Male genital system
Testis and Epididymis

- Distinct pathological conditions affect the testis and epididymis. In the epididymis, the most important and frequent conditions are inflammatory diseases, whereas in the testis the major lesions are tumors.

CONGENITAL ANOMALIES

- With the exception of undescended testes (cryptorchidism), congenital anomalies are extremely rare and include absence of one or both testes and fusion of the testes (so-called *synorchism*).

Cryptorchidism

- Cryptorchidism is found in approximately 1% of 1-year-old boys. This anomaly represents a complete or incomplete failure of the intra-abdominal testes to descend into the scrotal sac. It usually occurs as an isolated anomaly but may be accompanied by other malformations of the genitourinary tract, such as hypospadias.

- Testicular descent occurs in two morphologically and hormonally distinct phases. During the first, the transabdominal, phase, the testis comes to lie within the lower abdomen or brim of the pelvis. This phase is believed to be controlled by a hormone called *müllerian-inhibiting substance*. In the second, or the inguinoscrotal, phase, the testes descend through the inguinal canal into the scrotal sac. This phase is androgen dependent and is possibly mediated by androgen-induced release of calcitonin gene–related peptide, from the genitofemoral nerve.

- Although testes may be arrested anywhere along their pathway of descent, defects in transabdominal descent are uncommon, accounting for approximately 5% to 10% of cases. In most patients the undescended testis is palpable in the inguinal canal. *Even though testicular descent is controlled by hormonal factors, cryptorchidism is only rarely associated with a well-defined hormonal disorder*. The condition is completely asymptomatic, and it is found by the patient or the examining physician only when the scrotal sac is discovered not to contain the testis.

- **Morphology**. Cryptorchidism is unilateral in most cases, but it may be bilateral in 25% of patients. Histologic changes in the malpositioned testis begin as early as 2 years of age. They are characterized by an arrest in the development of germ cells associated with marked hyalinization and thickening of the basement membrane of the spermatic tubules . Eventually the tubules appear as dense cords of hyaline connective tissue outlined by prominent basement membranes. There is concomitant increase in interstitial stroma. Because Leydig cells are spared, they appear to be prominent. As might be expected with progressive tubular atrophy, the cryptorchid testis is small in size and is firm in consistency as a result of fibrotic changes. Histologic deterioration, associated with a paucity of germ cells, has also been noted in the contralateral (descended) testis in males with unilateral cryptorchidism, supporting an intrinsic defect in testicular development.

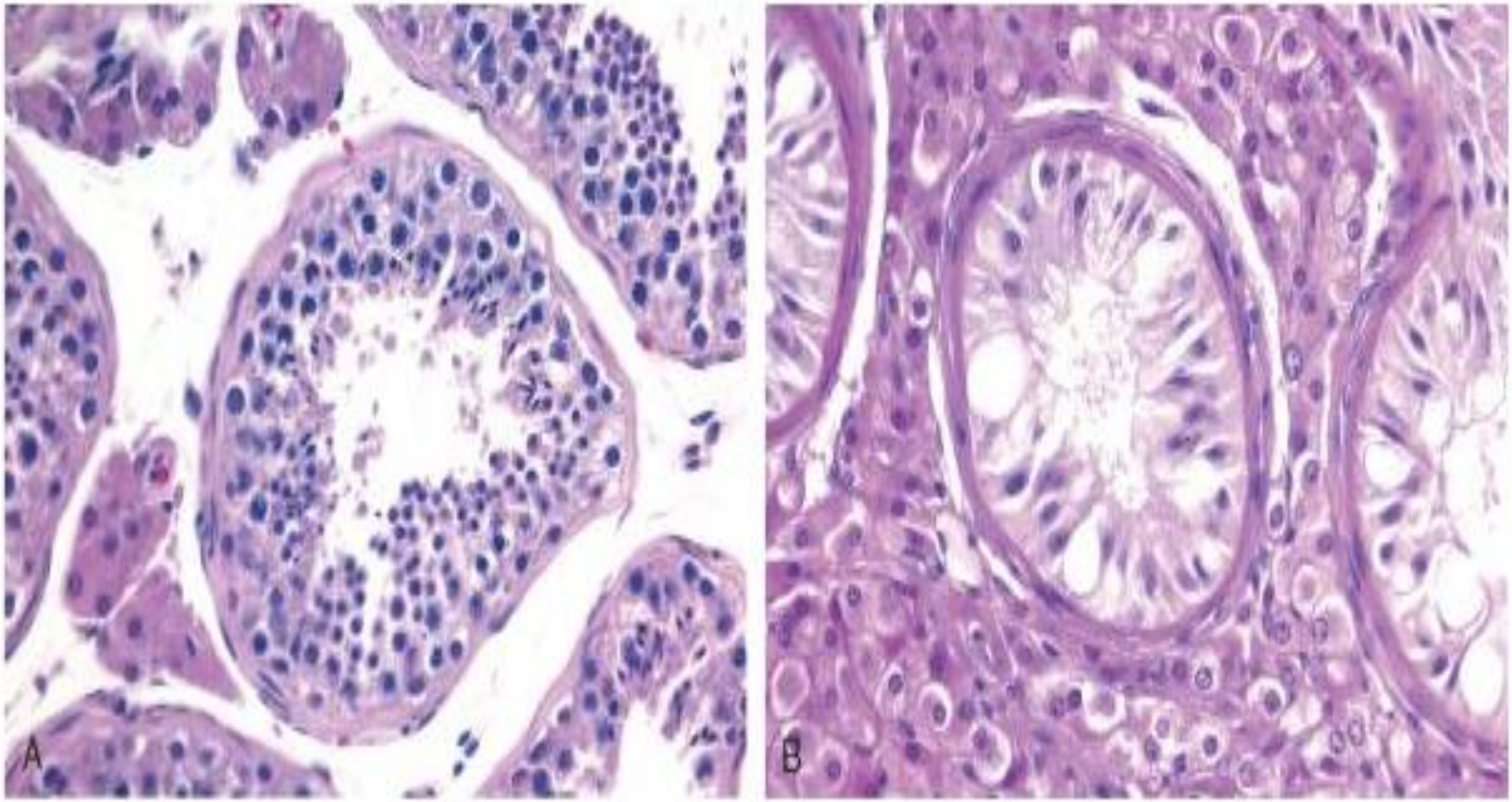


FIGURE 21-20 **A**, Normal testis shows tubules with active spermatogenesis. **B**, Testicular atrophy in cryptorchidism. The tubules show Sertoli cells but no spermatogenesis. There is thickening of basement membranes and an apparent increase in interstitial Leydig cells.

- In addition to sterility, cryptorchidism can be associated with other morbidity. When the testis lies in the inguinal canal, it is particularly exposed to trauma and crushing against the ligaments and bones. A concomitant inguinal hernia accompanies the undescended testis in about 10% to 20% of cases. In addition, the undescended testis is at a greater risk of developing testicular cancer than is the descended testis. During the first year of life the majority of inguinal cryptorchid testes descend spontaneously into the scrotum.
- Those that remain undescended require surgical correction, preferably before histologic deterioration sets in at around 2 years of age.Orchiopexy (placement in the scrotal sac) does not guarantee fertility; deficient spermatogenesis has been reported in 10% to 60% of patients in whom surgical repositioning was performed. To what extent the risk of cancer is reduced after orchiopexy is also unclear.

- According to some studies, orchiopexy of unilateral cryptorchidism before 10 years of age protects against cancer development. This is not universally accepted, however. Malignant change may occur in the contralateral, normally descended testis. These observations suggest that cryptorchidism is associated with a defect in testicular development and cellular differentiation that is unrelated to anatomic position.

REGRESSIVE CHANGES
Atrophy and Decreased Fertility

- Atrophy is a regressive change that affects the scrotal testis and can have any of several causes, including (1) progressive atherosclerotic narrowing of the blood supply in old age, (2) the end stage of an inflammatory orchitis, (3) cryptorchidism, (4) hypopituitarism, (5) generalized malnutrition or cachexia, (6) irradiation, (7) prolonged administration of antiandrogens (treatment for advanced carcinoma of the prostate), and (8) exhaustion atrophy, which may follow the persistent stimulation produced by high levels of follicle-stimulating pituitary hormone. The gross and microscopic alterations follow the pattern already described for cryptorchidism. *Atrophy occasionally occurs as a primary failure of genetic origin, such as in Klinefelter syndrome* .

Atrophy is an end-stage pattern of testicular injury. Before this terminal histologic appearance is reached, several other patterns are associated with decreased fertility. These include hypospermatogenesis, maturation arrest, and findings associated with vas deferens obstruction. In some instances a specific cause for the testicular injury can be found, and if it can be removed before the development of atrophy, testicular function can be restored.

INFLAMMATION

- Inflammations are distinctly more common in the epididymis than in the testis. Of the three major specific inflammatory states that affect the testis and epididymis, *gonorrhea and tuberculosis almost invariably arise in the epididymis, whereas syphilis affects first the testis*.

Nonspecific Epididymitis and Orchitis

- Epididymitis and possible subsequent orchitis are commonly related to infections in the urinary tract (cystitis, urethritis, prostatitis), which reach the epididymis and the testis through either the vas deferens or the lymphatics of the spermatic cord.
- The cause of epididymitis varies with the age of the patient. Though uncommon in children, epididymitis in childhood is usually associated with a congenital genitourinary abnormality and infection with gram-negative rods. In sexually active men younger than age 35 years, the sexually transmitted pathogens *C. trachomatis* and *Neisseria gonorrhoeae* are the most frequent culprits. In men older than age 35 the common urinary tract pathogens, such as *E. coli* and *Pseudomonas*, are responsible for most infections.

- **Morphology**. The bacterial invasion induces nonspecific acute inflammation characterized by congestion, edema, and infiltration by neutrophils, macrophages, and lymphocytes. Although the infection, in the early stage, is more or less limited to the interstitial connective tissue, it rapidly extends to involve the tubules and may progress to frank abscess formation or complete suppurative necrosis of the entire epididymis . Usually, having involved the epididymis, the infection extends into the testis to evoke a similar inflammatory reaction. Such inflammatory involvement of the epididymis and testis is often followed by fibrous scarring, which in many cases leads to sterility. Usually the interstitial cells of Leydig are not totally destroyed, so sexual activity is not disturbed.

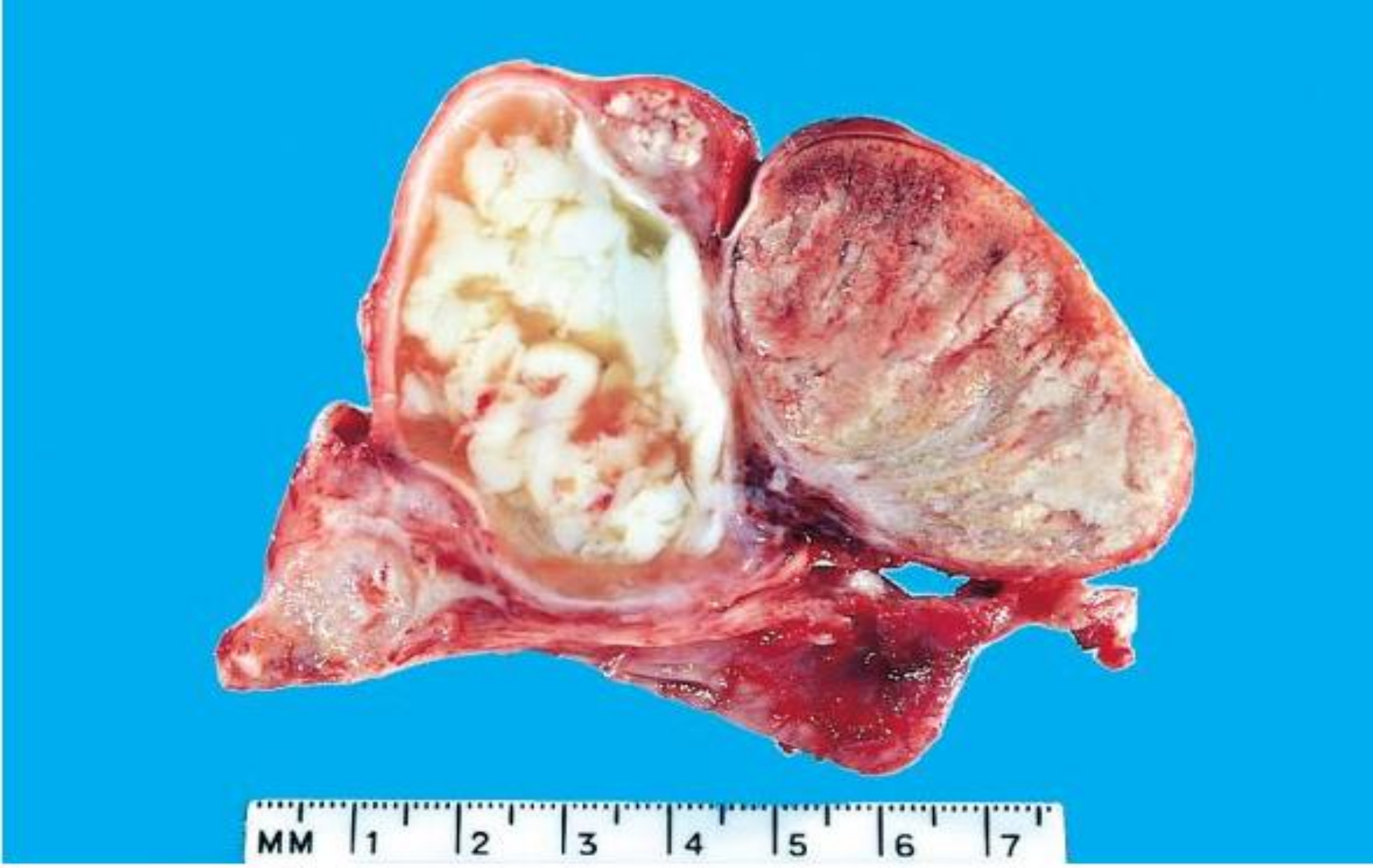


FIGURE 21-21 Acute epididymitis caused by gonococcal infection. The epididymis is replaced by an abscess. Normal testis is seen on the *right*.

Granulomatous (Autoimmune) Orchitis

- Idiopathic granulomatous orchitis presents in middle age as a moderately tender testicular mass of sudden onset sometimes associated with fever. It may appear insidiously, however, as a painless testicular mass mimicking a testicular tumor, hence its importance. Histologically the orchitis is distinguished by granulomas restricted to spermatic tubules. The lesions closely resemble tubercles but differ in that the granulomatous reaction is present diffusely throughout the testis and is confined to the seminiferous tubules. Although an autoimmune basis is suspected, the cause of these lesions remains unknown.

Specific Inflammations
Gonorrhea

- Extension of infection from the posterior urethra to the prostate, seminal vesicles, and then to the epididymis is the usual course of a neglected gonococcal infection. Inflammatory changes similar to those described for nonspecific infections occur, with the development of frank abscesses in the epididymis, which may lead to extensive destruction of this organ. In neglected cases, the infection may spread to the testis and produce suppurative orchitis.

Mumps

- Mumps is a systemic viral disease that most commonly affects school-aged children. Testicular involvement is extremely uncommon in this age group. In postpubertal males, however, orchitis may develop and has been reported in 20% to 30% of male patients. Most often, acute interstitial orchitis develops about 1 week after the onset of swelling of the parotid glands.

- **Tuberculosis**
- *Tuberculosis almost invariably begins in the epididymis and may spread to the testis*. The infection invokes the classic morphologic reactions of caseating granulomatous inflammation characteristic of tuberculosis elsewhere.
- **Syphilis**
- The testis and epididymis are affected in both acquired and congenital syphilis, but *almost invariably the testis is involved first by the infection*. In many cases, the orchitis is not accompanied by epididymitis. The morphologic pattern of the reaction takes two forms: the production of gummas or a diffuse interstitial inflammation characterized by edema and lymphocytic and plasma cell infiltration with the characteristic hallmark of all syphilitic infections (i.e., obliterative endarteritis with perivascular cuffing of lymphocytes and plasma cells).

VASCULAR DISORDERS
Torsion

- Twisting of the spermatic cord typically cuts off the venous drainage of the testis. The thick-walled arteries remain patent, so that the intense vascular engorgement may be followed by hemorrhagic infarction. There are two types of testicular torsion. Neonatal torsion occurs either in utero or shortly after birth. It lacks any associated anatomic defect to account for its occurrence. Adult torsion is typically seen in adolescence presenting as sudden onset of testicular pain. It often occurs without any inciting injury; sudden pain heralding the torsion may even occur during sleep. *Torsion is one of the few urologic emergencies*. If the testis is explored surgically and manually untwisted within approximately 6 hours after the onset of torsion, there is a good chance that the testis will remain viable. In contrast to neonatal torsion, adult torsion results from a bilateral anatomic defect where the testis has increased mobility, giving rise to what is termed the *bell-clapper abnormality*. To prevent the catastrophic occurrence of subsequent torsion in the contralateral testis, the testis unaffected by torsion is surgically fixed to the scrotum (orchiopexy).

- **Morphology**. Depending on the duration of the process, the morphologic changes range from intense congestion to widespread extravasation of blood into the interstitial tissue to hemorrhagic testicular infarction . In these late stages the testis is markedly enlarged and is converted virtually into a sac of soft, necrotic, hemorrhagic tissue.

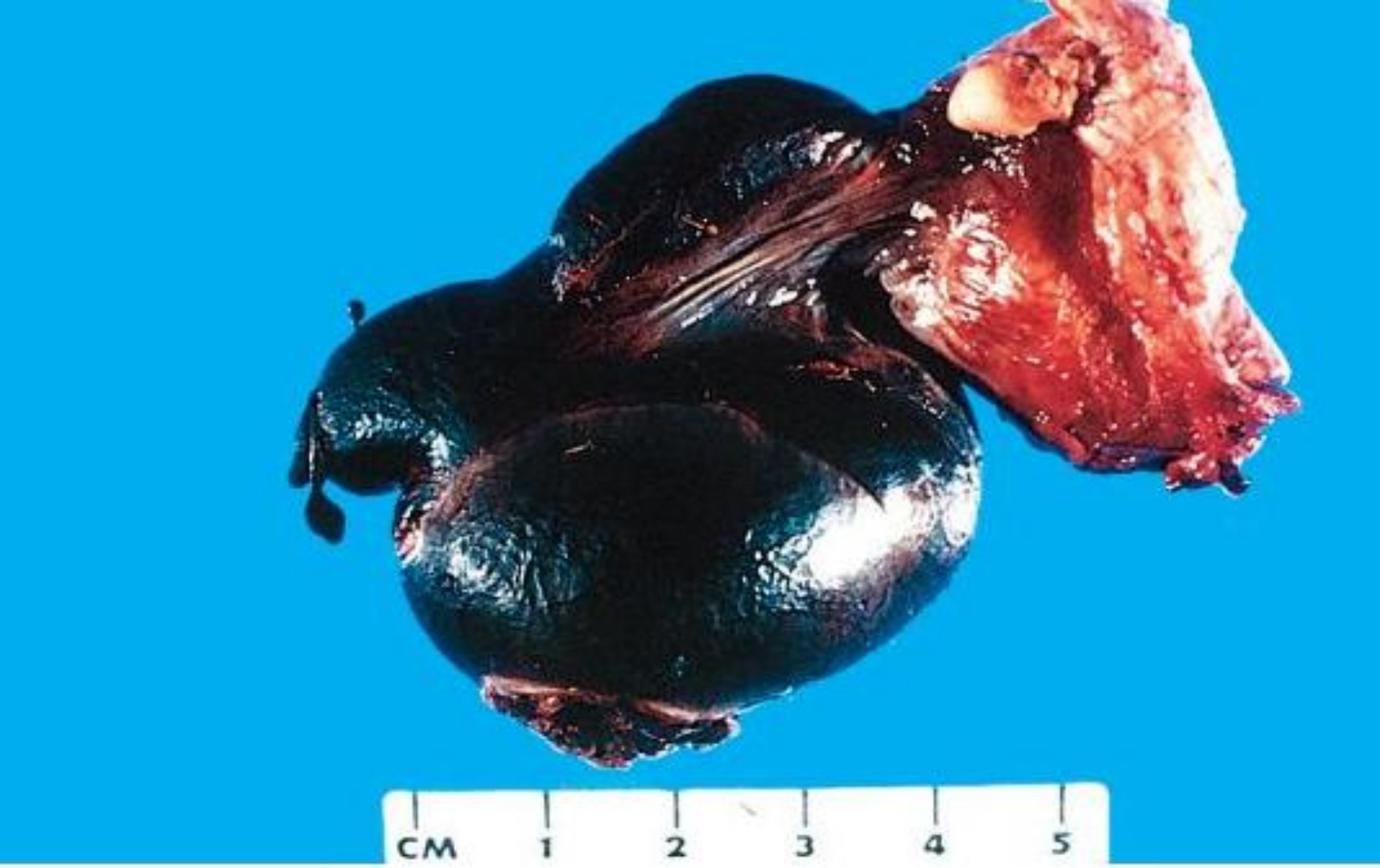


FIGURE 21-22 Torsion of testis.

SPERMATIC CORD AND PARATESTICULAR TUMORS

- *Lipomas* are common lesions involving the proximal spermatic cord, identified at the time of inguinal hernia repair. Although diagnosed as “lipomas,” many of these lesions probably represent retroperitoneal adipose tissue that has been pulled into the inguinal canal along with the hernia sac, rather than a true neoplasm.
- The most common benign paratesticular tumor is *adenomatoid tumor*. Although these lesions are mesothelial in nature, they are not referred to as mesotheliomas to distinguish them from other mesothelial lesions that may occur at this site. Adenomatoid tumors are usually small nodules, typically occurring near the upper pole of the epididymis. Although grossly well circumscribed, microscopically they may be minimally invasive into the adjacent testis. The importance of this lesion is that it is one of the few benign tumors that occur near the testis. If the pathologist can identify the nature of this lesion in intraoperative frozen sections, local excision of the adenomatoid tumor can spare the patient orchiectomy.
- The most common malignant paratesticular tumors located at the distal end of the spermatic cord are rhabdomyosarcomas in children and liposarcomas in adults.

TESTICULAR TUMORS

- Testicular neoplasms span an amazing gamut of anatomic types. They are divided into two major categories: germ cell tumors and sex cord–stromal tumors (Table 21-5). Approximately 95% of testicular tumors arise from germ cells. Germ cell tumors are subdivided into seminomas and non-seminomas. Most germ cell tumors are aggressive cancers capable of rapid, wide dissemination, although with current therapy most can be cured. Sex cord–stromal tumors, in contrast, are generally benign.

Pathologic Classification of Common Testicular Tumors

- **Germ Cell Tumors**
- **Seminomatous tumors**
- Seminoma
- Spermatocytic seminoma
- **Non-seminomatous tumors**
- Embryonal carcinoma,
- Yolk sac (endodermal sinus) tumor
- Choriocarcinoma
- Teratoma
- **Sex Cord-Stromal Tumors**
- Leydig cell tumor
- Sertoli cell tumor

Germ cell tumors

- The incidence of testicular tumors in the United States is approximately 6 per 100,000, resulting in approximately 300 deaths per year. For unexplained reasons there is a worldwide increase in the incidence of these tumors. In the 15- to 34-year age group, they constitute the most common tumor of men and cause approximately 10% of all cancer deaths. In the United States these tumors are much more common in whites than in blacks (ratio 5 : 1).

Environmental Factors and Genetic Predisposition.

- Environmental factors play a role in the incidence of testicular germ cell tumors, as demonstrated by population migration studies. The incidence of testicular germ cell tumors in Finland is about two times lower than in Sweden; second generation Finnish immigrants to Sweden, have a tumor incidence that approaches that of the Swedish population. Testicular germ cell tumors are associated with a spectrum of disorders known as *testicular dysgenesis syndrome (TDS)*. This syndrome includes cryptorchidism, hypospadias, and poor sperm quality, and it has been proposed that some of these conditions might be influenced by in utero exposures to pesticides and nonsteroidal estrogens. Cryptorchidism, which is associated with approximately 10% of testicular germ cell tumors, is the most important risk factor. Klinefelter syndrome (a TDS condition) is associated with an increased risk (50 times greater than normal) for the development of mediastinal germ cell tumors, but these patients do not develop testicular tumors.

- There is a strong family predisposition associated with the development of testicular germ cell tumors. The relative risk of development of these tumors in fathers and sons of patients with testicular germ cell tumors is four times higher than normal, and is 8 to 10 times higher between brothers. It is possible that genetic polymorphisms at the Xq27 locus may be responsible for this susceptibility, but further studies are needed to validate this hypothesis.

Classification and Pathogenesis

- A simple classification of the most common types of testicular tumors is presented in Table 21-5 . Two broad groups are recognized. *Seminomatous tumors* are composed of cells that ressemble primordial germ cells or early gonocytes. The *non-seminomatous tumors* may be composed of undifferentiated cells that resemble embryonic stem cells, as in the case of embryonal carcinoma, but the malignant cells can differentiate into various lineages generating yolk sac tumors, choriocarcinomas and teratomas. Germ cell tumors may have a single tissue component, but in approximately 60% of cases, the tumors contain *mixtures of seminomatous and non-seminomatous components* and multiple tissues. In teratomas, tissues of the three germ layers are represented as a result of the differentiation of embryonal carcinoma cells. Seminomas constitute approximately 50% of all testicular germ cell neoplasms and are the most common testicular tumor.

- Most testicular germ cell tumors originate from lesions called *intratubular germ cell neoplasia (ITGCN)*, which is also referred to as *intratubular germ cell neoplasia unclassified (ITGCNU)*.However, ITGCN has not been implicated as a precursor lesion of pediatric yolk sac tumors and teratomas, or of adult spermatocytic seminoma. ITGCN is believed to occur in utero and stay dormant until puberty, when it may progress into seminomas or non-seminomatous tumors. The lesion consists of atypical primordial germ cells with large nuclei and clear cytoplasm, which are about twice the size of normal germ cells. These cells retain the expression of the transcription factors *OCT3/4* and *NANOG*, which are associated with pluripontentiality , and are expressed in normal embryonic stem cells. ITGCN share some of the genetic alterations found in germ cell tumors such as the gain of additional copies of the short arm of chromosome 12 (12p) in the form of an isochromosome of its short arm, i(12p).

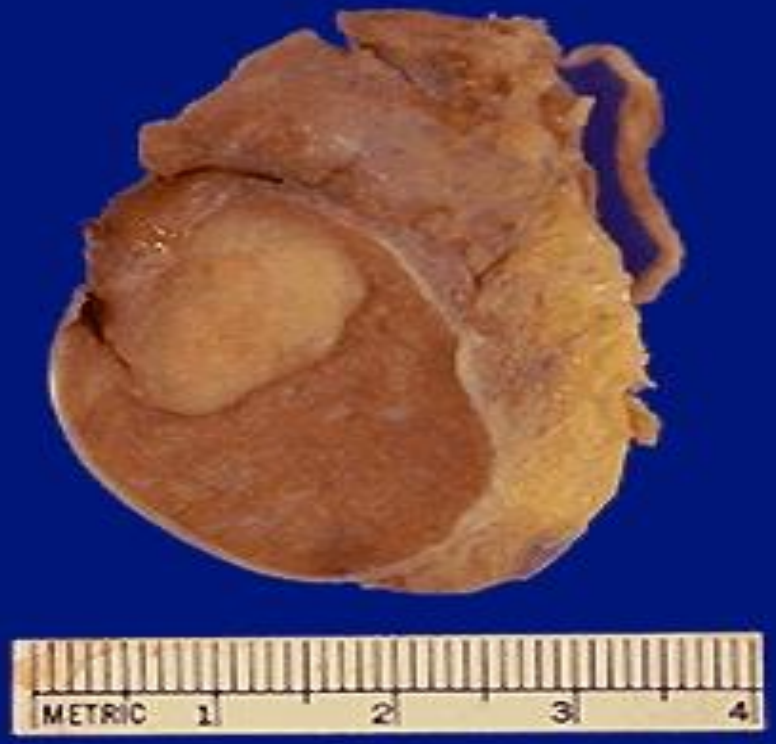
- This change is invariably found in invasive tumors regardless of histological type. Activating mutations of c-KIT, which may be present in seminomas, are also present in ITGCN. About 50% of individuals with ITGCN develop invasive germ cell tumors within five years after diagnosis, and it has been proposed that practically all patients with ITGCN eventually develop invasive tumors. ITGCN is essentially a type of carcinoma in situ (CIS), although the term *CIS* is not frequently used to refer to this lesion.

Seminoma

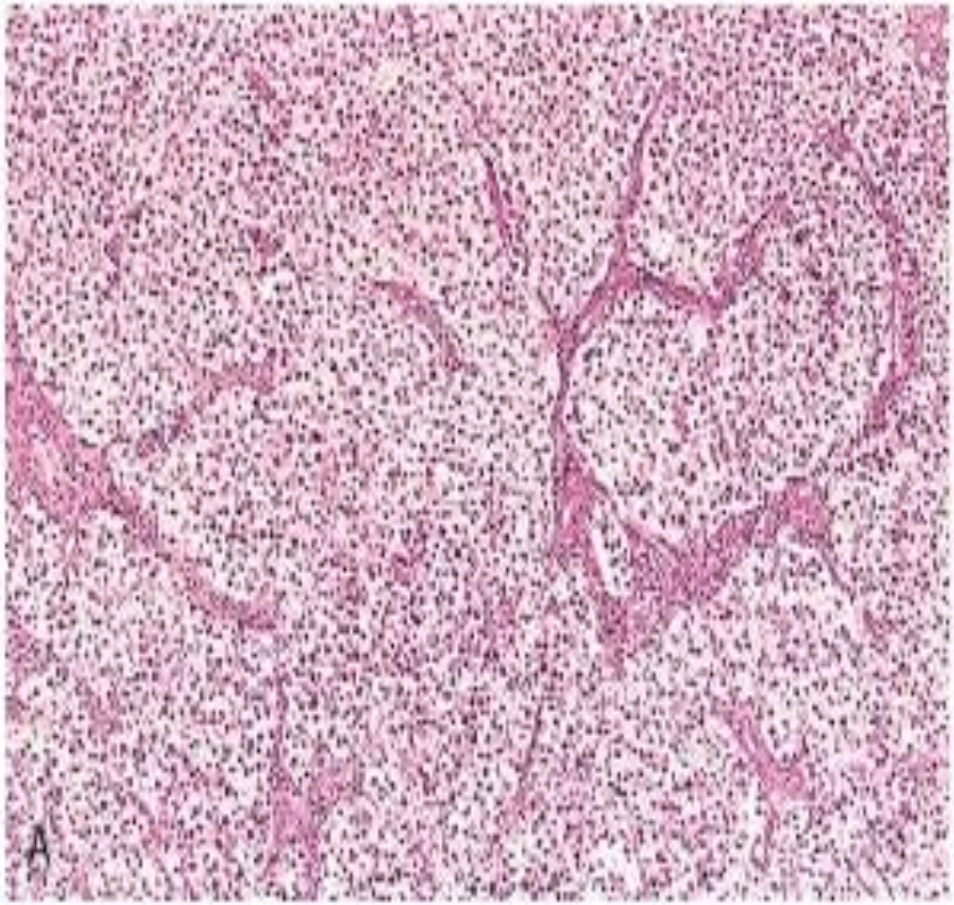
- Seminomas are the most common type of germ cell tumor, making up about 50% of these tumors. The peak incidence is the third decade and they almost never occur in infants. An identical tumor arises in the ovary, where it is called *dysgerminoma*. Seminomas contain an isochromosome 12p, and express *OCT3/4* and *NANOG*. Approximately 25% of these tumors have c-KIT activating mutations. c-KIT amplification has also been repeated, but increased *c-KIT* expression may occur without genetic defects.

- **Morphology**. If not otherwise specified, “seminoma” refers to “classical” or “typical” seminoma that consists of a uniform population of cells. Spermatocytic seminoma, despite its nosologic similarity, is a distinct tumor discussed later. Seminomas produce bulky masses, sometimes ten times the size of the normal testis. The typical seminoma has a homogeneous, gray-white, lobulated cut surface, usually devoid of hemorrhage or necrosis . Generally the tunica albuginea is not penetrated, but occasionally extension to the epididymis, spermatic cord, or scrotal sac occurs.

- Microscopically the typical seminoma is composed of sheets of uniform cells divided into poorly demarcated lobules by delicate septa of fibrous tissue containing a moderate amount of lymphocytes . **The classic seminoma cell is large and round to polyhedral and has a distinct cell membrane; a clear or watery-appearing cytoplasm; and a large, central nucleus with one or two prominent nucleoli**. Mitoses vary in frequency. The cytoplasm contains varying amounts of glycogen. Seminoma cells are diffusely positive for *c-KIT*, (regardless of c-KIT mutational status) *OCT4*, and placental alkaline phosphatase (PLAP), with sometimes scattered keratin-positive cells.
- Approximately 15% of seminomas contain syncytiotrophoblasts. In this subset of patients, serum human chorionic gonadotropin (HCG) levels are elevated, though not to the extent seen in patients with choriocarcinoma. Seminomas may also be accompanied by an ill-defined granulomatous reaction, in contrast to the well-formed discrete granulomas seen with tuberculosis.
- The term **anaplastic seminoma** is used by some to indicate greater cellular and nuclear irregularity with more frequent tumor giant cells and many mitoses. However, since “anaplastic seminoma” is not associated with a worse prognosis when matched stage for stage with classic seminoma and is not treated differently, most authorities do not recognize anaplastic seminoma as a distinct entity.
-



The mass lesion seen here in the testis is a seminoma



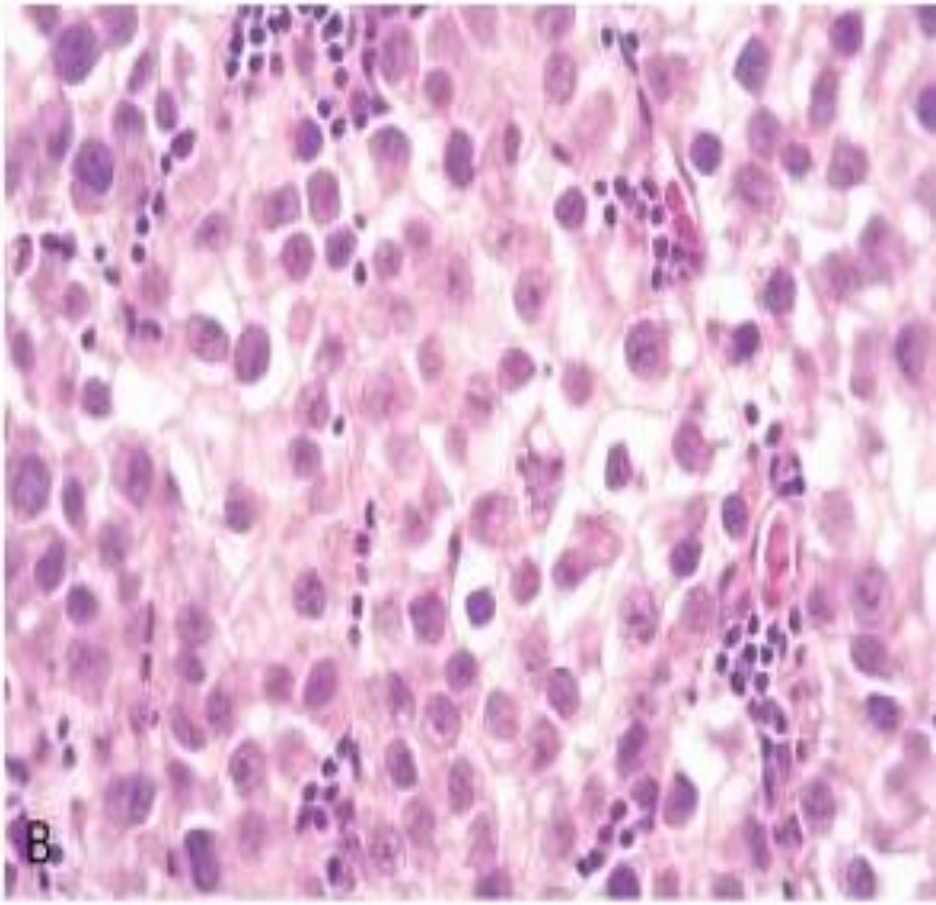


FIGURE 21-24 Seminoma. **A**, Low magnification shows clear seminoma cells divided into poorly demarcated lobules by delicate septa. **B**, Microscopic examination reveals large cells with distinct cell borders, pale nuclei, prominent nucleoli, and a sparse lymphocytic infiltrate.

Spermatocytic Seminoma

- Though related by name to seminoma, spermatocytic seminoma is a distinctive tumor both clinically and histologically. Spermatocytic seminoma is an uncommon tumor, representing 1% to 2% of all testicular germ cell neoplasms. The age of involvement is much later than for most testicular tumors: Affected individuals are generally over the age of 65 years. In contrast to classic seminoma, it is a slow-growing tumor that does not produce metastases, and hence the prognosis is excellent. In contrast to typical seminomas, spermatocytic seminomas lack lymphocytes, granulomas, syncytiotrophoblasts, extra-testicular sites of origin, admixture with other germ cell tumors, and association with ITGCN

- **Morphology**. Grossly, spermatocytic seminoma tends to have a soft, pale gray, cut surface that sometimes reveal mucoid cysts. Spermatocytic seminomas contain three cell populations, all intermixed: (1) medium-sized cells, the most numerous, containing a round nucleus and eosinophilic cytoplasm; (2) smaller cells with a narrow rim of eosinophilic cytoplasm resembling secondary spermatocytes; and (3) scattered giant cells, either uninucleate or multinucleate. The chromatin in some intermediate-sized cells is similar to that seen in the meiotic phase of non-neoplastic spermatocytes (spireme chromatin).

Embryonal Carcinoma

- Embryonal carcinomas occur mostly in the 20- to 30-year age group. These tumors are more aggressive than seminomas.
- **Morphology**. Grossly, the tumor is smaller than seminoma and usually does not replace the entire testis. On cut surfaces the mass is often variegated, poorly demarcated at the margins, and punctuated by foci of hemorrhage or necrosis. Extension through the tunica albuginea into the epididymis or cord frequently occurs. **Histologically the cells grow in alveolar or tubular patterns, sometimes with papillary convolutions**. Embryonal carcinomas lack the well-formed glands with basally situated nuclei and apical cytoplasm seen in teratomas. **More undifferentiated lesions may display sheets of cells**. The neoplastic cells have an epithelial appearance, are large and anaplastic, and have hyperchromatic nuclei with prominent nucleoli. In contrast to seminoma, the cell borders are usually indistinct, and there is considerable variation in cell and nuclear size and shape. Mitotic figures and tumor giant cells are frequently seen. Embryonal carcinomas share some markers with seminomas such as OCT 3/4 and PLAP, but differ by being positive for cytokeratin and CD30, and negative for c-KIT.

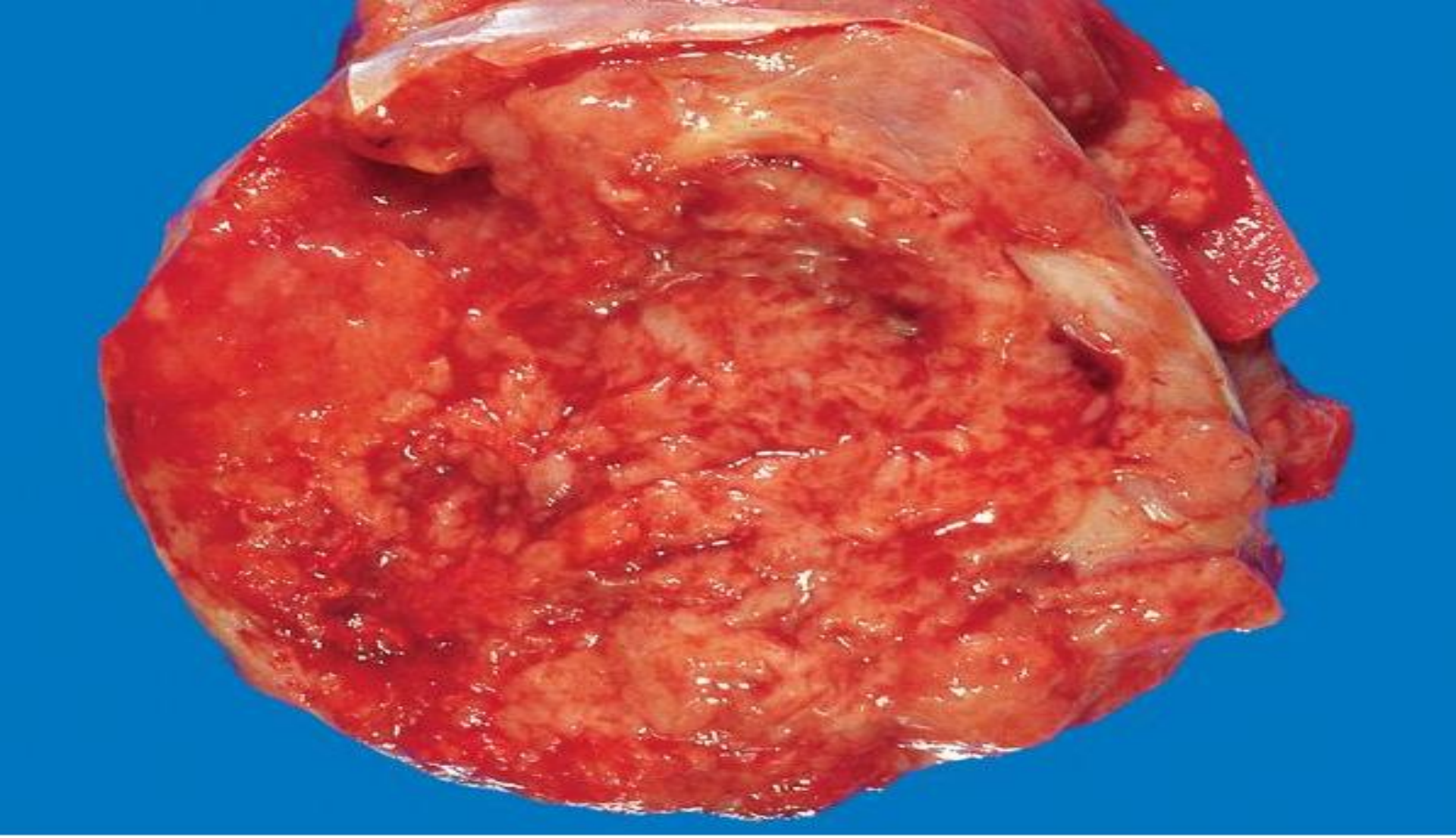


FIGURE 21-25 Embryonal carcinoma. In contrast to the seminoma illustrated in Figure 21-23 , the embryonal carcinoma is a hemorrhagic mass.

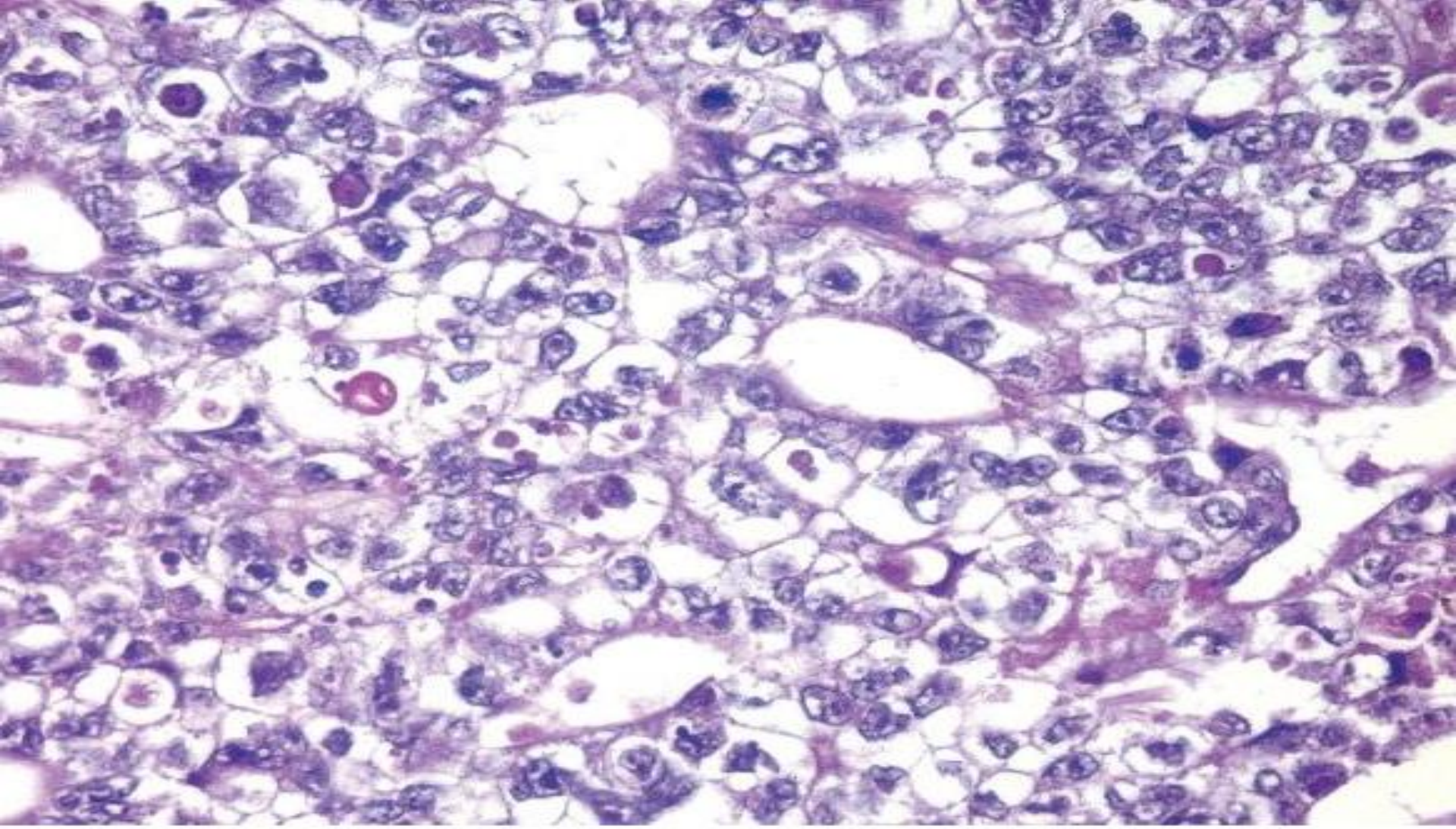


FIGURE 21-26 Embryonal carcinoma shows sheets of undifferentiated cells as well as primitive glandular differentiation. The nuclei are large and hyperchromatic.

Yolk Sac Tumor

- Also known as *endodermal sinus tumor*, yolk sac tumor is of interest because it is the most common testicular tumor in infants and children up to 3 years of age. In this age group it has a very good prognosis. In adults the pure form of this tumor is rare; instead, yolk sac elements frequently occur in combination with embryonal carcinoma.
- **Morphology**. Grossly, the tumor is nonencapsulated, and on cross-section it presents a homogeneous, yellow-white, mucinous appearance. Characteristic on microscopic examination is a lacelike (reticular) network of medium-sized cuboidal or flattened cells. In addition, papillary structures, solid cords of cells, and a multitude of other less common patterns may be found. In approximately 50% of tumors, structures resembling endodermal sinuses (Schiller-Duval bodies) may be seen; these consist of a mesodermal core with a central capillary and a visceral and parietal layer of cells resembling primitive glomeruli. Present within and outside the cytoplasm are eosinophilic, hyaline-like globules in which α-fetoprotein (AFP) and α_1-antitrypsin can be demonstrated by immunocytochemical staining. The presence of AFP in the tumor cells is highly characteristic, and it underscores their differentiation into yolk sac cells.

Choriocarcinoma

- Choriocarcinoma is a highly malignant form of testicular tumor. In its “pure” form choriocarcinoma is rare, constituting less than 1% of all germ cell tumors.
- **Morphology. Often they cause no testicular enlargement and are detected only as a small palpable nodule**. Typically, these tumors are small, rarely larger than 5 cm in diameter. Hemorrhage and necrosis are extremely common. Histologically the tumors contain two cell types . The syncytiotrophoblastic cells are large and have many irregular or lobular hyperchromatic nuclei and an abundant eosinophilic vacuolated cytoplasm. HCG can be readily demonstrated in the cytoplasm. The cytotrophoblastic cells are more regular and tend to be polygonal, with distinct borders and clear cytoplasm; they grow in cords or masses and have a single, fairly uniform nucleus.

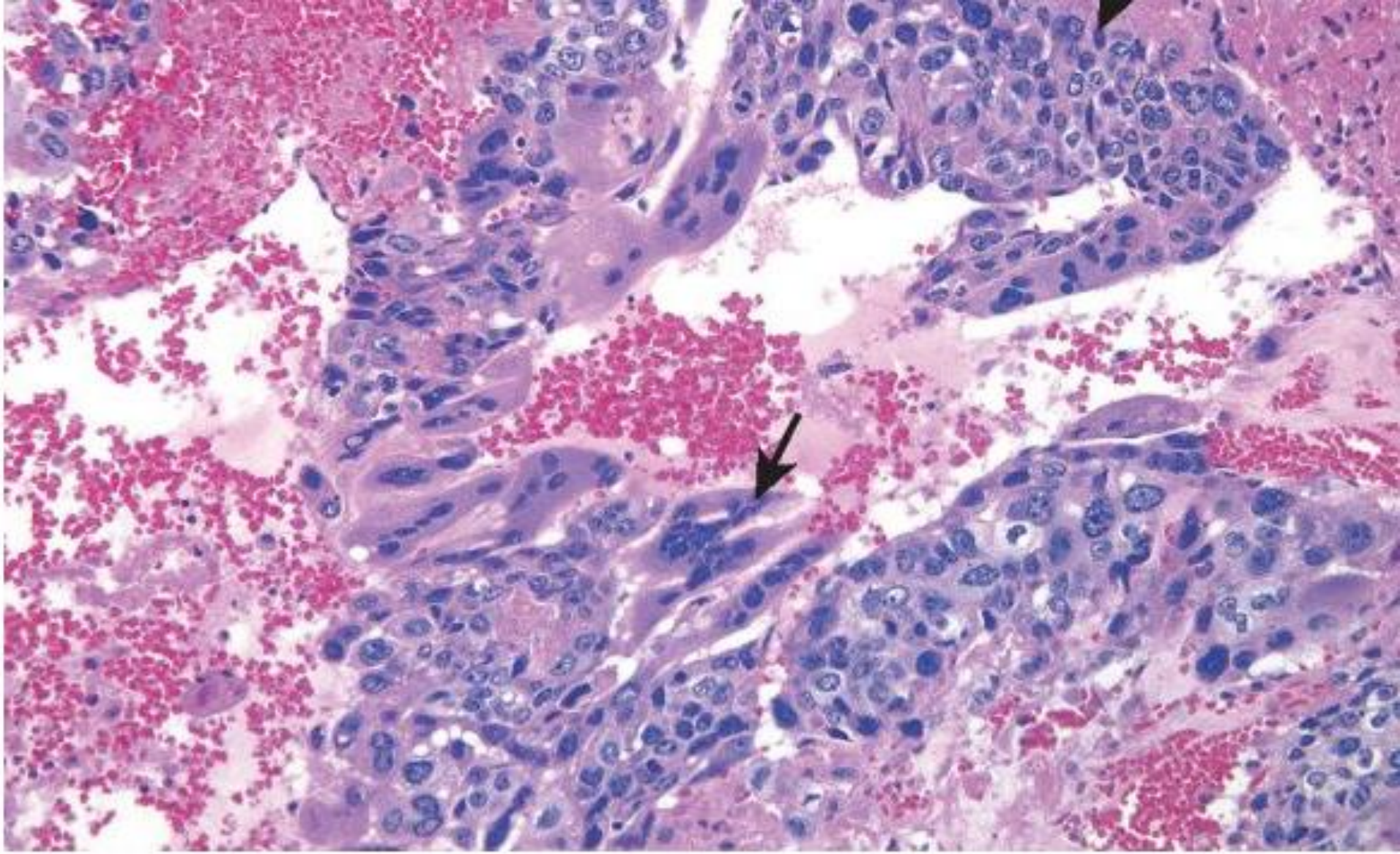


FIGURE 21-27 Choriocarcinoma shows clear cytotrophoblastic cells *(arrowhead)* with central nuclei and syncytiotrophoblastic cells *(arrow)* with multiple dark nuclei embedded in eosinophilic cytoplasm. Hemorrhage and necrosis are seen in the *upper right field*.

Teratoma

- The designation *teratoma* refers to a group of complex testicular tumors having various cellular or organoid components reminiscent of normal derivatives from more than one germ layer. They may occur at any age from infancy to adult life. Pure forms of teratoma are fairly common in infants and children, second in frequency only to yolk sac tumors. In adults, pure teratomas are rare, constituting 2% to 3% of germ cell tumors. However, the frequency of teratomas mixed with other germ cell tumors is approximately 45%.
- **Morphology**. Grossly, teratomas are usually large, ranging from 5 to 10 cm in diameter. Because they are composed of various tissues, the gross appearance is heterogeneous with solid, sometimes cartilaginous, and cystic areas. Hemorrhage and necrosis usually indicate admixture with embryonal carcinoma, choriocarcinoma, or both.

- **Teratomas** are composed of a heterogeneous, helter-skelter collection of differentiated cells or organoid structures, such as neural tissue, muscle bundles, islands of cartilage, clusters of squamous epithelium, structures reminiscent of thyroid gland, bronchial or bronchiolar epithelium, and bits of intestinal wall or brain substance, all embedded in a fibrous or myxoid stroma. Elements may be mature (resembling various adult tissues) or immature (sharing histologic features with fetal or embryonal tissue). Dermoid cysts and epidermoid cysts, are a form of teratoma that are common in the ovary , but rare in the testis. Unlike testicular teratomas, they have a uniformly benign behavior.
- Rarely, a malignant non–germ cell tumors may arise in teratoma. This phenomenon is referred to as “teratoma with malignant transformation,” where there is malignancy in derivatives of one or more germ cell layers. Thus, there may be a focus of squamous cell carcinoma, mucin-secreting adenocarcinoma, or sarcoma. The importance of recognizing a non–germ cell malignancy arising in a teratoma is that the non–germ cell component does not respond to chemotherapy when it spreads outside of the testis. In this case, the only hope for cure resides in the resectability of the tumor. These non–germ cell malignancies have an isochromosome 12p, similar to the germ cell tumors from which they arose.

- **Teratomas** are composed of a heterogeneous, helter-skelter collection of differentiated cells or organoid structures, such as neural tissue, muscle bundles, islands of cartilage, clusters of squamous epithelium, structures reminiscent of thyroid gland, bronchial or bronchiolar epithelium, and bits of intestinal wall or brain substance, all embedded in a fibrous or myxoid stroma. Elements may be mature (resembling various adult tissues) or immature (sharing histologic features with fetal or embryonal tissue). Dermoid cysts and epidermoid cysts, are a form of teratoma that are common in the ovary , but rare in the testis. Unlike testicular teratomas, they have a uniformly benign behavior.
- Rarely, a malignant non–germ cell tumors may arise in teratoma. This phenomenon is referred to as “teratoma with malignant transformation,” where there is malignancy in derivatives of one or more germ cell layers. Thus, there may be a focus of squamous cell carcinoma, mucin-secreting adenocarcinoma, or sarcoma. The importance of recognizing a non–germ cell malignancy arising in a teratoma is that the non–germ cell component does not respond to chemotherapy when it spreads outside of the testis. In this case, the only hope for cure resides in the resectability of the tumor. These non–germ cell malignancies have an isochromosome 12p, similar to the germ cell tumors from which they arose.

- In the child, differentiated mature teratomas usually follow a benign course. *In the postpubertal male all teratomas are regarded as malignant*, capable of metastatic behavior whether the elements are mature or immature. Consequently, it is not critical to detect immaturity in a testicular teratoma of a postpubertal male.

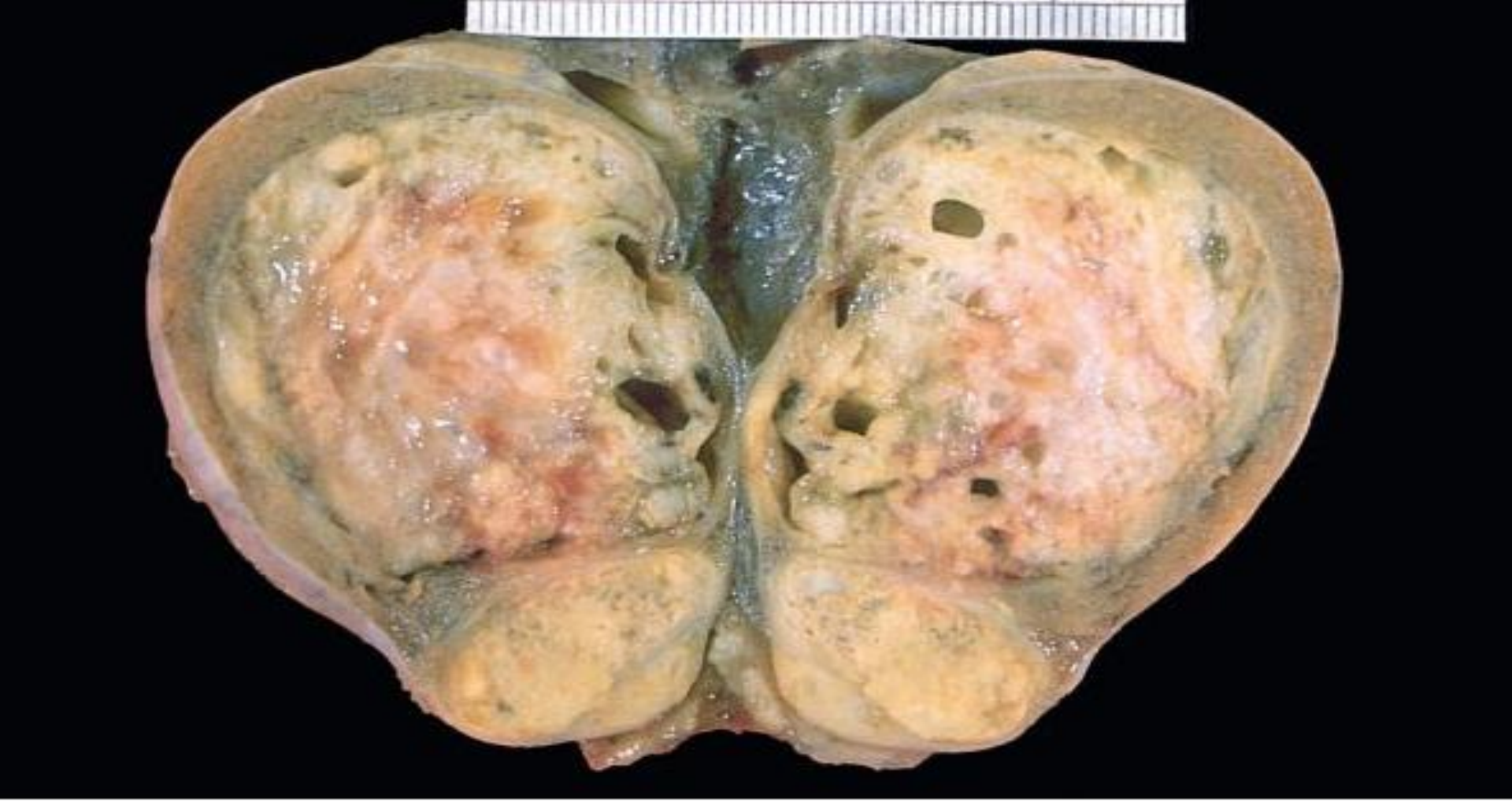


FIGURE 21-28 Teratoma of testis. The variegated cut surface with cysts reflects the multiplicity of tissue found histologically.

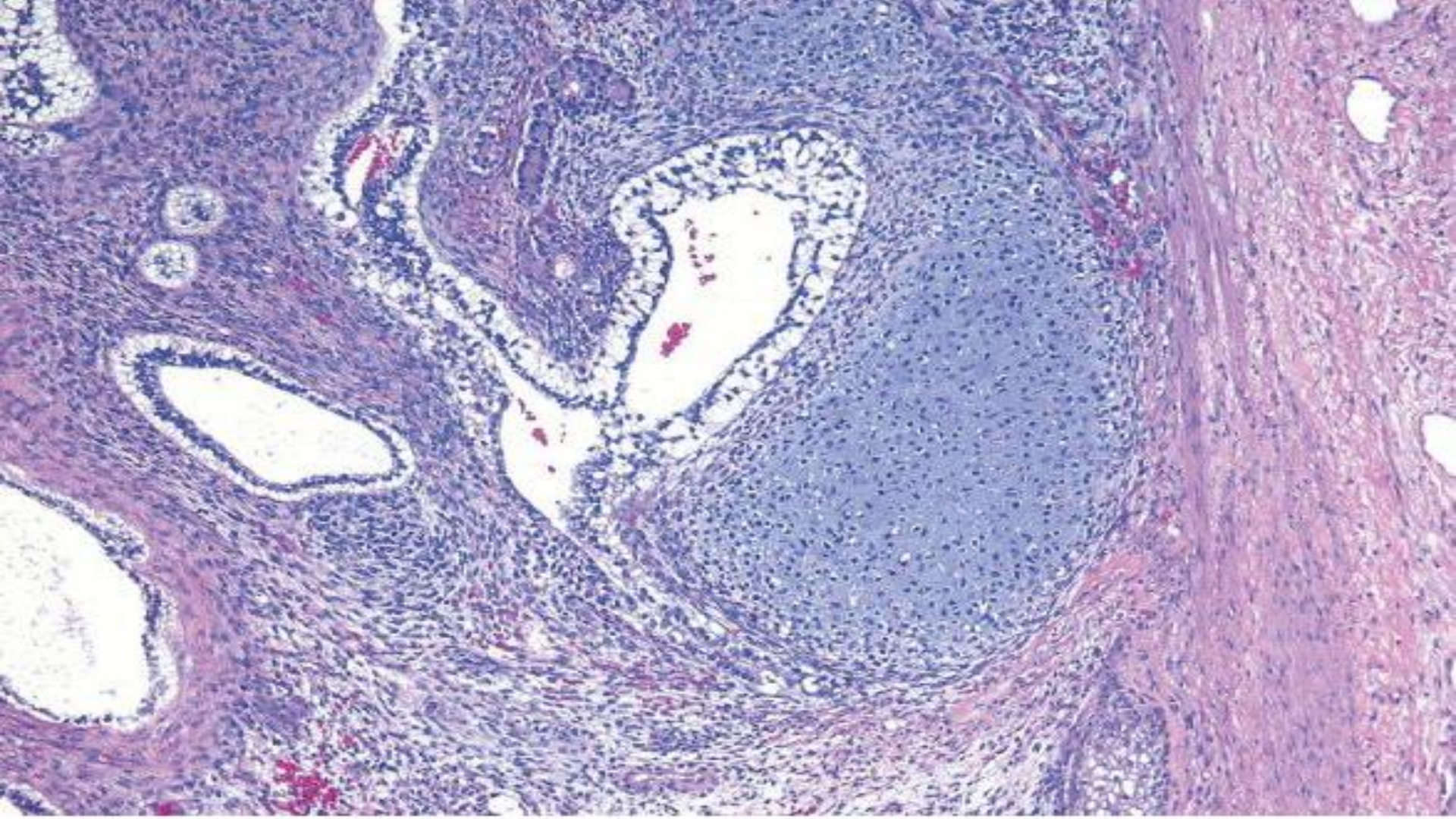


FIGURE 21-29 Teratoma of the testis consisting of a disorganized collection of glands, cartilage, smooth muscle, and immature stroma.

Mixed tumors

- About 60% of testicular tumors are composed of more than one of the “pure” patterns. Common mixtures include: teratoma, embryonal carcinoma, and yolk sac tumor; seminoma with embryonal carcinoma; and embryonal carcinoma with teratoma *(teratocarcinoma)*. In most instances the prognosis is worsened by the inclusion of the more aggressive element.

Clinical Features of Germ Cell Testicular Tumors.

- Although *painless enlargement of the testis* is a characteristic feature of germ cell neoplasms, *any solid testicular mass should be considered neoplastic unless proved otherwise*. Biopsy of a testicular neoplasm is associated with a risk of tumor spillage, which would necessitate excision of the scrotal skin in addition to orchiectomy. Consequently, the standard management of a solid testicular mass is radical orchiectomy based on the presumption of malignancy.
- Testicular tumors have a characteristic mode of spread. *Lymphatic spread* is common to all forms of testicular tumors. In general retroperitoneal para-aortic nodes are the first to be involved. Subsequent spread may occur to mediastinal and supraclavicular nodes.

- . *Hematogenous spread* is primarily to the lungs, but liver, brain, and bones may also be involved. The histology of metastases may sometimes be different from that of the testicular lesion. For example, an embryonal carcinoma may present a teratomatous picture in the secondary deposits. As discussed earlier, because all these tumors are derived from pluripotent germ cells, the apparent “forward” and “backward” differentiation seen in different locations is not entirely surprising. Another explanation for the differing morphologic patterns in the primary and metastatic site is that minor components in the primary tumor that were unresponsive to chemotherapy survive, resulting in the dominant metastatic pattern.

- From a clinical standpoint, tumors of the testis are segregated into two broad categories: *seminoma* and *nonseminomatous germ cell tumors* (NSGCTs). Seminomas tend to remain localized to the testis for a long time, and hence approximately 70% present in clinical stage I . In contrast, approximately 60% of males with NSGCTs present with advanced clinical disease (stages II and III). Metastases from seminomas typically involve lymph nodes. Hematogenous spread occurs later in the course of dissemination. NSGCTs not only metastasize earlier but also use the hematogenous route more frequently. The rare pure choriocarcinoma is the most aggressive NSGCT. It may not cause any testicular enlargement but instead spreads predominantly and rapidly by the bloodstream. Therefore, lungs and liver are involved early in virtually every case. From a therapeutic viewpoint, seminomas are extremely radiosensitive, whereas NSGCTs are relatively radioresistant. *To summarize, as compared with seminomas, NSGCTs are biologically more aggressive and in general have a poorer prognosis*.

- In the United States, three clinical stages of testicular tumors are defined:
- Stage I: tumor confined to the testis, epididymis, or spermatic cord
- Stage II: distant spread confined to retroperitoneal nodes below the diaphragm
- Stage III: metastases outside the retroperitoneal nodes or above the diaphragm

Germ cell tumors of the testis often secrete polypeptide hormones and certain enzymes that can be detected in blood by sensitive assays. Such biologic markers include HCG, AFP, and lactate dehydrogenase, which are valuable in the diagnosis and management of testicular cancer. The elevation of lactate dehydrogenase correlates with the mass of tumor cells, and provides a tool to assess tumor burden. Marked elevation of serum AFP or HCG levels are produced by yolk sac tumor and choriocarcinoma elements, respectively. Both of these markers are elevated in more than 80% of individuals with NSGCT at the time of diagnosis.

- As stated earlier, approximately 15% of seminomas have syncytiotrophoblastic giant cells and minimal elevation of HCG levels, which does not affect prognosis. In the context of testicular tumors, the value of serum markers is fourfold:
- In the evaluation of testicular masses
- In the staging of testicular germ cell tumors. For example, after orchiectomy, persistent elevation of HCG or AFP concentrations indicates stage II disease even if the lymph nodes appear of normal size by imaging studies.
- In assessing tumor burden
- In monitoring the response to therapy. After eradication of tumors there is a rapid fall in serum AFP and HCG. With serial measurements it is often possible to predict recurrence before the patients become symptomatic or develop any other clinical signs of relapse.

- The therapy and prognosis of testicular tumors depend largely on clinical stage and on the histologic type. Seminoma, which is extremely radiosensitive and tends to remain localized for long periods, has the best prognosis. More than 95% of patients with stage I and II disease can be cured. Among NSGCTs, the histologic subtype does not influence the prognosis significantly, and hence these are treated as a group. Approximately 90% of patients with NSGCTs can achieve complete remission with aggressive chemotherapy, and most can be cured. Pure choriocarcinoma has a poor prognosis. However, when it is a minor component of a mixed germ cell tumor, the prognosis is less adversely affected. With all testicular tumors, distant metastases, if present, usually occur within the first 2 years after treatment.

Tumors of Sex Cord–Gonadal Stroma

As indicated in Table 21-5 , sex cord–gonadal stroma tumors are subclassified based on their presumed histogenesis and differentiation. The two most important members of this group—Leydig cell tumors and Sertoli cell tumors—are described here. Details of other tumors in this group can be found in a review.

- **Leydig Cell Tumors**

Tumors of Leydig cells are particularly interesting, because they may elaborate androgens and in some cases both androgens and estrogens, and even corticosteroids. They may arise at any age, although most cases occur between 20 and 60 years of age. As with other testicular tumors, the most common presenting feature is testicular swelling, but in some patients gynecomastia may be the first symptom. In children, hormonal effects, manifested primarily as sexual precocity, are the dominating features.

- **Morphology**. These neoplasms form circumscribed nodules, usually less than 5 cm in diameter. They have a distinctive golden brown, homogeneous cut surface. Histologically, neoplastic Leydig cells usually are remarkably similar to their normal counterparts in that they are large and round or polygonal, and they have an abundant granular eosinophilic cytoplasm with a round central nucleus. The cytoplasm frequently contains lipid granules, vacuoles, or lipofuscin pigment, and, most characteristically, rod-shaped crystalloids of Reinke occur in about 25% of the tumors. Approximately 10% of the tumors in adults are invasive and produce metastases; most are benign.

- **Sertoli Cell Tumors**

Most Sertoli cell tumors are hormonally silent and present as a testicular mass.

- **Morphology**. These neoplasms appear as firm, small nodules with a homogeneous gray-white to yellow cut surface. Histologically the tumor cells are arranged in distinctive trabeculae that tend to form cordlike structures and tubules. Most Sertoli cell tumors are benign, but occasional tumors (~10%) pursue a malignant course.
- Gonadoblastoma :

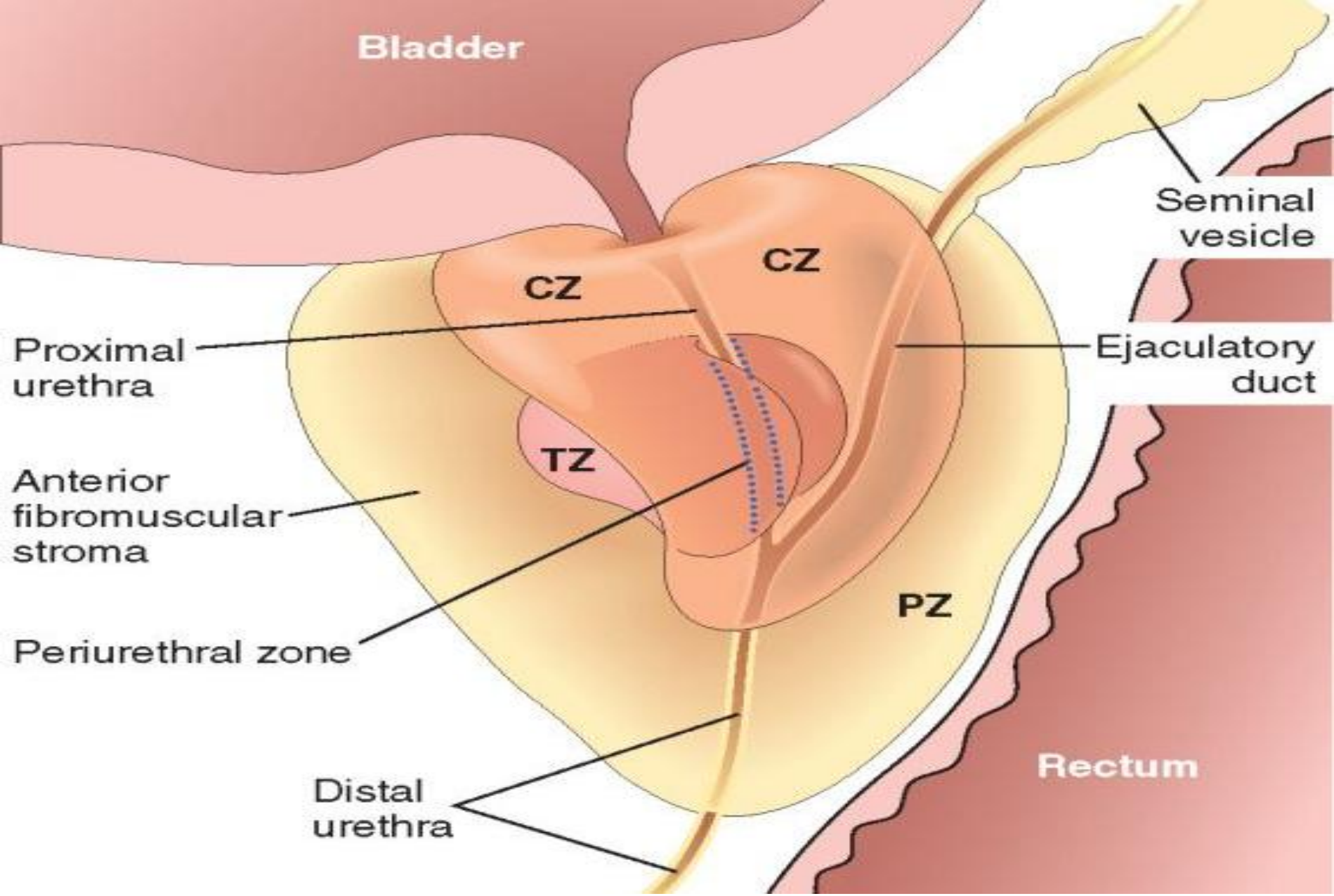
Gonadoblastomas are rare neoplasms containing a mixture of germ cells and gonadal stromal elements, that almost always arise in gonads with some form of testrcular dysgenesis (discussed earlier). In some cases the germ cell component becomes malignant, giving rise to seminoma.

Testicular Lymphoma

- Although an uncommon tumor of the testis, testicular lymphoma is included here because affected patients present with only a testicular mass, mimicking other, more common, testicular tumors. Aggressive non-Hodgkin lymphomas account for 5% of testicular neoplasms, *and are the most common form of testicular neoplasms in men over the age of 60*. In most cases, the disease is already disseminated at the time of detection. The most common testicular lyphomas, in decreasing order of frequency, are diffuse large B cell lymphoma, Burkitt Lymphoma, and EBV-positive extranodal NK/T cell lymphoma. Patients with testicular lymphomas have a higher incidence of central nervous system involvement than those similar tumors located elsewhere.

Prostate

- In the normal adult the prostate weighs approximately 20 gm. The prostate is a retroperitoneal organ encircling the neck of the bladder and urethra, and is devoid of a distinct capsule. In the adult, prostatic parenchyma can be divided into four biologically and anatomically distinct zones or regions: the peripheral, central, and transitional zones, and the region of the anterior fibromuscular stroma. The types of proliferative lesions are different in each region. For example, most hyperplasias arise in the transitional zone, whereas most carcinomas originate in the peripheral zone.


Bladder
Seminal vesicle
CZ
CZ
Proximal urethra
Ejaculatory duct
TZ
Anterior fibromuscular stroma
PZ
Periurethral zone
Rectum
Distal urethra

- Histologically the prostate is composed of glands lined by two layers of cells: a basal layer of low cuboidal epithelium covered by a layer of columnar secretory cells. In many areas there are small papillary infoldings of the epithelium. These glands are separated by abundant fibromuscular stroma. Testicular androgens control the growth and survival of prostatic cells. Castration leads to atrophy of the prostate caused by widespread apoptosis.

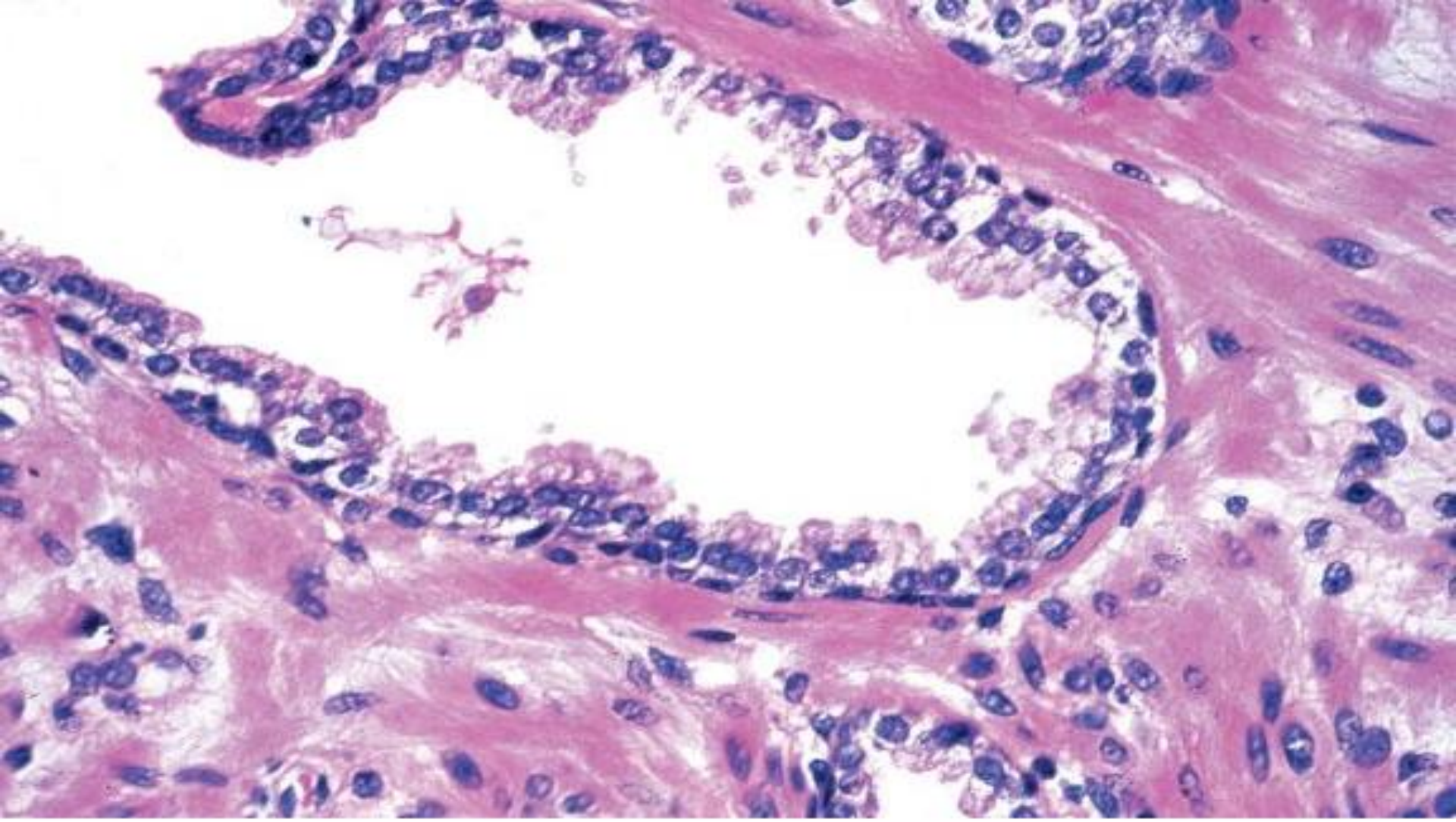


FIGURE 21-31 Benign prostate gland with basal cell and secretory cell layer.

INFLAMMATION

- Prostatitis may be divided into several categories: acute and chronic bacterial prostatitis, chronic abacterial prostatitis, and granulomatous prostatitis.
- *Acute bacterial prostatitis* typically results from bacteria similar to those that cause urinary tract infections. Thus, most cases are caused by various strains of *E. coli*, other gramnegative rods, enterococci, and staphylococci. The organisms become implanted in the prostate usually by intraprostatic reflux of urine from the posterior urethra or from the urinary bladder, but occasionally they seed the prostate by lymphohematogenous routes from distant foci of infection. Prostatitis sometimes follows surgical manipulation of the urethra or prostate gland itself, such as catheterization, cystoscopy, urethral dilation, or resection procedures on the prostate. Clinically, acute bacterial prostatitis is associated with fever, chills, and dysuria. On rectal examination the prostate is exquisitely tender and boggy. The diagnosis can be established by urine culture and clinical features.

- *Chronic bacterial prostatitis* is difficult to diagnose and treat. It may present with low back pain, dysuria, and perineal and suprapubic discomfort. Alternatively, it may be virtually asymptomatic. *Patients often have a history of recurrent urinary tract infections (cystitis, urethritis) caused by the same organism*. Because most antibiotics penetrate the prostate poorly, bacteria find safe haven in the parenchyma and constantly seed the urinary tract. Diagnosis of chronic bacterial prostatitis depends on the demonstration of leukocytosis in the expressed prostatic secretions, along with positive bacterial cultures. In most cases, there is no antecedent acute attack, and the disease appears insidiously and without obvious provocation. The implicated organisms are the same as those cited as causes of acute prostatitis.

- *Chronic abacterial prostatitis* is the most common form of prostatitis seen today. *Clinically, it is indistinguishable from chronic bacterial prostatitis. There is no history, however, of recurrent urinary tract infection*. Expressed prostatic secretions contain more than 10 leukocytes per high-power field, but bacterial cultures are uniformly negative.
- *Granulomatous prostatitis* may be specific, where an etiologic infectious agent may be identified or non-specific. In the United States the most common cause is related to instillation of BCG within the bladder for treatment of superficial bladder cancer, discussed earlier in this chapter. BCG is an attenuated mycobacterial strain that gives rise to a histologic picture indistinguishable from that seen with systemic tuberculosis. However, in this setting the finding of granulomas in the prostate is of no clinical significance, and requires no treatment. Fungal granulomatous prostatitis is typically seen only in immunocompromised hosts. Nonspecific granulomatous prostatitis is relatively common and represents a reaction to secretions from ruptured prostatic ducts and acini. Although some of these men have a recent history of urinary tract infection, bacteria are not seen within the tissue in nonspecific granulomatous prostatitis.

- **Morphology. Acute prostatitis** may appear as minute, disseminated abscesses; as large, coalescent focal areas of necrosis; or as diffuse edema, congestion, and boggy suppuration of the entire gland.
- In men with symptoms of acute or chronic prostatitis, biopsy or surgical specimens are uncommonly examined microscopically, because the disease is diagnosed on clinical and laboratory findings. In fact biopsy of a man with acute prostatitis is contraindicated, as it may lead to sepsis. It is common in prostate specimens removed surgically to find histologic evidence of acute or chronic inflammation in men with no clinical symptoms of acute or chronic prostatitis. In these instances etiologic infectious agents have yet to be identified. So as not to be confused with the clinical syndromes of acute and chronic prostatitis, these prostate specimens are instead diagnosed in descriptive terms as showing “acute inflammation” or “chronic inflammation” and not as “prostatitis.”

BENIGN ENLARGEMENT

Benign Prostatic Hyperplasia (BPH) or Nodular Hyperplasia

- BPH is an extremely common disorder in men over age 50. 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 and narrow the urethral canal to cause partial, or sometimes virtually complete, obstruction of the urethra.

Incidince

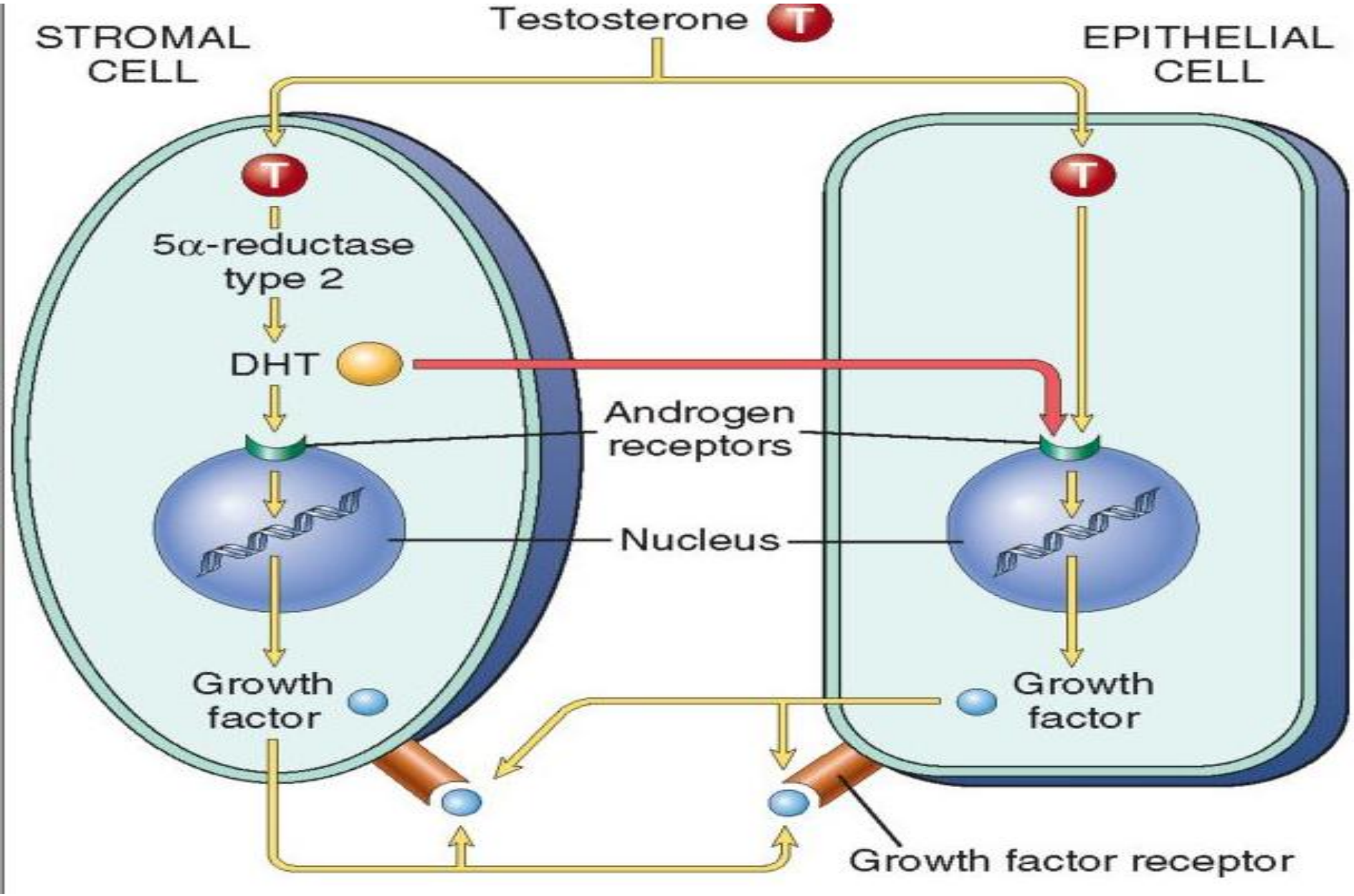
- Histologic evidence of BPH can be seen in approximately 20% of men 40 years of age, a figure that increases to 70% by age 60 and to 90% by age 80. There is no direct correlation, however, between histologic changes and clinical symptoms. Only 50% of those who have microscopic evidence of BPH have clinically detectable enlargement of the prostate, and of these individuals, only 50% develop clinical symptoms. BPH is a problem of enormous magnitude, with approximately 30% of white American males over 50 years of age having moderate to severe symptoms.

Etiology and Pathogenesis.

- Despite the fact that there is an increased number of epithelial cells and stromal components in the periurethral area of the prostate, there is no clear evidence of increased epithelial cell proliferation in human BPH. Instead, it is believed that the main component of the “hyperplastic” process is impaired cell death. It has been proposed that there is an overall reduction of the rate of cell death, resulting in the accumulation of senescent cells in the prostate. In keeping with this androgens (discussed below), which are required for the development of BPH, can not only increase cellular proliferation, but also inhibit cell death.

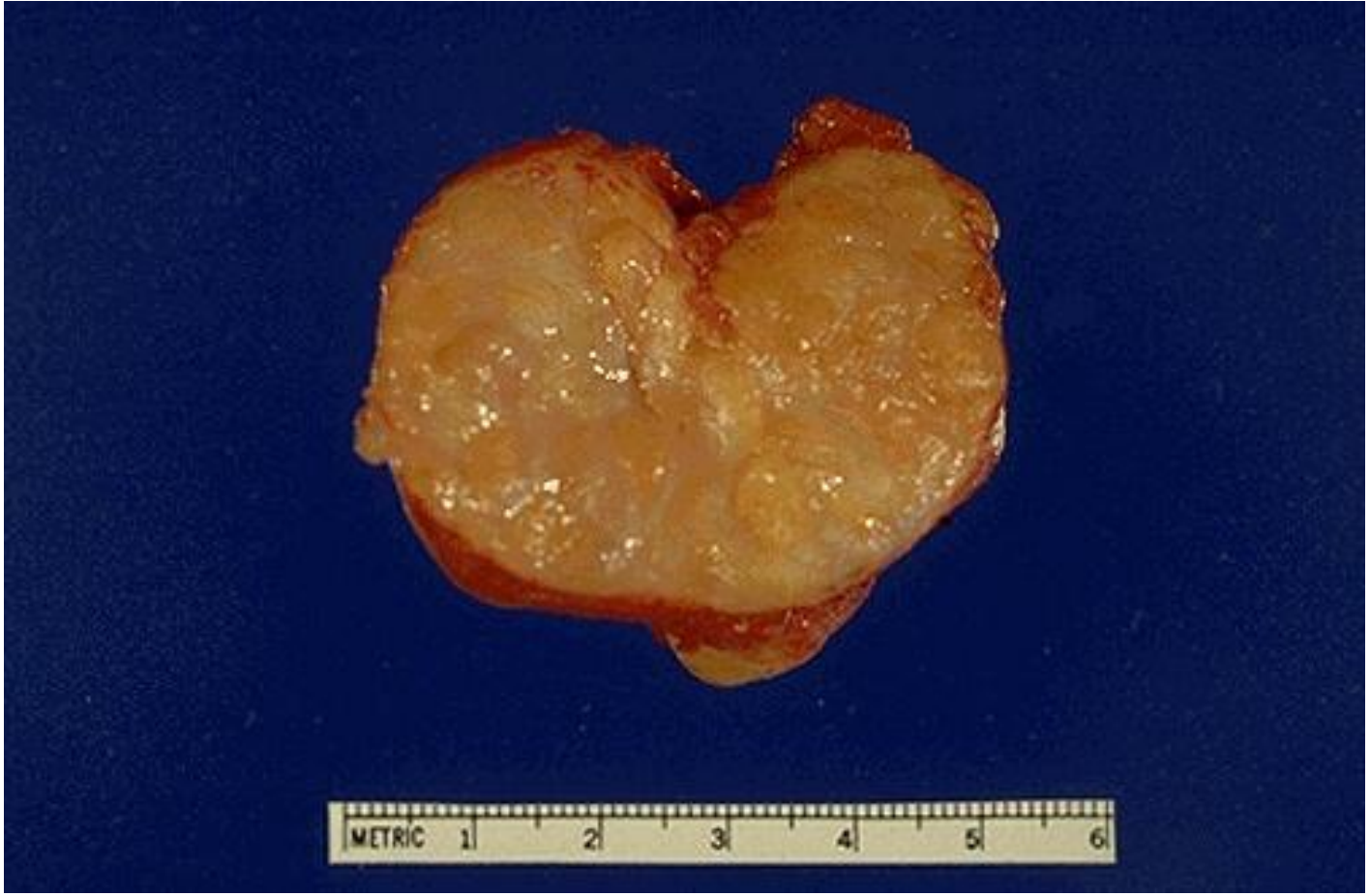
- The main androgen in the prostate, constituting 90% of total prostatic androgens, is dihydrotestosterone (DHT). It is formed in the prostate from the conversion of testosterone by the enzyme type 2 5α-reductase. This enzyme is located almost entirely in stromal cells; epithelial cells of the prostate do not contain type 2 5α reductase, with the exception of a few basal cells. *Thus stromal cells are responsible for androgen-dependent prostatic growth*. Type 1 5α-reductase is not detected in the prostate, or is present at very low levels. However this enzyme may produce DHT from testosterone in liver and skin, and circulating DHT may act in the prostate by an endocrine mechanism.

- DHT binds to the nuclear androgen receptor (AR) present in both stromal and epithelial prostate cells. DHT is more potent than testosterone because it has a higher affinity for AR and forms a more stable complex with the receptor. Binding of DHT to AR activates the transcription of androgen-dependent genes. DHT is not a direct mitogen for prostate cells, instead DHT-mediated transcription of genes results in the increased production of several growth factors and their receptors. Most important among these are members of the fibroblast growth factor (FGF) family, and particularly FGF-7. FGF-7, produced by stromal cells, is probably the most important factor mediating the paracrine regulation of androgen-stimulated prostatic growth. Other growth factors produced in BPH are FGFs 1 and 2, and TGFβ, which promote fibroblast proliferation. Although the ultimate cause of BPH is unknown, it is believed that DHT-induced growth factors act by increasing the proliferation of stromal cells and decreasing the death of epithelial cells.

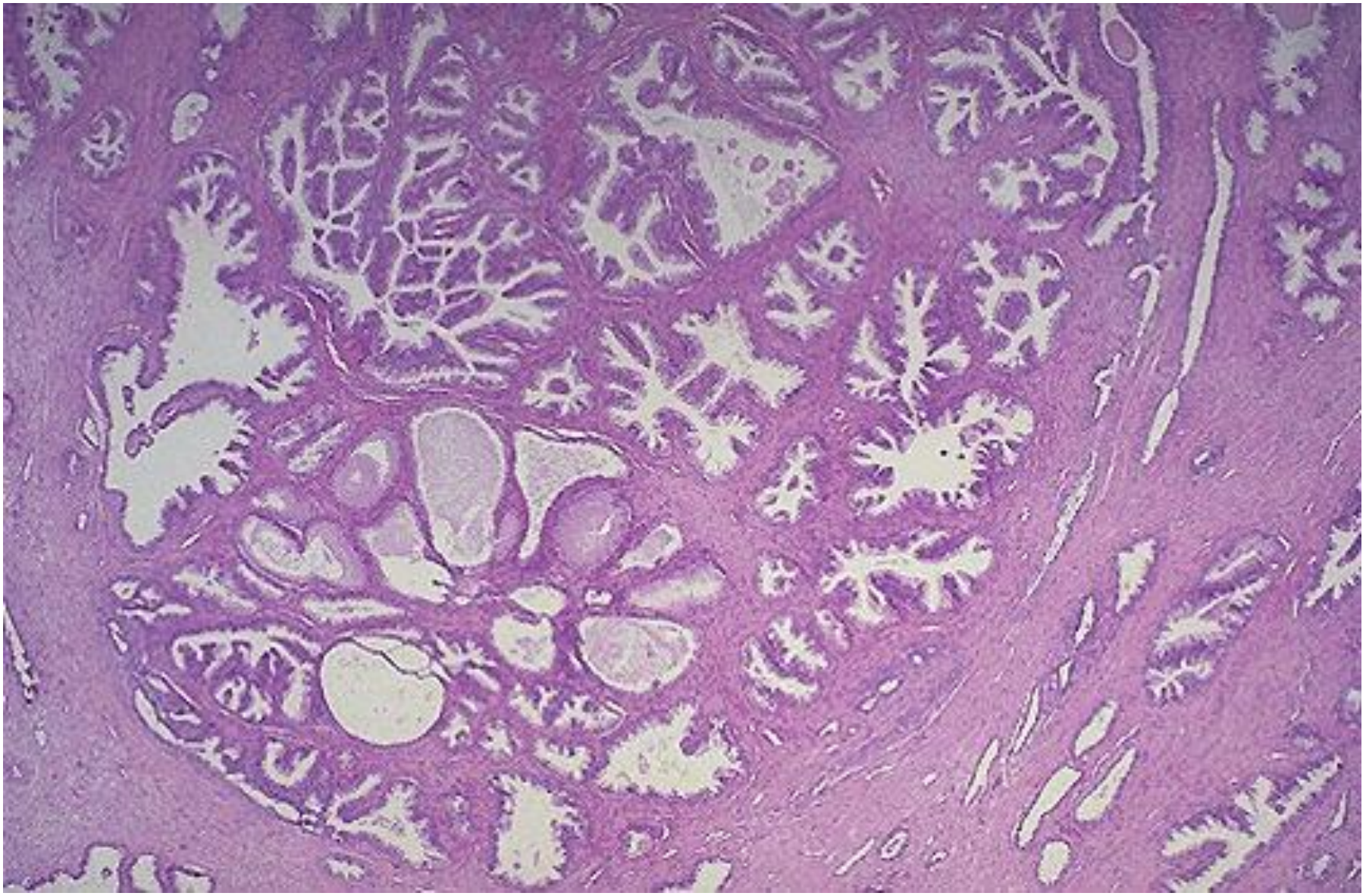

STROMAL CELL
Testosterone
T
EPITHELIAL CELL
T
T
5α-reductase type 2
DHT
Androgen receptors
Nucleus
Growth factor
Growth factor
Growth factor receptor

- **Morphology**. In the usual case of prostatic enlargement, the prostate weighs between 60 and 100 gm. Nodular hyperplasia of the prostate originates almost exclusively in the inner aspect of the prostate gland (transition zone). The early nodules are composed almost entirely of stromal cells, and later predominantly epithelial nodules arise. From their origin in this strategic location the nodular enlargements may encroach on the lateral walls of the urethra to compress it to a slitlike orifice . In some cases, nodular enlargement may project up into the floor of the urethra as a hemispheric mass directly beneath the mucosa of the urethra, which is termed **median lobe hypertrophy** by clinicians.
- On cross-section, the nodules vary in color and consistency. In nodules that contain mostly glands, the tissue is yellow-pink with a soft consistency, and a milky-white prostatic fluid oozes out of these areas. In nodules composed primarily of fibromuscular stroma, each nodule is pale gray, is tough, does not exude fluid, and is less clearly demarcated from the surrounding uninvolved prostatic tissue. Although the nodules do not have true capsules, the compressed surrounding prostatic tissue creates a plane of cleavage about them.

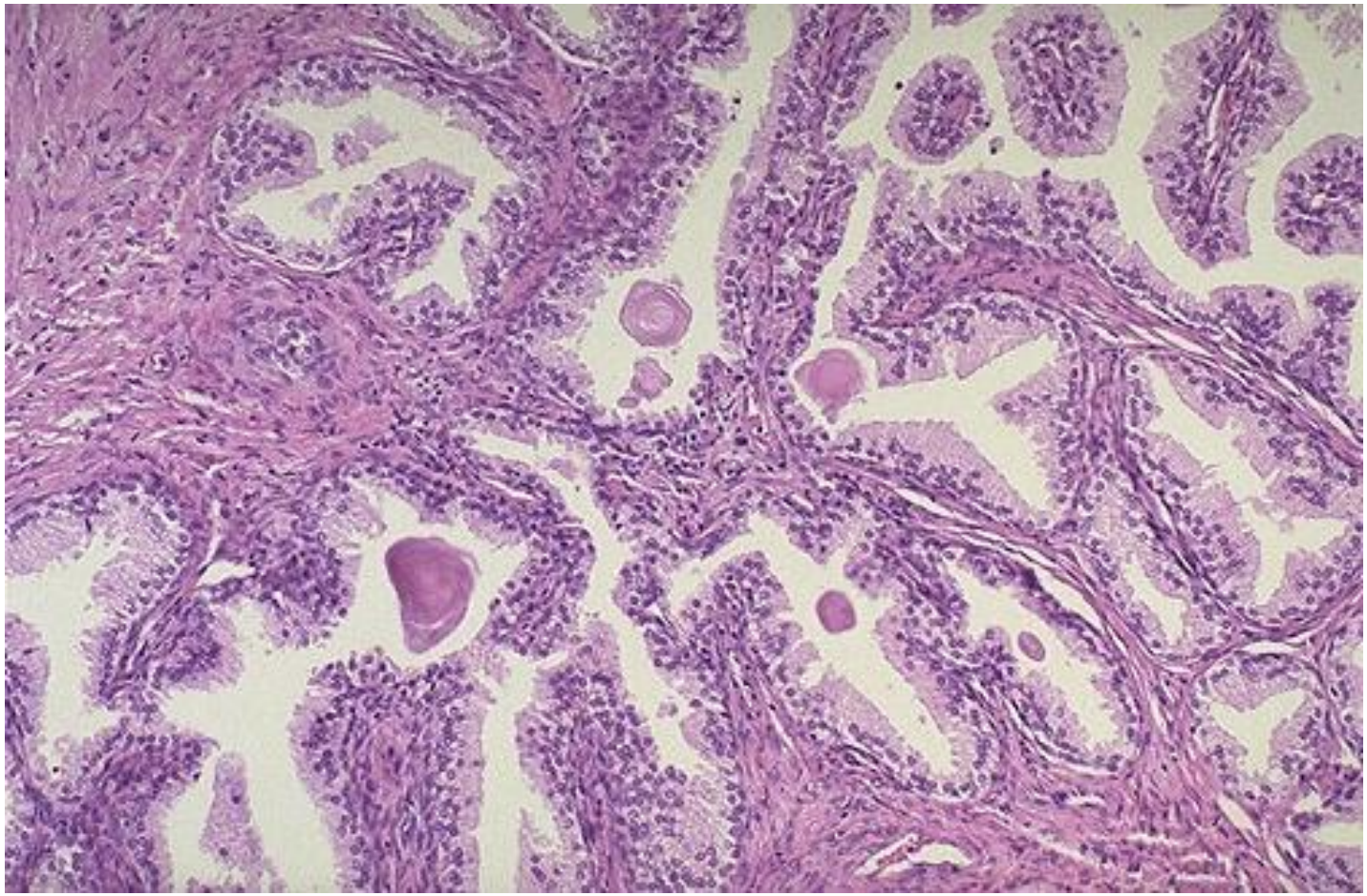
- Microscopically, the hallmark of BPH is nodularity . The composition of the nodules ranges from purely stromal fibromuscular nodules to fibroepithelial nodules with a glandular predominance. Glandular proliferation takes the form of aggregations of small to large to cystically dilated glands, lined by two layers, an inner columnar and an outer cuboidal or flattened epithelium. The diagnosis of BPH cannot usually be made on needle biopsy, since the histology of glandular or mixed glandular-stromal nodules of BPH cannot be appreciated in limited samples. Also, needle biopsies do not typically sample the transition zone where BPH occurs. Occasionally foci of reactive squamous metaplasia histologically mimicking urothelial carcinoma can be seen adjacent to prostatic infarcts in prostates with prominent BPH.



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



Microscopically, benign prostatic hyperplasia hyperplastic nodule of glands is seen.



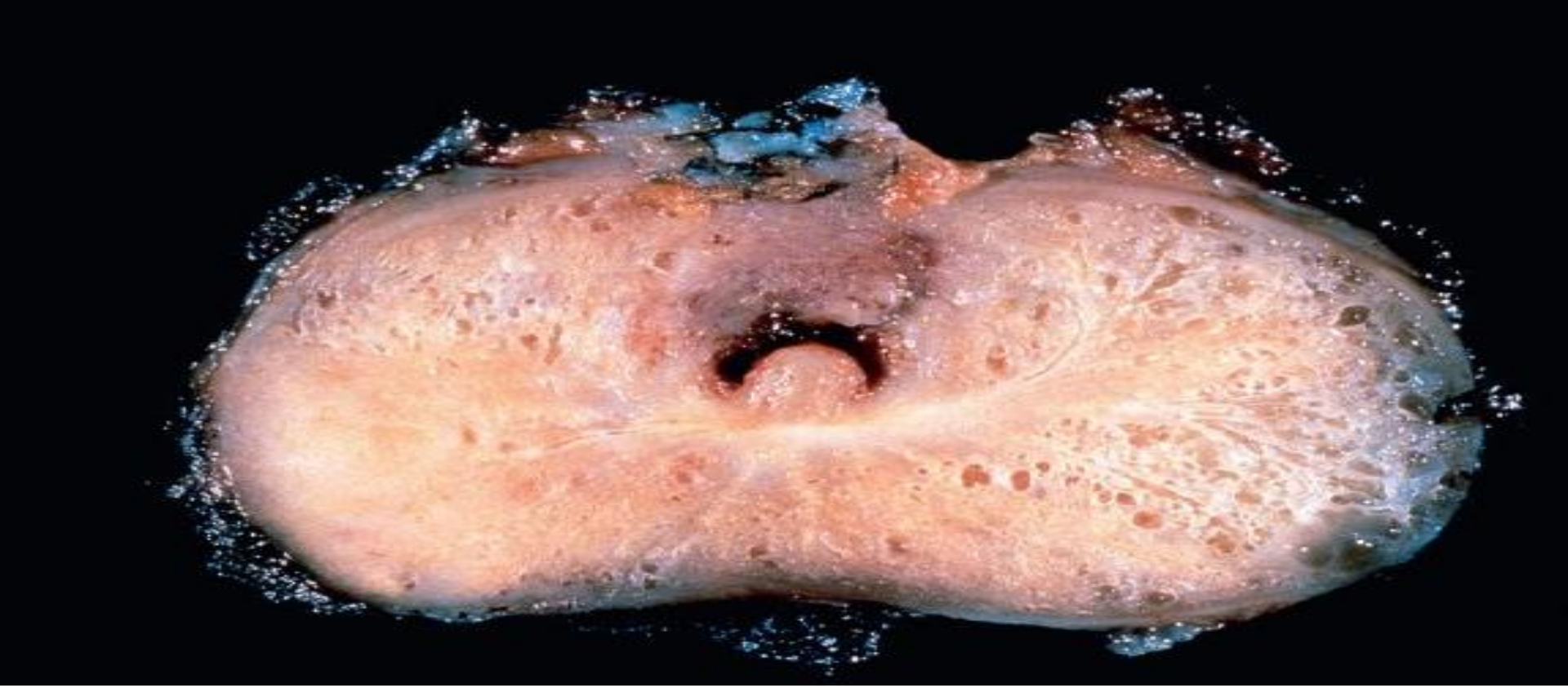
The enlarged prostate has glandular hyperplasia. The glands are well-differentiated and still have some intervening stroma. The small laminated pink concretions within the glandular lumens are known as corpora amylacea.

Carcinoma of the prostate

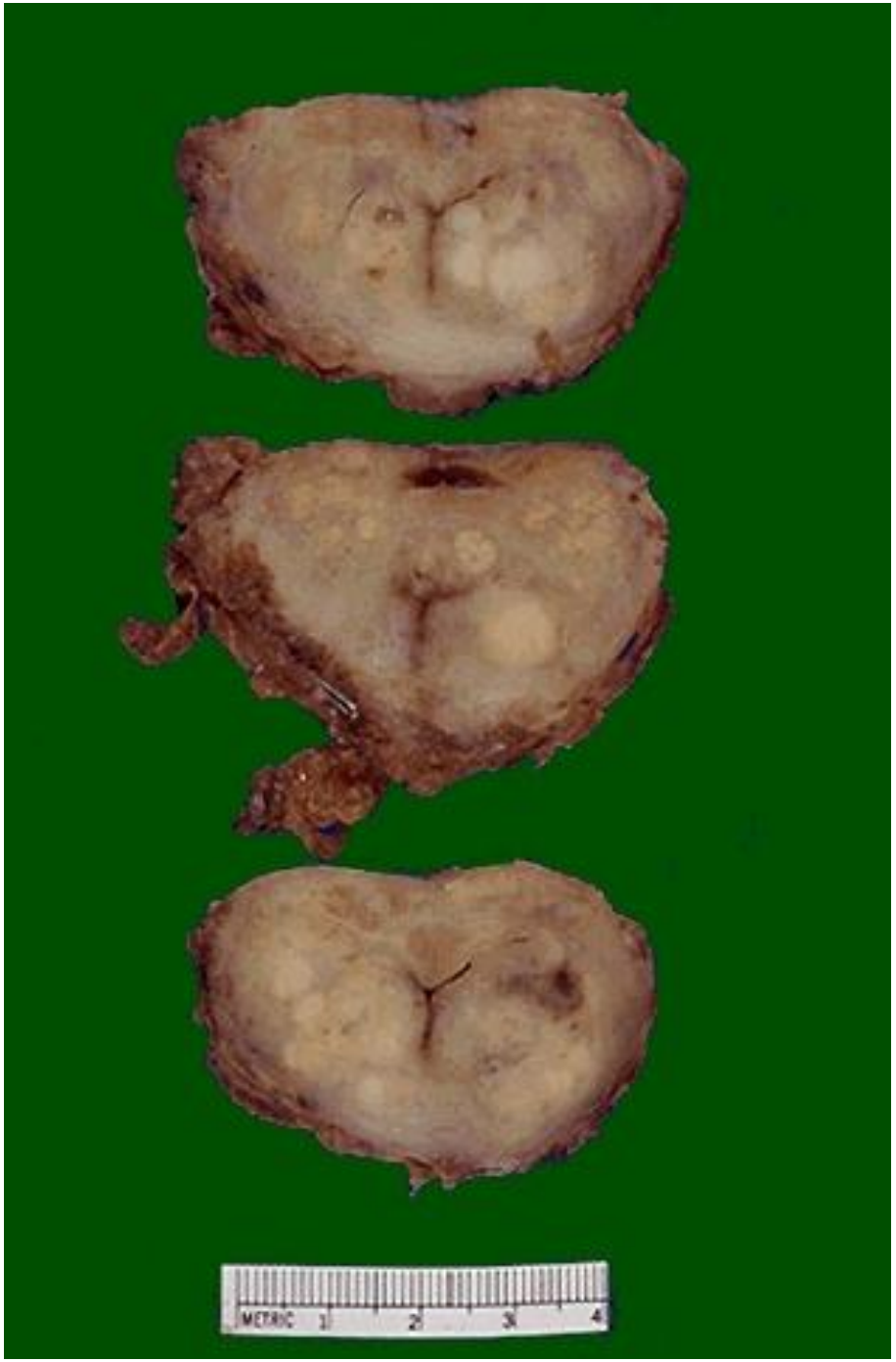
Macroscopically

70% of the carcinomas arise in the outer glands

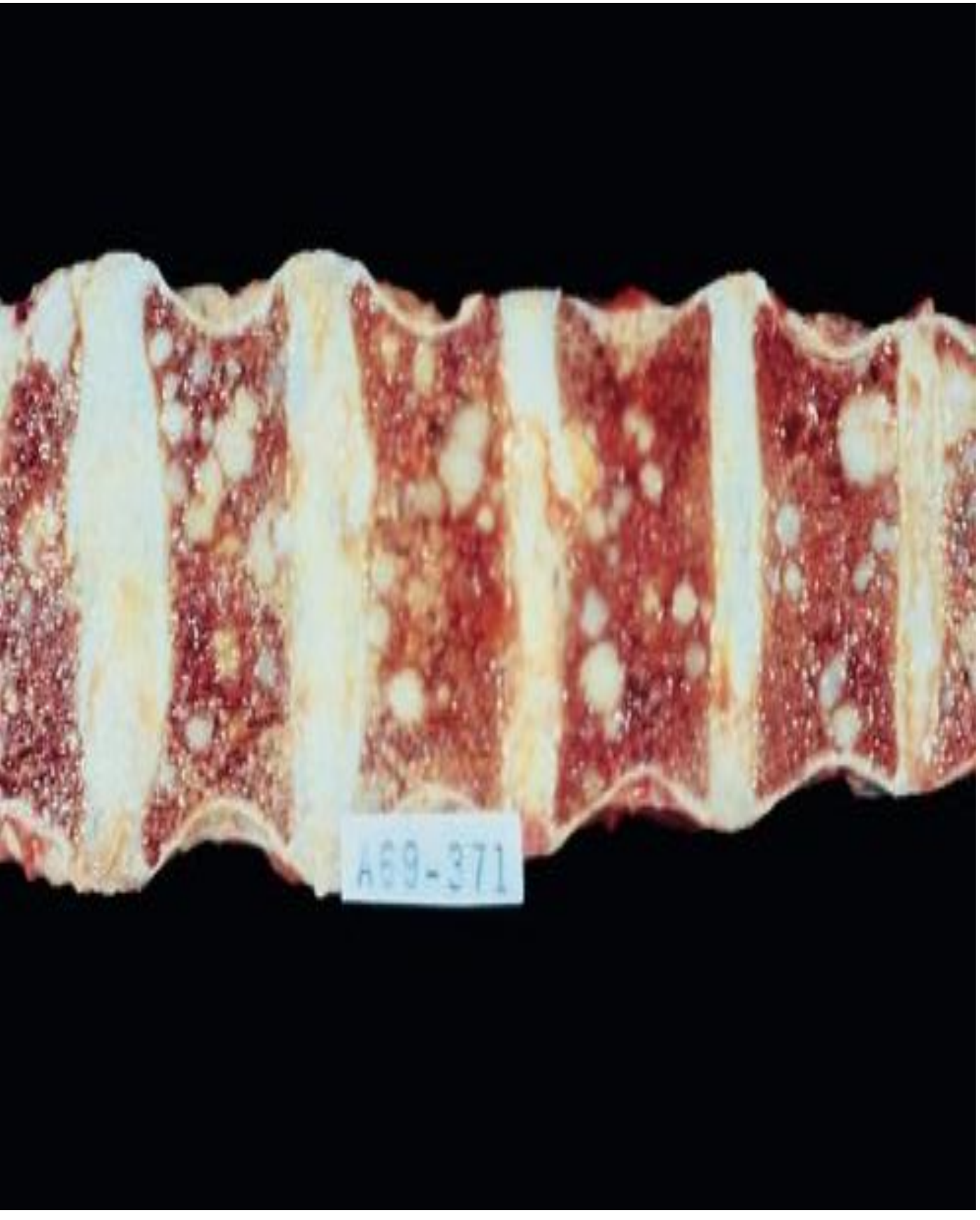
On cut surface ; foci of carcinoma appear as firm ‘ gray-white to yellow lesions that infiltrate the adjacent gland with ill-defined margins



Adenocarcinoma of the prostate. Carcinomatous tissue is seen on the posterior aspect *(lower left)*. Note solid whiter tissue of cancer in contrast to spongy appearance of benign peripheral zone in the contralateral side.



These sections through a prostate reveal irregular yellowish nodules, This proved to be prostatic adenocarcinoma. Prostate glands containing adenocarcinoma are not necessarily enlarged.


A69-371

Carcinoma of the prostate

- Adenocarcinoma most common over age of 50
- Etiology:
- Environmental factors; lycopenes;vit.A,E; selenium; soy products
- Common in Scandinavian, un common in Japan and other Asian countries
- Androgen (variation in CAG repeats in androgen receptors.

Macroscopically

- Peripheral zone (70%), post. Location so palpable by DRE
- Cross section, grity and firm, S.T. non visualized.
- Spread: direct through blood and L.N.; hematogenous spread to bones (axial skeleton: lumber spine, proximal femur, pelvis, thoracic spine and ribs.

microscopically

Most prostatic carcinomas are adenocarcinomas

The better differentiated lesions are composed of small glands that infiltrate the adjacent stroma in an irregular ‘ haphazard fashion

Glands are not encircled by collagen or stromal cells but rather lie (back to back)

The neoplastic glands are lined by a single layer of cuboidal cells with conspicuous nucleoli ‘ the basal cell layer is absent

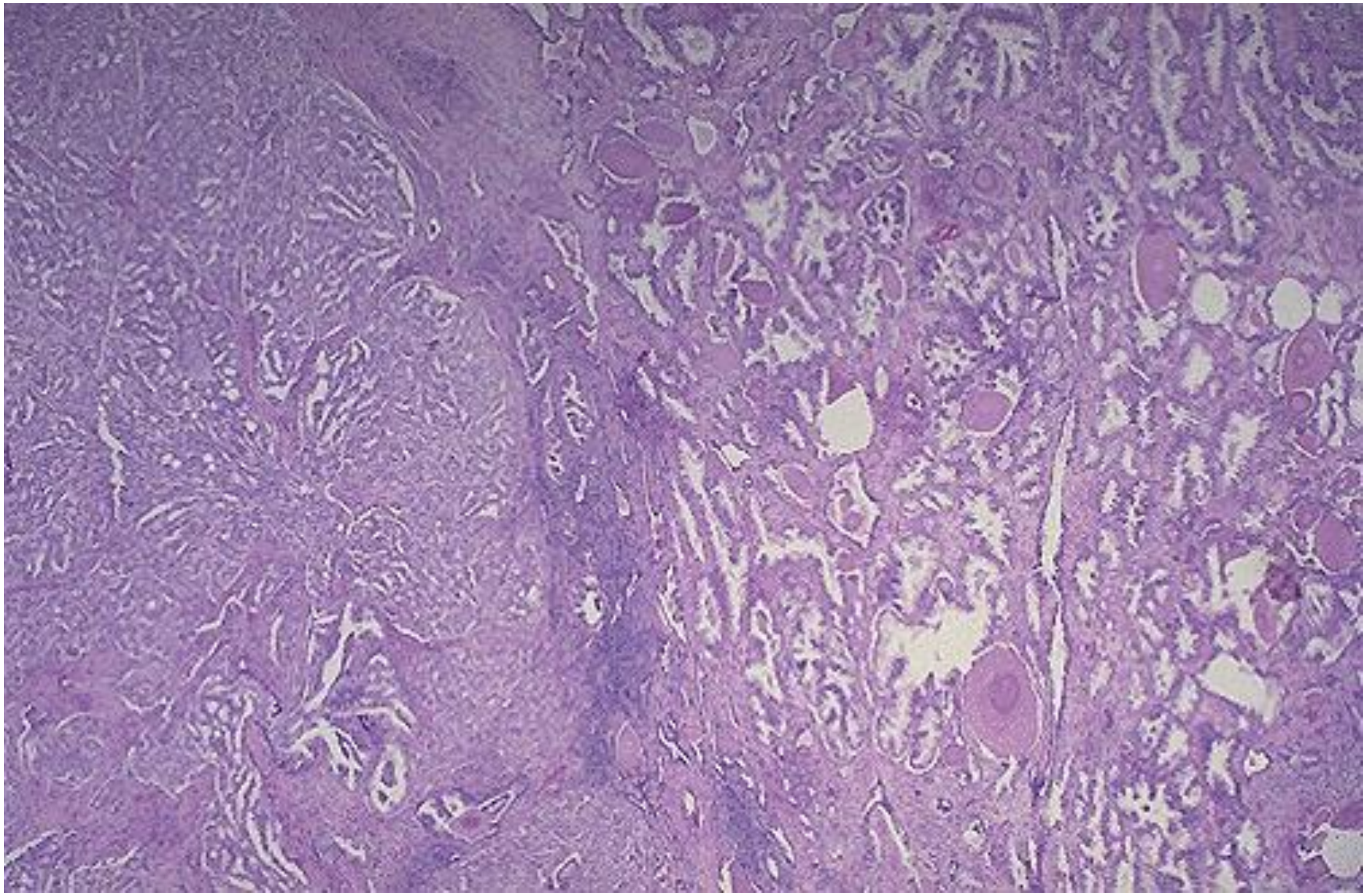
Carcinoma of the prostate microscopically

With increasing degrees of anaplasia

Irregular ‘ ragged glandular structures ‘

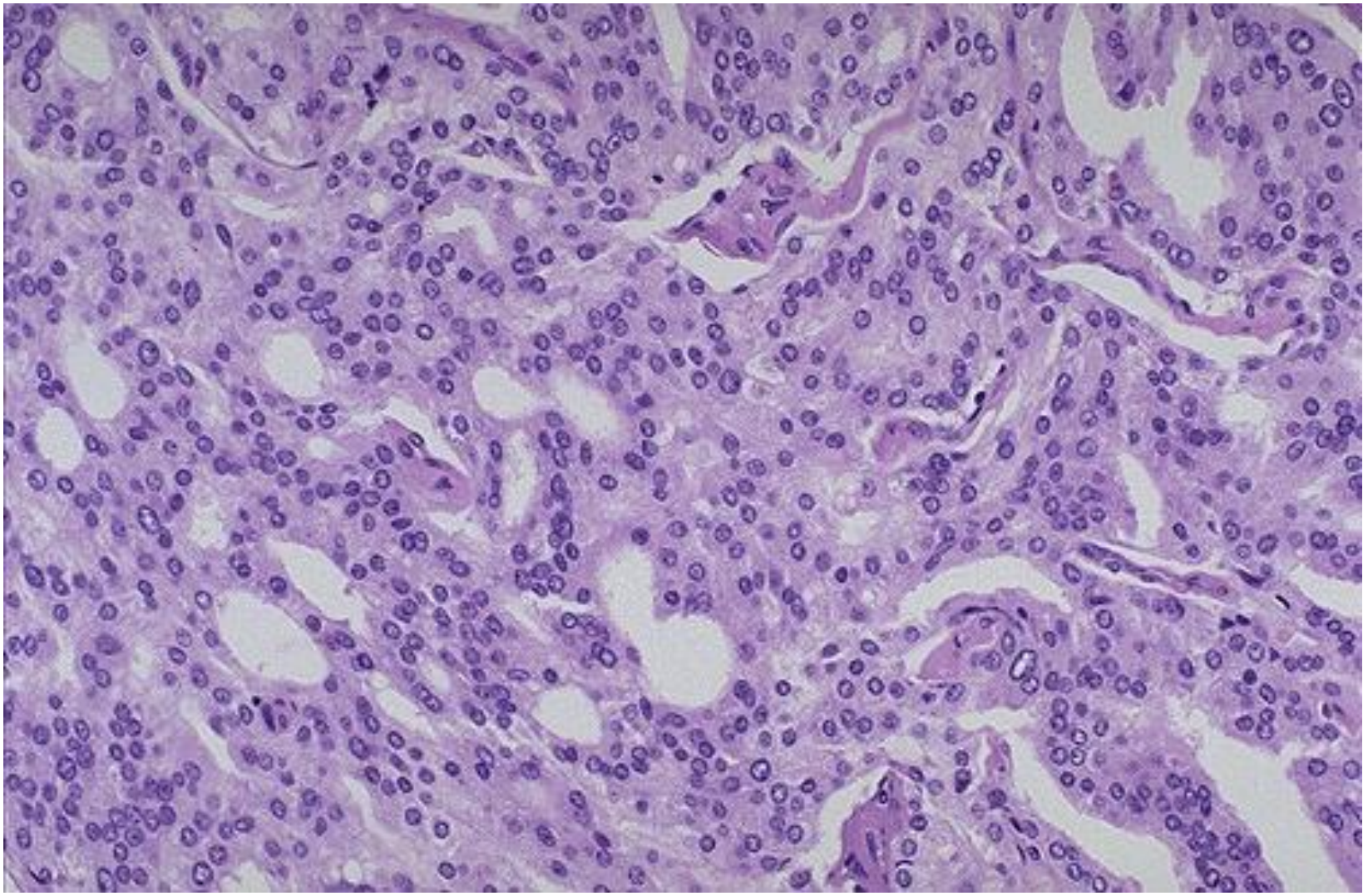
Papillary or cribriform epithelial structures

and in extreme cases ‘ sheets of poorly differentiated cells are noted

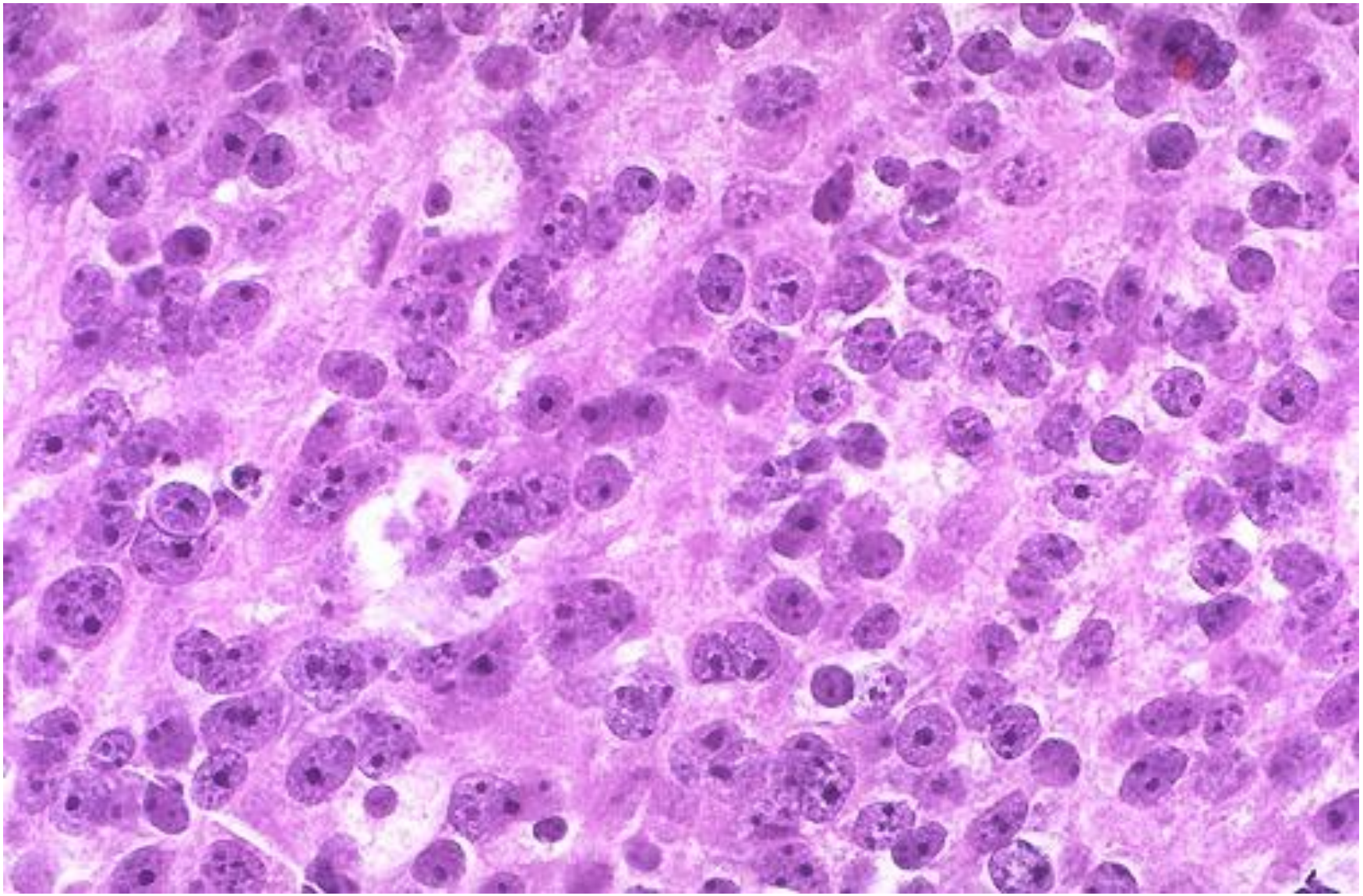


At the right are normal prostatic glands

At the left is prostatic adenocarcinoma.



The neoplastic glands of prostatic adenocarcinoma are still recognizable as glands, but there is no intervening stroma and the nuclei are hyperchromatic.



Prominent nucleoli are seen in the nuclei of this prostatic adenocarcinoma

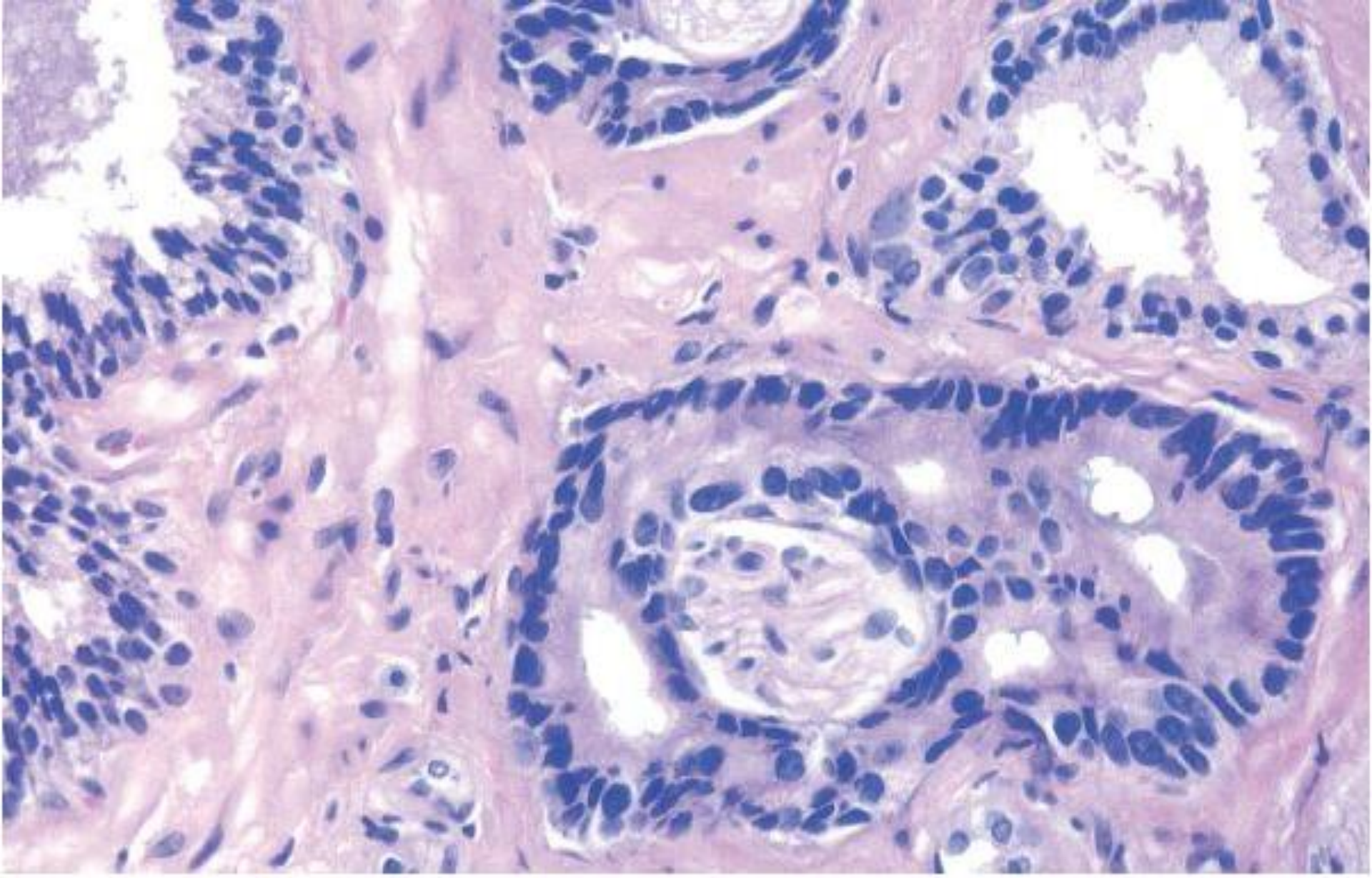


FIGURE 21-37 Carcinoma of prostate showing perineural invasion by malignant glands. Compare to benign gland *(left)*.