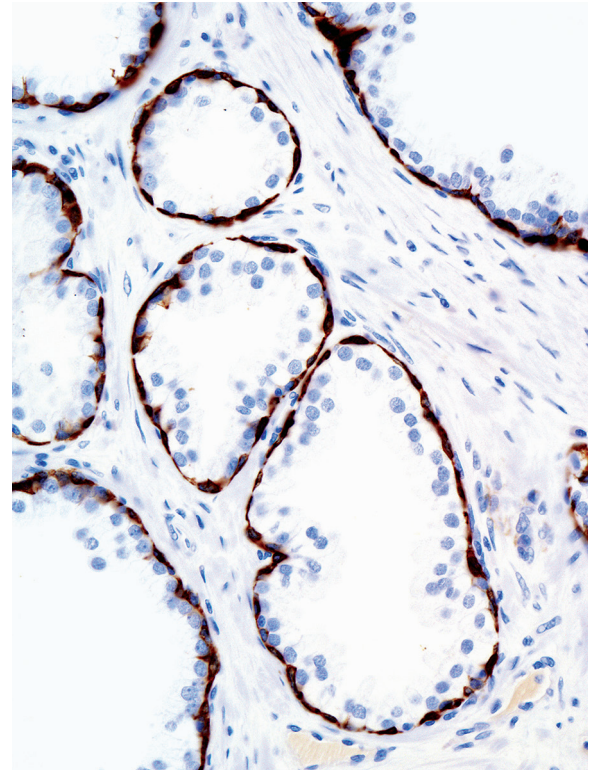


Figure 1-30

HIGH MOLECULAR WEIGHT CYTOKERATIN

High-molecular weight cytokeratin polypeptides in the cytoplasm of basal cells of normal glands, as detected by antibody 34 β E12.

These markers are sensitive in the immunolabeling of prostatic carcinoma (69), and useful in differentiating prostate from urothelial carcinoma (69,70). In normal prostatic tissues, PSMA is weakly expressed in benign luminal cells (71,72). P501S is strongly expressed in benign luminal cells, with prominent dotlike Golgi complex staining (73,74). Two proPSA molecular forms differ in expression in benign glands, with strong or moderate/diffuse [-5/-7]proPSA expression and negative or weak [-2]proPSA expression (75). NKX3.1 immunostains show intense labeling of most secretory luminal cell nuclei, with weak staining of basal cell nuclei (76).

Chromogranin stains neuroendocrine cells throughout the prostate gland, but is most concentrated in the periurethral region and prostatic ducts (77). A variety of neuroendocrine markers, including chromogranin, neuron-specific enolase, serotonin, thyroid-stimulating

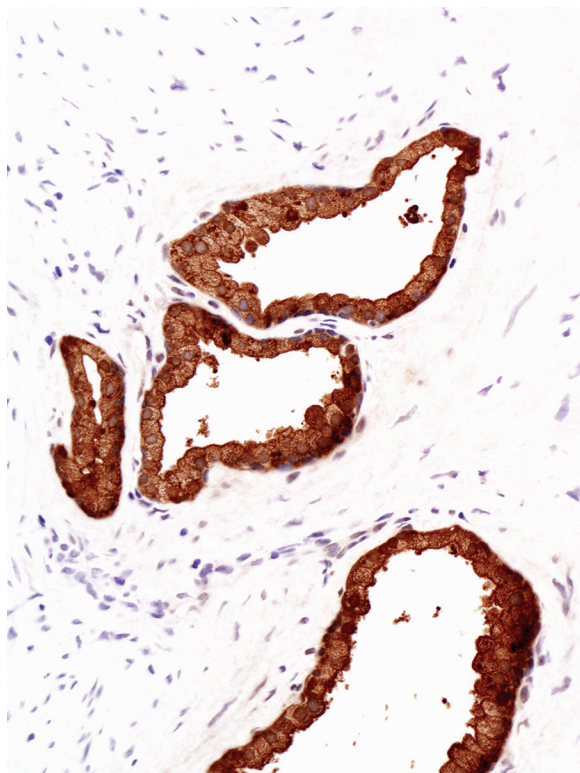


Figure 1-31

PROSTATE-SPECIFIC ANTIGEN

Prostate-specific antigen (PSA) in the cytoplasm of benign secretory epithelial cells. The immunoreaction signal is typically homogeneous and strong in nonatrophic benign secretory cells.

hormone-like peptide, calcitonin, bombesin, gastrin-releasing peptide, somatostatin, parathormone-related protein, and neurotensin, also have been identified in these cells by immunohistochemistry (78). These immunostains highlight the highly interdigitating nature of these cells, which exhibit slender, cytoplasmic dendritic process that may be up to 200 μm long.

Basement membrane immunostains, such as those directed against collagen type IV, laminin, and heparan sulfate proteoglycan, are not useful in diagnosis. Specifically, they are not used to diagnose invasion since non-neoplastic acini may lose basement membrane secondary to inflammation, some invasive prostatic carcinomas retain their basement membrane, and there is extensive stromal staining of capillary and smooth muscle external lamina by collagen type IV and laminin immunostains (79–82).

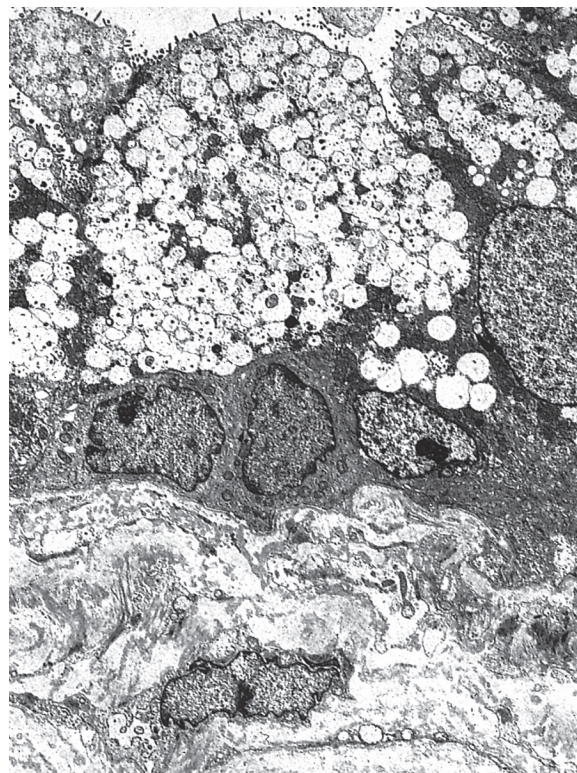


Figure 1-32

SECRETORY AND BASAL CELLS: ULTRASTRUCTURE

The secretory cell cytoplasm contains numerous apical vacuoles and granules. The underlying basal cells have darker cytoplasm with tonofilaments. At the bottom, stromal cells lie within ground substance and collagen.

ULTRASTRUCTURAL FINDINGS

Ultrastructural examination of basal cells reveals a poorly differentiated cell with no secretory vacuoles, numerous mitochondria, free ribosomes, and scattered tonofilaments (fig. 1-32) (44,83). Basal cells sit upon a 0.07- to 0.10- μm -thick basement membrane.

Secretory cells show abundant cytoplasm joined by tight junctional complexes and desmosomes (84–86). The cytoplasm contains mitochondria, endoplasmic reticulum, and Golgi apparatus, with numerous apical secretory vacuoles (fig. 1-32). On the luminal surface are small microvilli.

Neuroendocrine cells display dense core granules of varying sizes and shapes (fig. 1-33). Electron microscopy is not used in diagnostic surgical pathology of the prostate gland.

PROSTATE FUNCTION

The main function of the prostate gland is the formation of secretions that constitute half to two thirds of the 3 mL volume of the ejaculate. The precise biologic purpose of many of the biochemical substances secreted into the seminal plasma is uncertain (1,87). One exception is the well-defined role for several enzymes that participate in the clotting and lysis of the seminal plasma clot, including PSF1, which is a serine protease and esterase that cleaves semenogelin, a protein involved in clotting (88). Additional substances that are found in high concentration in prostatic fluid include fructose, citric acid, spermine, prostaglandins, zinc, potassium, amino acids, and a variety of enzymes including proteases, esterases, and phosphatases. Many of these factors likely promote fertility by providing a buffering effect, increasing sperm motility and survival, and enhancing sperm transport in both the male and female reproductive tracts (87). An antimicrobial role has been suggested for a few of these substances, such as zinc, spermine, and proteases.

Physically, by mass effect, musculature, and location, the prostate gland may contribute to control of normal urine outflow from the urinary bladder. The prostate is not vital for life and it may be surgically excised; the major complications are incontinence and impotence

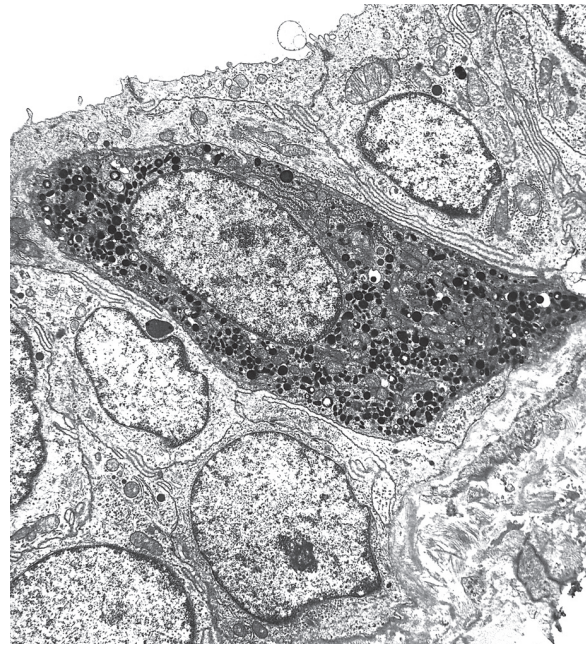


Figure 1-33

NEUROENDOCRINE CELL IN THE PROSTATE

Numerous cytoplasmic dark dense-core granules are seen.

(related to damage to periprostatic neurovascular bundles). Failure of the gland to form, as in 5α -reductase deficiency (89) and testicular feminization (90), is not lethal.

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