Table 24.7 Comparative Features of Type 1 and Type 2 Diabetes

Type 1 Diabetes	Type 2 Diabetes
Clinical	
Onset: usually childhood and adolescence	Onset: usually adult; increasing incidence in childhood and adolescence
Normal weight or weight loss preceding diagnosis	Vast majority are obese (80%)
Progressive decrease in insulin levels	Increased blood insulin (early); normal or moderate decrease in insulin (late)
Circulating islet autoantibodies (anti-insulin, anti-GAD, anti-ICA512)	No islet autoantibodies
Diabetic ketoacidosis in absence of insulin therapy	Nonketotic hyperosmolar coma more common
Genetics	
Major linkage to MHC class II genes; also linked to polymorphisms in *CTLA4* and *PTPN22*, and insulin gene VNTRs	No HLA linkage; linkage to candidate diabetogenic and obesity-related genes (e.g., *TCF7L2*, *PPARG*, *FTO*)
Pathogenesis	
Dysfunction in T-cell selection and regulation leading to breakdown in self-tolerance to islet autoantigens	Insulin resistance in peripheral tissues, failure of compensation by β cells
Pathology	
Insulitis (inflammatory infiltrate of T cells and macrophages)	No insulitis; amyloid deposition in islets
β-cell depletion, islet atrophy	Mild β-cell depletion

HLA, Human leukocyte antigen; *MHC*, major histocompatibility complex; *VNTRs*, variable number of tandem repeats.

costs stemming from the reduced productivity of individuals with diabetes.

Diagnosis

Blood glucose is normally maintained in a very narrow range of 70 to 120 mg/dL. According to the ADA and WHO, diagnostic criteria for diabetes include the following:

1. A fasting plasma glucose ≥126 mg/dL
2. A random plasma glucose ≥200 mg/dL (in a patient with classic hyperglycemic signs, as discussed later)

3. A 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test (OGTT) with a loading dose of 75 g
4. A glycated hemoglobin (HbA1c) level ≥6.5% (glycated hemoglobin is further discussed later in the chapter)

All tests, except the random blood glucose test in a patient with classic hyperglycemic signs, need to be repeated and confirmed on a separate day. If there is discordance between two assays (e.g., fasting glucose and HbA1c level), the result with the greatest degree of abnormality is considered the "readout." Of note, many acute stresses, such as severe infections, burns, or trauma, can lead to transient hyperglycemia due to secretion of hormones such as catecholamines and cortisol that oppose the action of insulin. The diagnosis of diabetes requires persistence of hyperglycemia following resolution of the acute illness.

Prediabetes, a state of dysglycemia that often precedes development of frank T2D, is defined by one or more of the following:

1. A fasting plasma glucose between 100 and 125 mg/dL ("impaired fasting glucose"),
2. A 2-hour plasma glucose between 140 and 199 mg/dL following a 75-g oral glucose tolerance test (OGTT) ("impaired glucose tolerance"), and/or
3. A glycated hemoglobin (HbA1c) level between 5.7% and 6.4%

As many as one-fourth of individuals with impaired glucose tolerance will develop overt diabetes over 5 years, [illegible] family history

changes. These include accumulation of bilirubin (cholestasis), as well as ballooning, a change marked by cell swelling, cytoplasmic clearing, and clumping of intermediate filaments, which when prominent, may form *Mallory hyaline*. Ballooned hepatocytes are a hallmark of

Table 18.1 Laboratory Evaluation of Liver Disease

Test Category	Serum Measurement
Hepatocyte integrity	Cytosolic hepatocellular enzymes[a] Serum aspartate aminotransferase (AST) Serum alanine aminotransferase (ALT) Serum lactate dehydrogenase (LDH)
Biliary excretory function	Substances normally secreted in bile[a] Serum bilirubin Total: unconjugated plus conjugated Direct: conjugated only Urine bilirubin Serum bile acids Plasma membrane enzymes (from damage to bile canaliculus)[a] Serum alkaline phosphatase Serum γ-glutamyl transpeptidase (GGT)
Hepatocyte synthetic function	Proteins secreted into the blood Serum albumin[b] Coagulation factors[b] Prothrombin time (PT) and partial thromboplastin time (PTT): fibrinogen, prothrombin, factors V, VII, IX, and X Hepatocyte metabolism Serum ammonia[a] Aminopyrine breath test (hepatic demethylation)[b]

[a]Increased in liver disease.

[b]Decreased in liver disease.

adds an irreversible component to the obstructive disease.

Bronchiectasis

Bronchiectasis is a disorder in which destruction of smooth muscle and elastic tissue by inflammation stemming from persistent or severe infections leads to permanent dilation of bronchi and bronchioles. Because of better control of lung infections, bronchiectasis is now uncommon, but may still develop in association with the following:

- *Congenital or hereditary conditions that predispose to chronic infections*, including cystic fibrosis, intralobar sequestration of the lung, immunodeficiency states, primary ciliary dyskinesia, and Kartagener syndrome.
- *Severe necrotizing pneumonia* caused by bacteria, viruses, or fungi; this may be a single severe episode or recurrent infections.
- *Bronchial obstruction*, due to tumor, foreign body, or mucus impaction; in each instance the bronchiectasis is localized to the obstructed lung segment.
- *Immune disorders*, including rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, and the posttransplant setting (chronic rejection after lung transplant and chronic graft-versus-host disease after hematopoietic stem cell transplantation).
- Up to 50% of cases are *idiopathic*, lacking the aforementioned associations, in which there appears to be dysfunctional host immunity to infectious agents leading to chronic inflammation.

Pathogenesis

Obstruction and infection are the major conditions associated with bronchiectasis. **The infections that lead to bronchi-**

mucopurulent bronchitis

Cigarette smoke predisposes to chronic bronchitis in several ways. Not only does it damage airway-lining cells, leading to chronic inflammation, but it also interferes with the ciliary action of the respiratory epithelium, preventing the clearance of mucus and increasing the risk of infection.

MORPHOLOGY

Grossly, there is hyperemia, swelling, and edema of the mucous membranes, frequently accompanied by excessive mucinous or mucopurulent secretions. Sometimes, heavy casts of secretions and pus fill the bronchi and bronchioles. The characteristic microscopic features are chronic inflammation of the airways (predominantly lymphocytes and macrophages); thickening of the bronchiolar wall due to smooth muscle hypertrophy, deposition of extracellular matrix in the muscle layer, and peribronchial fibrosis; goblet cell hyperplasia; and enlargement of the mucus-secreting glands of the trachea and bronchi. Of these, the most striking change is an increase in the size of the mucous glands. This increase can be assessed by the ratio of the thickness of the mucous gland layer to the thickness of the wall between the epithelium and the cartilage **(Reid index)**. The Reid index (normally 0.4) is increased in chronic bronchitis, usually in proportion to the severity and duration of the disease. The mucus plugging, inflammation, and fibrosis may lead to marked narrowing of bronchioles, and in the most severe cases, there may be obliteration of lumen due to fibrosis **(bronchiolitis obliterans)**. The bronchial epithelium may also exhibit squamous metaplasia and dysplasia due to the irritating and mutagenic effects of substances in tobacco smoke.

Table 20.5 Summary of Major Primary Glomerulonephritides

Disease	Most Frequent Clinical Presentation	Pathogenesis	Glomerular Pathology		
			Light Microscopy	Fluorescence Microscopy	Electron Microscopy
Postinfectious glomerulonephritis	Nephritic syndrome	Immune complex mediated; circulating or planted antigen	Diffuse endocapillary proliferation; leukocytic infiltration	Granular IgG and C3 in GBM and mesangium; Granular IgA in some cases	Primarily subepithelial humps; subendothelial deposits in early disease stages
Crescentic (rapidly progressive) glomerulonephritis	Nephritic syndrome; rapid progression	Anti-GBM antibody mediated; immune complex mediated; ANCA mediated and unknown	Extracapillary proliferation with crescents; necrosis	Linear IgG and C3 in anti-GBM antibody mediated GN; granular IgG, other Igs, and/or complement in immune complex mediated GN; or no deposits in ANCA mediated GN	No deposits in anti-GBM and ANCA mediated GN; immune complexes at various locations in immune complex mediated GN
Membranous nephropathy	Nephrotic syndrome	In situ immune complex PLA_2R antigen in most cases of primary disease	Diffuse capillary wall thickening	Granular IgG and C3; diffuse	Subepithelial deposits
Minimal change disease	Nephrotic syndrome	Unknown; loss of glomerular polyanion; podocyte injury	Normal; lipid in tubules	Negative	Effacement of foot processes; no deposits
Focal segmental glomerulosclerosis	Nephrotic syndrome; non-nephrotic proteinuria	Unknown Ablation nephropathy Plasma factor (?); podocyte injury	Focal and segmental sclerosis and hyalinosis	Focal; IgM + C3 in many cases	Effacement of foot processes; epithelial denudation
Membranoproliferative glomerulonephritis (MPGN) type I	Nephritic/nephrotic syndrome	Immune complex	Mesangial proliferative or membranoproliferative patterns of proliferation; GBM thickening; splitting	IgG ++ C3; C1q ++ C4	Subendothelial deposits
Dense-deposit disease (MPGN type II)	Hematuria Chronic renal failure	Acquired or genetic dysregulation of the alternative complement pathway	Mesangial proliferative or membranoproliferative patterns of proliferation; GBM thickening; splitting	C3; no C1q or C4	Dense deposits
IgA nephropathy	Recurrent hematuria or proteinuria	Unknown	Focal mesangial proliferative glomerulonephritis; mesangial widening	IgA ± IgG, IgM, and C3 in mesangium	Mesangial and paramesangial dense deposits

ANCA, Antineutrophil cytoplasmic antibodies; *GBM*, glomerular basement membrane.

b. Discuss the

Q4. Two weeks after recovery from a severe bout of pharyngitis, an 11 year old girl is seen because of the acute onset of periorbital edema, hematuria, malaise, nausea. and headache.

a. What is the most likely diagnosis? Acute proliferative glomerulonephritis (01)
b. Give the etiology & pathogenesis of this disease. Group A streptococcus (03)
c. Give the classic diagnostic morphological features of this disease. Appearence of "HUMPS" that are discrete, amorphous electron dense. (01)

a. A 40 years man had swelling in his left testis, orchiectomy is done. The testis on sectioning reveals a firm, lobulated, light tan mass without hemorrhage or necrosis.

a. Which of the neoplasm is most likely? Seminoma Semonoma (01)
b. Classify Testicular tumor? 975
c. Name different tumor markers helpful in diagnosis of testicular tumours Ans ~~Laboratory~~ α Feto Protien, HCG, LDH, (01)

KIT, OCT4, AFP - Yolk Sac tumor
PLAP. HCG - Choriocarcinoma
LDH - Seminoma & mass of tumor cells

Table 21.7 Pathologic Classification of Common Testicular Tumors

Germ Cell Tumors Derived From Germ Cell Neoplasia in Situ
Noninvasive germ cell neoplasia
Germ cell neoplasia in situ
Tumors of a single histologic type (pure forms)
Seminoma
Nonseminomatous germ cell tumors
Embryonal carcinoma
Yolk sac tumor, postpubertal type
Choriocarcinoma
Teratoma, postpubertal type
Teratoma with somatic-type malignancy
Nonseminomatous germ cell tumors of more than one histologic type
Mixed germ cell tumor
Germ Cell Tumors Unrelated to Germ Cell Neoplasia in Situ
Spermatocytic tumor
Teratoma, prepubertal type
Yolk sac tumor, prepubertal type
Mixed teratoma and yolk sac tumor, prepubertal type
Sex Cord–Stromal Tumors
Pure tumors
Leydig cell tumor
Sertoli cell tumor
Other
Tumor Containing Both Germ Cell and Sex Cord–Stromal Elements
Gonadoblastoma

From World Health Organization (WHO): *Histologic Classification of Testicular Tumors*, Geneva, 2016, WHO.

Q5. A 58-year-old man has undergone personality changes over the last year. MR imaging of the brain is performed and shows a 3 cm diameter left frontal lobe mass with areas of calcification.

a. What will be the likely findings on microscopic examination of this mass? (02)

b. Describe the morphological features of the Astrocytoma. (03)

Q6. Write short notes on:

a. Pheochromocytoma (02)

b. Papillary carcinoma of thyroid (03)

Q8. A 14 years old boy presented with a mass around the knee joint. X-ray showed a large destructive mixed lytic and blastic mass lifting the periosteum with reactive periosteal bone formation.

a. What is the most likely diagnosis? (01)

b. What will be the features of this tumor on histological examination? (02)

c. What are the other common sites of this tumour? (02)

and morphology of chronic cholecystitis. (03)

lead to evasion of senescence (either telomerase mutations or mutations that lead to alternative lengthening of telomeres); escape from normal growth controls (biallelic *CDKN2A* deletion); activation of growth factor signaling pathways (*EGFR* or *PDGFR* gene amplification); and resistance to apoptosis (*TP53* mutation).

MORPHOLOGY

Diffuse astrocytomas are poorly defined, gray, infiltrative tumors that expand and distort involved brain (Fig. 28.45A). These tumors range in size from a few centimeters to lesions that replace nearly the entire brain. The cut surface of the tumor may be either firm or soft and gelatinous; cystic degeneration may be seen. The tumor may appear well demarcated, but is more commonly ill-defined due to infiltration beyond the perceived margins.

Microscopically, these tumors are hypercellular compared to normal white matter and feature enlarged, elongated or irregular, hyperchromatic nuclei embedded within a fibrillar background (Fig. 28.45B) that is often GFAP-immunoreactive. An immunostain for the IDH1 R132H mutant protein highlights the tumor cells in up to 90% of cases (Fig. 28.45B, *inset*); *IDH1* and IDH2 sequencing is required to identify less common pathogenic IDH mutations, and is done when the immunostain is negative. Individual tumor cells infiltrate brain tissue some distance away from the main lesion.

Anaplastic astrocytomas have a similar appearance, but are more densely cellular and have readily detectable mitotic activity. In **glioblastomas**, variation in the appearance of the tumor from region to region is characteristic; some areas are firm and gray-white, while others are soft and yellow due to necrosis or red due to hemorrhage and hypervascularity (Fig. 28.46). The histologic appearance is similar to anaplastic astrocytoma with the additional features of necrosis and/or microvascular proliferation. Necrosis in glioblastoma often occurs in a serpentine pattern with tumor hypercellularity along the edges of the necrotic regions, a histologic pattern referred to as palisading (Fig. 28.47). The microvascular cell proliferation produces tufts of cells that pile

tumors). Neuroblastomas and other neuroblastic tumors are discussed in Chapter 10.

Pheochromocytoma

Pheochromocytomas are neoplasms composed of chromaffin cells, which synthesize and release catecholamines and, in some instances, peptide hormones. It is important to recognize these tumors because they are a rare cause of surgically correctable hypertension. Traditionally, the features of pheochromocytomas have been summarized by the "rule of 10s".

- *Ten percent of pheochromocytomas are extra-adrenal*, occurring in sites such as the organs of Zuckerkandl and the carotid body. Pheochromocytomas that develop in extra-adrenal paraganglia are designated *paragangliomas* and are discussed in Chapter 16.
- *Ten percent of sporadic adrenal pheochromocytomas are bilateral*; this figure may rise to as high as 50% in cases that are associated with familial tumor syndromes (see later).
- *Ten percent of adrenal pheochromocytomas are biologically malignant*, defined by the presence of metastatic disease. Malignancy is more common (20% to 40%) in extra-adrenal paragangliomas, and in tumors arising in the setting of certain germline mutations (see later).
- *Ten percent of adrenal pheochromocytomas are not associated with hypertension*. Of the 90% that present with hypertension, approximately two-thirds have "paroxysmal"

ntravagal
ted along
is found
mpathetic
side of the
lose to the

episodes associated with a sudden rise in blood pressure and palpitations, which can, on occasion, be fatal.

One "traditional" 10% rule that has now been modified pertains to familial cases. It is now recognized that as many as 25% of individuals with pheochromocytomas and paragangliomas harbor an oncogenic germline mutation. These mutations can involve at least a dozen genes, the most which are listed in Table 24.11. Patients with younger at presentation

adjacent parenchyma and have ill-defined margins. The tumors may contain areas of fibrosis and calcification and are often cystic. The cut surface sometimes reveals papillary foci that point to the diagnosis. **Papillary microcarcinoma** is defined as an otherwise conventional papillary carcinoma, but less than 1 cm in size. As stated earlier, they are considered putative precursor lesions of more typical papillary carcinomas.

The microscopic hallmarks of papillary neoplasms include the following (Fig. 24.19):

- Branching **papillae** having a fibrovascular stalk covered by a single to multiple layers of cuboidal epithelial cells. In most neoplasms, the epithelium covering the papillae consists of well-differentiated, uniform, orderly cuboidal cells, but at the other extreme are those with fairly anaplastic epithelium showing considerable variation in cell and nuclear morphology. When present, the papillae differ from those seen in areas of hyperplasia in being more complex and having dense fibrovascular cores.
- Nuclei with finely dispersed chromatin and an optically clear or empty appearance, giving rise to the designation **ground-glass** or **Orphan Annie eye nuclei.** In addition, invaginations of the nuclear membrane may give the appearance of nuclear inclusions ("pseudo-inclusions") or grooves. **The diagnosis of papillary carcinoma can be made based on these nuclear features,** even in the absence of papillary architecture.
- Concentrically calcified structures termed **psammoma bodies** are often present, usually within the cores of papillae. These

structures are almost never found in follicular and medullary carcinomas, and they are a strong indication that the lesion is a papillary carcinoma when present in fine-needle aspiration material.

- Foci of lymphatic invasion by tumor are often present, but involvement of blood vessels is uncommon, particularly in smaller lesions. Metastases to adjacent cervical lymph nodes occur in up to one-half of cases.

There are over a dozen histologic variants of papillary carcinoma that can mimic other thyroid lesions or harbor distinct prognostic implications; most are beyond the scope of this book. The **tall cell variant** has tall columnar cells with intensely eosinophilic cytoplasm. These tumors tend to occur in older individuals and have higher frequencies of vascular invasion, extrathyroidal extension, and cervical and distant metastases than conventional PTC. Tall cell variant papillary carcinomas almost always harbor *BRAF* mutations, and often have *RET/PTC* translocations as well. The co-occurrence of these two aberrations may contribute to the aggressive behavior of this variant.

An unusual **diffuse sclerosing variant** of papillary carcinoma occurs in younger individuals, including children. The tumor has a prominent papillary growth pattern intermixed with solid areas containing nests of squamous metaplasia. As the name suggests, there is extensive, diffuse fibrosis throughout the thyroid gland, often associated with a prominent lymphocytic infiltrate, simulating Hashimoto thyroiditis. Lymph node metastases are present in almost all cases. The diffuse sclerosing variant carcinomas lack *BRAF* mutations, but *RET/PTC* translocations are found in approximately one-half of cases.

The **follicular variant of PTC** has the characteristic nuclear features of papillary carcinoma and an almost totally follicular architecture. As mentioned earlier, genetic analyses have shown that encapsulated follicular variants of PTC harbor distinct molecular abnormalities from conventional PTCs. As already discussed, encapsulated follicular variants of papillary thyroid cancer without capsular invasion are designated noninvasive follicular thyroid carcinoma with papillary-like nuclear features and have a very low risk of recurrence or metastasis, whereas invasive tumors are referred to as invasive encapsulated follicular variant of papillary thyroid carcinoma.

lifted, has laid down a proximal triangular shell of reactive bone known as a Codman triangle *(arrow)*.

Osteosarcoma

MORPHOLOGY

Osteosarcomas are bulky, gritty, gray-white tumors that often contain hemorrhage and cystic degeneration (Fig. 26.24). The tumor frequently destroys the surrounding cortices to produce soft tissue masses, spread extensively in the medullary canal, and replace hematopoietic marrow. Tumors infrequently penetrate the epiphyseal plate or enter the joint, where they may grow along tendoligamentous structures or through the attachment site of the joint capsule.

Osteosarcomas demonstrate pleomorphism, large hyperchromatic nuclei, bizarre tumor giant cells, and abundant mitoses including abnormal (e.g., tripolar) forms. Extensive necrosis and intravascular invasion are also common. Diagnosis of osteosarcoma requires the presence of malignant tumor cells producing unmineralized osteoid or mineralized bone (Fig. 26.25), which is typically fine and lacelike, but can also form broad sheets or primitive trabeculae. Neoplastic cells can also produce cartilage; if abundant, such tumors are classified as **chondroblastic osteosarcoma.**

Gastric Adenocarcinoma

Adenocarcinoma is the most common malignancy of the stomach, comprising more than 90% of all gastric cancers. As discussed in more detail later, gastric adenocarcinoma is separated morphologically into intestinal type, which tends to form bulky masses, and diffuse type, which infiltrates and thickens the gastric wall. Early symptoms of both types of gastric adenocarcinoma resemble those of chronic gastritis and peptic ulcer disease, including dyspepsia, dysphagia, and nausea. As a result, these tumors are often discovered at advanced stages, when symptoms such as weight loss, anorexia, early satiety (primarily in diffuse cancers), anemia, and hemorrhage appear.

Gastric Cancer Lauren intestinal
classification diffuse
unclassified

* Spread

transperitoneal
e.g. ovary

later
and

Adenocarcinoma of the stomach was the most common cause of cancer death in the United States in 1930. However, since that time the incidence has fallen by 85%, and, gastric adenocarcinoma now accounts for only 2.5% of cancer deaths in the United States. Decreased gastric cancer incidence is largely attributed to reduced rates of *H. pylori* infection and primarily relates to intestinal-type cancers. Other environmental and dietary factors, including decreased consumption of dietary carcinogens such as N-nitroso compounds and benzo[*a*]pyrene (because of the reduced use of salt and smoking for food preservation) and the widespread availability of refrigeration may have also contributed to the decreased incidence. Consistent with an environmental, rather than genetic, cause, migrants from high- to low-risk regions maintain the risk of their original country, but their children have gastric cancer rates similar to those in the new country of residence.

Although the overall incidence of gastric adenocarcinoma is falling, cancer of the gastric cardia is on the rise. This is probably related to Barrett esophagus and may reflect the increasing incidence of chronic GERD and obesity. Consistent with this presumed shared pathogenesis, gastric cardia adenocarcinomas and distal esophageal adenocarcinomas are similar in morphology, clinical behavior, and therapeutic responses.

Pathogenesis

While the majority of gastric cancers are not hereditary, mutations identified in familial gastric cancer have provided important insights into mechanisms of carcinogenesis in sporadic cases. Familial gastric cancer is strongly associated with germline loss-of-function mutations in the tumor suppressor gene *CDH1*, which encodes the cell adhesion protein E-cadherin (discussed in Chapter 7). Loss-of-function mutations in *CDH1* are also present in about 50% of sporadic diffuse gastric tumors, while E-cadherin expression is drastically decreased in the remainder of diffuse tumors, often by hypermethylation and silencing of the *CDH1* promoter. **Thus, E-cadherin loss is a key step in the development of diffuse gastric cancer.** *CDH1* mutations are also common in sporadic and familial lobular carcinoma of the breast, which, like diffuse gastric cancer (see later), tends to infiltrate as single cells.

In contrast to diffuse gastric cancers, **intestinal-type gastric cancers are strongly associated with mutations that result in increased signaling via the Wnt pathway.** These include loss-of-function mutations in the adenomatous polyposis coli (*APC*) tumor suppressor gene and gain-of-function mutations in the gene encoding β-catenin. Other genes commonly affected by loss-of-function mutations or silencing include those involved in TGF-β signaling (*TGFβRII*), regulation of apoptosis (*BAX*), and cell cycle control (*CDKN2A*), all of which are discussed in more detail in Chapter 7. FAP patients with germline *APC* mutations have an increased risk of intestinal-type gastric cancer, particularly in those who reside in high-risk areas like Japan. Variants of pro-inflammatory genes such as IL-1β and IL-1 receptor, are associated with elevated risk of gastric cancer in those who have *H. pylori* gastritis. Thus, both host genetic background and environmental factors affect risk. Other associations between chronic inflammation and cancer are discussed

and in Chapter 7.

leather bottle appearance

MORPHOLOGY

Diffuse type = linitis plastica = mucosal lining

Gastric adenocarcinomas are classified according to their location and gross and histologic morphology. Most distal gastric adenocarcinomas occur in the gastric antrum; the lesser curvature is involved more often than the greater curvature. Gastric tumors with an **intestinal morphology form bulky tumors** (Fig. 17.18A) and are composed of glandular structures (Fig. 17.19A), while cancers with a **diffuse infiltrative growth pattern** (Fig. 17.18B) are typically composed of **signet-ring cells** (Fig. 17.19B). Although they may penetrate the gastric wall, intestinal-type adenocarcinomas frequently grow along broad cohesive fronts to form either an exophytic mass or an ulcerated infiltrative tumor. The neoplastic cells often contain apical mucin vacuoles, and abundant mucin may be present in gland lumina. In contrast, diffuse cancers permeate the gastric wall as small clusters and individual discohesive cells due to the absence of E-cadherin. These cells do not form glands but instead have large mucin vacuoles that expand the cytoplasm and push the nucleus to the periphery, creating a signet-ring cell morphology. They be mistaken for inflammatory cells at low magnification. Release of extracellular

mucin in either type of gastric cancer can result in formation of large mucin lakes that dissect tissue planes.

A mass may be difficult to appreciate in diffuse gastric cancer, but these infiltrative tumors often evoke a **desmoplastic** reaction that stiffens the gastric wall. When there are large areas of infiltration, diffuse rugal flattening and a rigid, thickened wall may impart a leather bottle appearance termed **linitis plastica** (Fig. 17.18B).

intestinal- and diffuse-type gastric cancers are now similar in many regions.

The depth of invasion and the extent of nodal and distant metastases remain the most powerful prognostic indicators in gastric cancer. Local invasion into the duodenum, pancreas, and retroperitoneum is common. In such cases efforts are usually focused on chemotherapy or radia-

2. Risk of papillary carcinoma increases with age; thus, it is more commonly seen in postmenopausal women.

III. FIBROADENOMA

Most Common Premenopausal Benign

A. Tumor of fibrous tissue and glands (Fig. 16.3)

B. Most common benign neoplasm of the breast; usually seen in premenopausal women

No discharge, pain, microcalcifications.

C. Presents as a well-circumscribed, mobile marble-like mass

grey white nodular cut surface, solitary, discreet rubbery, freely movable

Morphology

D. Estrogen sensitive—grows during pregnancy and may be painful during the menstrual cycle

E. Benign, with no increased risk of carcinoma

IV. PHYLLODES TUMOR (Leaf like)

Most Common Postmenopausal Can be Malignant

A. Fibroadenoma-like tumor with overgrowth of the fibrous component; characteristic 'leaf-like' projections are seen on biopsy (Fig. 16.4).

B. Most commonly seen in postmenopausal women

C. Can be malignant in some cases

D. Both stromal and epithelial components.

Ductal: in situ (comedo, paget); invasive (tubular, mucinous, medullary, inflammatory)

Lobular: in situ, invasive

BREAST CANCER

incidence (excluding skin cancer)

These tumors are termed "biphasic" because they also include a non-neoplastic epithelial component, the proliferation of which may be stimulated by growth factors elaborated by the stromal cells. Both fibroadenoma and phyllodes tumor are driven by somatic mutations in *MED12*, a component of a multiple protein complex called mediator that links RNA polymerase II to specific DNA-binding transcription factors. It is no doubt not coincidental that the other tumor that is strongly associated with *MED12* mutations, uterine leiomyoma, also arises from stromal cells within an organ that is responsive to female sex hormones. Perhaps, by deranging mediator function, *MED12* mutations alter the expression of sex hormone–regulated genes that control the proliferation and survival of certain types of stromal cells. In contrast, interlobular stroma is the source of the same types of tumors found in connective tissue in other sites of the body (e.g., lipomas and angiosarcomas), as well as tumors arising more commonly in the breast (e.g., myofibroblastoma and fibrous tumors), and consist only of stromal cells.

MED (mediator complex subunit)

Fibroadenoma

Fibroadenoma is the most common benign tumor of the female breast. Two-thirds of fibroadenomas harbor driver mutations in *MED12*. The pathogenesis of the remainder is uncertain.

MORPHOLOGY

Fibroadenomas vary in size from less than 1 cm to large tumors that replace most of the breast. They usually present as a palpable mass in young women and as a mammographic density (Fig. 23.23A) or clustered calcifications in older women. The tumors are well-circumscribed, rubbery, grayish white nodules that bulge above the surrounding tissue and often contain slit-like spaces lined by epithelium (Fig. 23.23B). The delicate and often myxoid stroma resembles normal intralobular stroma. The epithelium may be surrounded by stroma (pericanalicular pattern) or compressed and distorted by it (intracanalicular pattern) (Fig. 23.23C). In older women, the stroma typically becomes densely hyalinized and the epithelium atrophic.

Phyllodes Tumor

Phyllodes tumor, like fibroadenoma, arises from intralobular stroma but is much less common. *Cystosarcoma phyllodes* is a term sometimes used for these lesions, but *phyllodes tumor* is preferred, since most behave in a benign fashion and are not cystic. Like fibroadenomas, the majority of phyllodes tumors have *MED12* mutations. Benign-appearing phyllodes tumors that have only a slight propensity to recur often have *MED12* mutations and few other genetic changes. In contrast, tumors that display malignant behavior are more likely to have mutations in additional genes, such as *TERT*, the gene that encodes telomerase.

MORPHOLOGY

Most phyllodes tumors are detected ~~as palpable masses~~, while a few are found by mammography. The tumors vary in size from a few centimeters to massive lesions involving the entire breast. The larger lesions often have bulbous protrusions (*phyllodes* is Greek for "leaf-like") due to the presence ~~of nodules of proliferating~~ stroma covered by epithelium (Fig. 23.24). In some tumors these

protrusions extend into a cystic space. This growth pattern also may occasionally be seen in large fibroadenomas and is not an indication of malignancy. Phyllodes tumor is distinguished from fibroadenoma on the basis of higher cellularity, higher mitotic rate, nuclear pleomorphism, stromal overgrowth, and infiltrative borders. Low-grade (benign) lesions resemble fibroadenomas but are more cellular and are mitotically active. High-grade (malignant) lesions may be difficult to distinguish from sarcomas.

Clinical Features

Most phyllodes tumors present in the sixth decade, 10 to 20 years later than the peak age for fibroadenoma. Most have low-grade (benign) cytologic features; these occasionally recur locally but do not metastasize. In contrast, borderline and high-grade (malignant) phyllodes tumors often recur locally unless they are treated with wide excision or mastectomy. Regardless of grade, lymphatic spread is rare, and axillary lymph node dissection is contraindicated. The uncommon high-grade lesions give rise to distant hematogenous metastases in about one-third of cases. Only the stromal component metastasizes.

Proliferative Lesions of Breast

Table 23.1 Epithelial Breast Lesions and Risk of Developing Invasive Carcinoma

Pathologic Lesions	Relative Risk (Absolute Lifetime Risk)[a]
Nonproliferative breast changes (mild hyperplasia, duct ectasia, cysts, apocrine metaplasia, adenosis, fibroadenoma without complex features)	1.0 (~3%)
Proliferative disease without atypia (moderate or florid hyperplasia, sclerosing adenosis, complex sclerosing lesion, fibroadenoma with complex features)	1.5–2 (~5%–7%)
Proliferative disease with atypia (atypical ductal hyperplasia, atypical lobular hyperplasia)	4–5 (~13%–17%)
Carcinoma in situ (lobular carcinoma in situ, ductal carcinoma in situ)	8–10 (~25%–30%)

[a]Relative risk is the likelihood of developing invasive carcinoma compared to women without any risk factors. Absolute lifetime risk is the percentage of women expected to develop invasive carcinoma in the absence of an intervention.

Table 17.8 Features That Differ Between Crohn Disease and Ulcerative Colitis

Feature	Crohn Disease	Ulcerative Colitis
Macroscopic		
Bowel region	Ileum ± colon	Colon only
Distribution	Skip lesions	Diffuse
Stricture	Yes	Rare
Wall appearance	Thick	Normal
Microscopic		
Inflammation	Transmural	Limited to mucosa
Pseudopolyps	Moderate	Marked
Ulcers	Deep, knife-like	Superficial, broad-based
Lymphoid reaction	Marked	Moderate
Fibrosis	Marked	Mild to none
Serositis	Marked	Mild to none
Granulomas	Yes (~35%)	No
Fistulae/sinuses	Yes	No
Clinical		
Perianal fistula	Yes (in colonic disease)	No
Fat/vitamin malabsorption	Yes	No
Malignant potential	With colonic involvement	Yes
Recurrence after surgery	Common	No
Toxic megacolon	No	Yes

All features may not be present in a single case.

Table 11.5 Classification of Vascular Tumors and Tumor-Like Conditions

Benign Neoplasms, Developmental and Acquired Conditions
Hemangioma
Capillary hemangioma
Cavernous hemangioma
Pyogenic granuloma
Lymphangioma
Simple (capillary) lymphangioma
Cavernous lymphangioma (cystic hygroma)
Glomus tumor
Vascular ectasias
Nevus flammeus
Spider telangiectasia (arterial spider)
Hereditary hemorrhagic telangiectasis (Osler-Weber-Rendu disease)
Reactive vascular proliferations
Bacillary angiomatosis
Intermediate-Grade Neoplasms
Kaposi sarcoma
Hemangioendothelioma
Malignant Neoplasms
Angiosarcoma
Hemangiopericytoma

Clinical Features

Most VSDs that clinically manifest in the pediatric age group are associated with other congenital cardiac anomalies such as TOF; only 20% to 30% are isolated. Conversely, if a VSD is first detected only in an adult, it is usually an isolated defect. The functional consequences of a VSD depend on the size of the defect and whether there are associated right-sided malformations. Thus, large VSDs cause difficulties virtually from birth; smaller lesions are generally well tolerated for years and may not be recognized until much later in life. Moreover, approximately 50% of small muscular VSDs close spontaneously. Large defects are usually membranous or infundibular, and they generally cause significant left-to-right shunting, leading to early right ventricular hypertrophy and pulmonary hypertension. Over time, large unclosed VSDs almost universally lead to irreversible pulmonary vascular disease, ultimately resulting in shunt reversal and cyanosis. Surgical or catheter-based closure of asymptomatic VSD is generally delayed beyond infancy, in hope of spontaneous closure. Early correction, however, must be performed for large defects to prevent the development of irreversible obstructive pulmonary vascular disease.

Patent Ductus Arteriosus

The ductus arteriosus arises from the pulmonary artery and joins the aorta just distal to the origin of the left subclavian artery. During intrauterine life, it permits blood flow from

Right-to-Left Shunts

The diseases in this group cause cyanosis early in postnatal life (cyanotic CHD). TOF, the most common in this group, and TGA are illustrated schematically in Fig. 12.5. The others include persistent truncus arteriosus, tricuspid atresia, and total anomalous pulmonary venous connection. Note that the names of all of these conditions start with a T.

Tetralogy of Fallot

The four cardinal features of TOF are (1) VSD, (2) obstruction of the right ventricular outflow tract (subpulmonic stenosis), (3) an aorta that overrides the VSD, and (4) right ventricular hypertrophy (see Fig. 12.5A). The first three features result embryologically from anterosuperior displacement of the infundibular septum, and the right ventricular hypertrophy is a secondary consequence of the pressure overload.

MORPHOLOGY

The heart is typically enlarged and is classically "boot-shaped" due to marked right ventricular hypertrophy. The VSD is usually large with the aortic valve at the superior border, thereby overriding the defect and both ventricular chambers. The obstruction to right ventricular outflow is most often due to narrowing of the infundibulum (subpulmonic stenosis) but can be accompanied

Table 13.4 World Health Organization Classification of Lymphoid Neoplasms

I. Precursor B-Cell Neoplasms
B-cell acute lymphoblastic leukemia/lymphoma (B-ALL)
II. Peripheral B-Cell Neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Lymphoplasmacytic lymphoma
Splenic and nodal marginal zone lymphomas
Extranodal marginal zone lymphoma
Mantle cell lymphoma
Follicular lymphoma
Marginal zone lymphoma
Hairy cell leukemia
Plasmacytoma/plasma cell myeloma
Diffuse large B-cell lymphoma
Burkitt lymphoma
III. Precursor T-Cell Neoplasms
T-cell acute lymphoblastic leukemia/lymphoma (T-ALL)
IV. Peripheral T-Cell and NK-Cell Neoplasms
T-cell prolymphocytic leukemia
Large granular lymphocytic leukemia
Mycosis fungoides/Sézary syndrome
Peripheral T-cell lymphoma, unspecified
Anaplastic large-cell lymphoma
Angioimmunoblastic T-cell lymphoma
Enteropathy-associated T-cell lymphoma
Panniculitis-like T-cell lymphoma
Hepatosplenic γδ T-cell lymphoma
Adult T-cell leukemia/lymphoma
Extranodal NK/T-cell lymphoma
NK-cell leukemia
V. Hodgkin Lymphoma
Classic subtypes
Nodular sclerosis
Mixed cellularity
Lymphocyte-rich
Lymphocyte depletion
Nodular lymphocyte predominant

NK, Natural killer.

Rest from Dr. Fahad's Notes or

Table 13.8 Subtypes of Hodgkin Lymphoma

Subtype	Morphology and Immunophenotype	Typical Clinical Features
Nodular sclerosis	Frequent lacunar cells and occasional diagnostic RS cells; background infiltrate composed of T lymphocytes, eosinophils, macrophages, and plasma cells; fibrous bands dividing cellular areas into nodules. RS cells CD15+, CD30+; usually EBV−	Most common subtype; usually stage I or II disease; frequent mediastinal involvement; equal occurrence in males and females, most patients young adults
Mixed cellularity	Frequent mononuclear and diagnostic RS cells; background infiltrate rich in T lymphocytes, eosinophils, macrophages, plasma cells; RS cells CD15+, CD30+; 70% EBV+	More than 50% present as stage III or IV disease; occurrence greater in males than females; biphasic incidence, peaking in young adults and again in adults older than 55
Lymphocyte-rich	Frequent mononuclear and diagnostic RS cells; background infiltrate rich in T lymphocytes; RS cells CD15+, CD30+; 40% EBV+	Uncommon; occurrence greater in males than females; tends to be seen in older adults
Lymphocyte depletion	Reticular variant: Frequent diagnostic RS cells and variants and a paucity of background reactive cells; RS cells CD15+, CD30+; most EBV+	Uncommon; more common in older men, HIV-infected individuals, and people in low income countries; often presents with advanced disease
Nodular lymphocyte predominant	Frequent L&H (popcorn cell) variants in a background of follicular dendritic cells and reactive B cells; RS cells CD20+, CD15−, CD30−; EB−	Uncommon; young males with cervical or axillary lymphadenopathy; mediastinal

HIV, human immunodeficiency virus; *L&H*, lymphohistiocytic; *RS*, Reed-Sternberg.

Table 15.9 Histologic Classification of Malignant Epithelial Lung Tumors

Tumor Classification
Adenocarcinoma
Preinvasive
Lepidic, acinar, micropapillary, papillary, solid (according to predominant pattern)
Invasive mucinous adenocarcinoma
Minimally invasive adenocarcinoma (nonmucinous, mucinous)
Squamous cell carcinoma
Keratinizing, nonkeratinizing, basaloid
Neuroendocrine tumors
Small cell carcinoma
Combined small cell carcinoma
Large cell neuroendocrine carcinoma
Combined large-cell neuroendocrine carcinoma
Carcinoid tumor
Typical, atypical
Other uncommon types
Large cell carcinoma
Adenosquamous carcinoma
Sarcomatoid carcinoma
Pleomorphic, spindle cell, giant cell carcinoma, carcinosarcoma
Pulmonary blastoma
Others such as lymphoepithelioma-like carcinoma and NUT carcinoma
Salivary gland–type tumors

away from it.

Adenocarcinoma in situ (formerly called bronchioloalveolar carcinoma) is a lesion that is less than 3 cm in size and is composed entirely of dysplastic cells growing along pre-existing alveolar septa. The cells have more dysplasia than atypical adenomatous hyperplasia and may or may not have intracellular mucin (Fig. 15.42).

Adenocarcinoma is an invasive malignant epithelial tumor with glandular differentiation or mucin production by the tumor cells. Adenocarcinomas grow in various patterns, including acinar, lepidic, papillary, micropapillary, and solid. Compared with squamous cell cancers, these lesions are usually more peripherally located and tend to be smaller. They vary histologically from

EGFR→KRAS

well-differentiated tumors with obvious glandular elements (Fig. 15.43A), to papillary lesions resembling other papillary carcinomas, to solid masses with only occasional mucin-producing glands and cells. The majority express thyroid transcription factor-1 (TTF-1) (Fig. 15.43A inset), a protein first identified in the thyroid that is required for normal lung development. At the periphery of the tumor there is often a lepidic pattern of spread, in which the tumor cells "crawl" along normal-appearing alveolar septa. Tumors (≤3 cm) with a small invasive component (≤5 mm) associated with scarring and a peripheral lepidic growth pattern are called **microinvasive adenocarcinoma.** These have a far better prognosis than invasive carcinomas of the same size. **Mucinous adenocarcinomas** tend to spread aerogenously, forming satellite tumors; thus, these are less likely to be cured by surgery. They may present as a solitary nodule or as multiple nodules, or an entire lobe may be consolidated by tumor, mimicking lobar pneumonia.

20-25%

Squamous cell carcinoma is more common in

Autoimmune Cholangiopathies

Table 18.10 Main Features of Primary Biliary Cholangitis and Primary Sclerosing Cholangitis

Parameter	Primary Biliary Cholangitis	Primary Sclerosing Cholangitis
Age	Median age 50 years	Median age 30 years
Gender	90% female	70% male
Associated conditions	Sjögren syndrome (70%), thyroid disease, scleroderma	Inflammatory bowel disease (70%) Ulcerative Colitis
Serology	95% AMA-positive, 40%–50% ANA positive	65% ANCA-positive; ANA variable, AMA typically negative 6% ANA-positive
Radiology	Normal	Strictures and beading of large bile ducts; pruning of smaller ducts
Duct lesion	Florid duct lesions; loss of small ducts • feathery degeneration • lymphocytic granulomatous bile duct destruction	Inflammatory destruction of extrahepatic and large intrahepatic ducts; fibrotic obliteration of medium and small intrahepatic ducts; ductular reaction in smaller portal tracts • onion skin fibrosis • peri-ductal fibrosis

AMA, Antimitochondrial antibody; *ANA*, antinuclear antibody; *ANCA*, antineutrophil cytoplasmic antibody.

survival rate is approximately 80%.

Hepatocellular Carcinoma (HCC)

HCC accounts for approximately 5.4% of all cancers worldwide and is one of the most common cancers in geographic regions with high rates of hepatitis B infection. More than 85% of cases occur in countries in Asia (southeast China, Korea, Taiwan) and sub-Saharan Africa, where chronic HBV infection is common. The peak incidence of HCC in these areas is in young adults between 20 and 40 years of age who acquired hepatitis B virus by maternal-fetal transmission. Encouragingly, the incidence of HCC is decreasing in Asia due to hepatitis B vaccination, but at the same time the incidence is increasing in the Western countries owing to rising rates of hepatitis C infection and metabolic syndrome. For unclear reasons, there is a pronounced male predominance, as high as 8:1, in high-incidence areas.

Pathogenesis

Most HCCs occur in the setting of chronic liver disease with cirrhosis, while 15% to 20% arise in noncirrhotic livers (Fig. 18.52). The most common underlying diseases are chronic viral hepatitis (B and C), metabolic diseases

Choroplast

architecture, including [illegible] canaliculi) and thickened hepatocyte trabeculae.

such as hereditary hemochromatosis and α_1-antitrypsin deficiency, and alcoholic liver disease. Nonalcoholic fatty liver disease also increases the risk of HCC, even in the absence of cirrhosis. Although details are not clearly worked out, it is believed that the chronic injury, inflammation, and hepatocyte regeneration that are seen in these disorders contribute to the acquisition of driver mutations that lead to HCC development (described later). Part of the risk in Africa and Asia appears to be related to contamination of crops by aflatoxin, a mycotoxin produced by *Aspergillus* species that acts synergistically with alcohol and hepatitis B. The risk for HCC in cirrhosis related to other etiologies, like Wilson disease and chronic biliary diseases, is somewhat lower but still elevated above the population average.

As with other cancers, HCC is associated with complementary sets of driver mutations that lead to the acquisition of cancer hallmarks (Chapter 7). Among the most common are activating mutations in the β-catenin gene (40% of tumors), mutations in the *TERT* (telomerase transcriptase) gene promoter that up-regulate telomerase activity (50% to

A

B

Figure
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infection caus
B cells that is

60% of tumors), and inactivating mutations in *TP53* (up to 60% of tumors). One unusual histologic subtype that often occurs in adolescents and young adults in the absence of preexisting liver disease, *fibrolamellar HCC*, is strongly associated with a fusion gene that leads to aberrant activity of protein kinase A, an enzyme that participates in a signaling pathway regulated by cAMP.

Tumor Marker: α-fetoprotein

MORPHOLOGY

Several precursor lesions for HCC have been described. As discussed earlier, in noncirrhotic liver, HCC can arise in hepatocellular adenoma, especially those with β-catenin–activating mutations. In chronic liver disease, the earliest morphologic alterations that appear to correlate with the presence of "at-risk" hepatocytes are called "large cell change" and "small cell change" (Fig. 18.53). **Large cell change** refers to hepatocytes that are larger than normal and often have enlarged, multiple, pleomorphic nuclei, without an increase in nuclear-to-cytoplasmic ratio (see Fig. 18.53A). In **small cell change,** the hepatocytes have a high nuclear-to-cytoplasmic ratio and mild nuclear hyperchromasia and/or pleomorphism (see Fig. 18.53B). More ominous are nodular lesions

Aflatoxins
Low grade pleomorphism. Acinar cells carcinoma

differentiated cells grow in thick plates or trabeculae, pseudoglandular structures with bile plugs, or sheets (see Fig. 18.52B). The distinctive fibrolamellar variant shows a characteristic triad of features: large polygonal cells with granular (oncocytic) cytoplasm due to abundant mitochondria; vesicular nuclei with a prominent nucleolus; and parallel lamellae of dense collagen bundles (Fig. 18.55).

Clinical Features

The clinical manifestations of HCC are nonspecific and include abdominal pain, malaise, fatigue, weight loss, and hepatomegaly. Features of underlying chronic liver disease can be present. Elevated levels of serum α-fetoprotein is a frequent finding in advanced disease, but it is not sensitive as a screening test for early tumors and is not associated with the fibrolamellar variant. Ultrasonography is used for screening high-risk patients such as those with cirrhosis. Computed tomography and magnetic resonance imaging with contrast studies yield highly characteristic findings. Early enhancement of the tumor due to contrast uptake in the arterial phase, followed by rapid venous washout, is considered diagnostic of HCC.

Surgical resection when possible is the treatment of choice for tumors in noncirrhotic livers and in cirrhotic livers with

Table 12.4 Approximate Time of Onset of Key Events in Ischemic Cardiac Myocytes

Feature	Time
Onset of ATP depletion	Seconds
Loss of contractility	<2 minutes
ATP reduced	
to 50% of normal	10 minutes
to 10% of normal	40 minutes
Irreversible cell injury	20–40 minutes
Microvascular injury	>1 hour

ATP, Adenosine triphosphate.

MI

valves has greatly
persons with RHD.

Infective Endocarditis (IE)

IE is a microbial infection of the heart valves or the mural endocardium that leads to the formation of vegetations composed of thrombotic debris and organisms, often associated with destruction of the underlying cardiac tissues. The aorta, aneurysms, other blood vessels, and prosthetic devices can also become infected. Although fungi and other classes of microorganisms can be responsible, most infections are bacterial (bacterial endocarditis). Prompt diagnosis, identification of the offending agent, and effective treatment of IE is important in limiting morbidity and mortality.

Traditionally, IE has been classified on clinical grounds into acute and subacute forms based on severity and tempo (reflecting microbial virulence), and whether there is underlying valvular pathology. Thus, acute IE is typically caused by infection of a previously normal heart valve by a highly virulent organism (e.g., *Staphylococcus aureus*) that rapidly produces destructive lesions. These infections may be difficult to cure with antibiotics alone and often require surgery; despite appropriate treatment, there can be substantial morbidity and even mortality. In contrast, subacute IE is characterized by organisms with lower virulence (e.g., viridans streptococci) that cause insidious infections of deformed valves with overall less destruction. In such cases the disease may pursue a protracted course of weeks to months, and cures can often be achieved with antibiotics alone. Of note, a clear delineation between acute and subacute endocarditis does not always exist, and many cases fall somewhere along the spectrum between the two forms.

Pathogenesis

Although highly virulent organisms can infect previously normal valves, a variety of cardiac abnormalities increase the risk of developing IE. RHD with valvular scarring has historically been the major antecedent disorder; as RHD becomes less common, it has been supplanted by mitral

valve prolapse, degenerative calcific valvular stenosis, bicuspid aortic valve (whether calcified or not), artificial (prosthetic) valves, and congenital defects.

Endocarditis of native but previously damaged or otherwise abnormal valves is caused most commonly (50% to 60% of cases) by *Streptococcus viridans*, a normal component of the oral cavity flora. In contrast, more virulent *S. aureus* organisms commonly found on the skin can infect either healthy or deformed valves and are responsible for 20% to 30% of cases overall; notably, *S. aureus* is the major offender in IE among intravenous drug abusers. Other bacterial causes include enterococci and the so-called HACEK group (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,* and *Kingella*), all commensals in the oral cavity. More rarely, Gram-negative bacilli and fungi can be involved. Prosthetic valve endocarditis occurring in the 1 to 2 months after surgical implantation is typically caused by skin flora (*S. aureus* and *S. epidermidis*); prosthetic valve infections 1 year or more after surgery tend to be streptococci and *S. aureus* (see later discussion of prosthetic valves). In about 10% of all cases of endocarditis, no organism can be isolated from the blood ("culture-negative" endocarditis); reasons include prior antibiotic therapy, difficulties in isolating the offending agent, or because deeply embedded organisms within the enlarging vegetation are not released into the blood.

Foremost among the factors predisposing to endocarditis are those that cause microorganism seeding into the bloodstream (bacteremia or fungemia). The source may be an obvious infection elsewhere, a dental or surgical procedure, a contaminated needle shared by intravenous drug users, or seemingly trivial breaks in the epithelial barriers of the gut, oral cavity, or skin. In patients with valve abnormalities, or with known bacteremia, IE risk can be lowered by antibiotic prophylaxis.

MORPHOLOGY

Vegetations on heart valves are the classic hallmark of IE; these are friable, bulky, potentially destructive lesions containing fibrin, inflammatory cells, and bacteria or other organisms (Figs. 12.23 and 12.24). The aortic and mitral valves are the most common

sites of infection, although the valves of the right heart may also be involved, particularly in intravenous drug abusers. Vegetations can be single or multiple and may involve more than one valve; they can occasionally erode into the underlying myocardium and produce an abscess (ring abscess; see Fig. 12.24B). Vegetations are prone to embolization; because the embolic fragments often contain virulent organisms, abscesses frequently develop where they lodge, leading to sequelae such as septic infarcts or mycotic aneurysms.

The vegetations of subacute endocarditis are associated with less valvular destruction than those of acute endocarditis, although the distinction can be subtle. Microscopically, the vegetations of subacute IE typically exhibit granulation tissue at their bases indicative of healing. With time, fibrosis, calcification, and a chronic inflammatory infiltrate can develop.

Clinical Features

Acute endocarditis has a stormy onset with rapid onset of fever, chills, weakness, and lassitude. Although fever is the most consistent sign of IE, it can be slight or absent, particularly in older adults, and the only manifestations may be nonspecific fatigue, weight loss, and a flulike syndrome. Murmurs are present in the majority of patients with left-sided IE, either from a new valvular defect or from a preexisting abnormality. The modified Duke criteria (Table 12.9) facilitate diagnosis of individuals with suspected IE by taking into account predisposing factors, physical findings, blood culture results, echocardiographic findings, and laboratory information.

Complications of IE generally begin within the first few weeks of onset and can include glomerular antigen-antibody complex deposition causing glomerulonephritis (Chapter 20). Sepsis, arrhythmias (suggesting invasion into underlying myocardium and conduction system), and systemic embolization bode particularly ill for the patient. Left untreated, IE generally is fatal. However, with appropriate long-term (6 weeks or more) antibiotic therapy and/or valve replacement, mortality is reduced. For infections involving low-virulence organisms (e.g., *S. viridans*) the cure rate is 98%, and for enterococci and *S. aureus* infections, cure rates range from 60% to 90%; however, with infections due to gram-negative bacilli or fungi, one-half of the patients ultimately succumb. The cure rate for endocarditis arising on prosthetic valves is uniformly worse, and valve replacement is commonly required.

Earlier diagnosis and effective treatment has nearly eliminated some previously common clinical manifestations of long-standing IE—for example, microthromboemboli (manifest as splinter or subungual hemorrhages), erythematous or hemorrhagic nontender lesions on the palms or soles (Janeway lesions), subcutaneous nodules in the pulp of the digits (Osler nodes), and retinal hemorrhages in the eyes (Roth spots).

Table 12.9 Diagnostic Criteria for Infective Endocarditis[a]

Pathologic Criteria

- Microorganisms, demonstrated by culture or histologic examination, in a vegetation, embolus from a vegetation, or intracardiac abscess

Histologic confirmation of active endocarditis in a vegetation or intracardiac abscess

Clinical Criteria

Major

- Blood culture(s) positive for a characteristic organism or persistently positive for an unusual organism
- Echocardiographic identification of a valve-related or implant-related oscillating mass or abscess, or partial separation of artificial valve
- New valvular regurgitation

Minor

- Predisposing heart lesion or intravenous drug use
- Fever
- Vascular lesions, including major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions[b]
- Immunological phenomena, including glomerulonephritis, Osler nodes,[c] Roth spots,[d] and rheumatoid factor
- Microbiologic evidence, including a single culture positive for an unusual organism

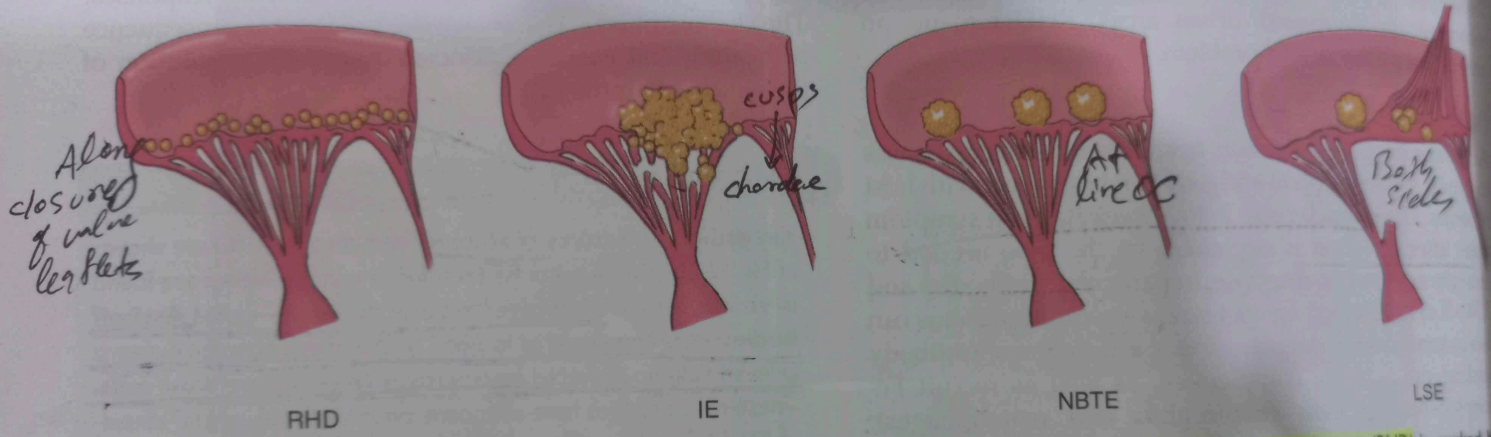

Figure 12.23 Comparison of the four major forms of vegetative endocarditis. The rheumatic fever phase of rheumatic heart disease *(RHD)* is marked by small, warty vegetations along the lines of closure of the valve leaflets. Infective endocarditis *(IE)* is characterized by large, irregular masses on the valve cusps that can extend onto the chordae (see Fig. 12.24A). Nonbacterial thrombotic endocarditis *(NBTE)* typically exhibits small, bland vegetations, usually attached at the line of closure. One or many may be present (see Fig. 12.25). Libman-Sacks endocarditis *(LSE)* has small- or medium-sized vegetations on either or both sides of the valve leaflets.

The diagnosis is established in accordance with the revised

finish our discussion by returning to the clinical features of COPD.

Emphysema

Emphysema is defined by irreversible enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of their walls. Subtle but functionally important small airway fibrosis (distinct from chronic bronchitis) is also present and is a significant contributor to airflow obstruction. Emphysema is classified according to its anatomic distribution within the lobule. Recall that the lobule is a cluster of acini, the terminal respiratory units. Based on the segments of the respiratory units that are involved, emphysema is subdivided into four major types: (1) *centriacinar*, (2) *panacinar*, (3) *paraseptal*, and (4) *irregular*. Of these, only the first two cause clinically significant airflow obstruction (Fig. 15.6).

- *Centriacinar (centrilobular) emphysema.* Centriacinar emphysema is the most common form, constituting more than 95% of clinically significant cases. It occurs predominantly in heavy smokers with COPD. In this type of emphysema the central or proximal parts of the acini, formed by respiratory bronchioles, are affected, whereas distal alveoli are spared (Figs. 15.6B and 15.7A). Thus,

both emphysematous and normal airspaces exist within the same acinus and lobule. The lesions are more common and usually more pronounced in the upper lobes, particularly in the apical segments. In severe centriacinar emphysema, the distal acinus may also be involved, making differentiation from panacinar emphysema difficult.

- *Panacinar (panlobular) emphysema.* Panacinar emphysema is associated with *α1-antitrypsin deficiency* (Chapter 18) and is exacerbated by smoking. In this type the acini are uniformly enlarged from the level of the respiratory bronchiole to the terminal blind alveoli (Figs. 15.6C and 15.7B). In contrast to centriacinar emphysema, panacinar emphysema tends to occur more commonly in the lower zones and in the anterior margins of the lung, and it is usually most severe at the bases.
- *Distal acinar (paraseptal) emphysema.* Distal acinar emphysema probably underlies many cases of spontaneous pneumothorax in young adults. In this type the proximal portion of the acinus is normal, and the distal part is predominantly involved. The emphysema is more striking adjacent to the pleura, along the lobular connective tissue septa, and at the margins of the lobules. It occurs adjacent to areas of fibrosis, scarring, or atelectasis and is usually more severe in the upper half of the lungs. The characteristic finding is multiple enlarged airspaces, ranging from less than 0.5 cm to more than 2.0 cm in diameter, which sometimes form cyst-like structures.

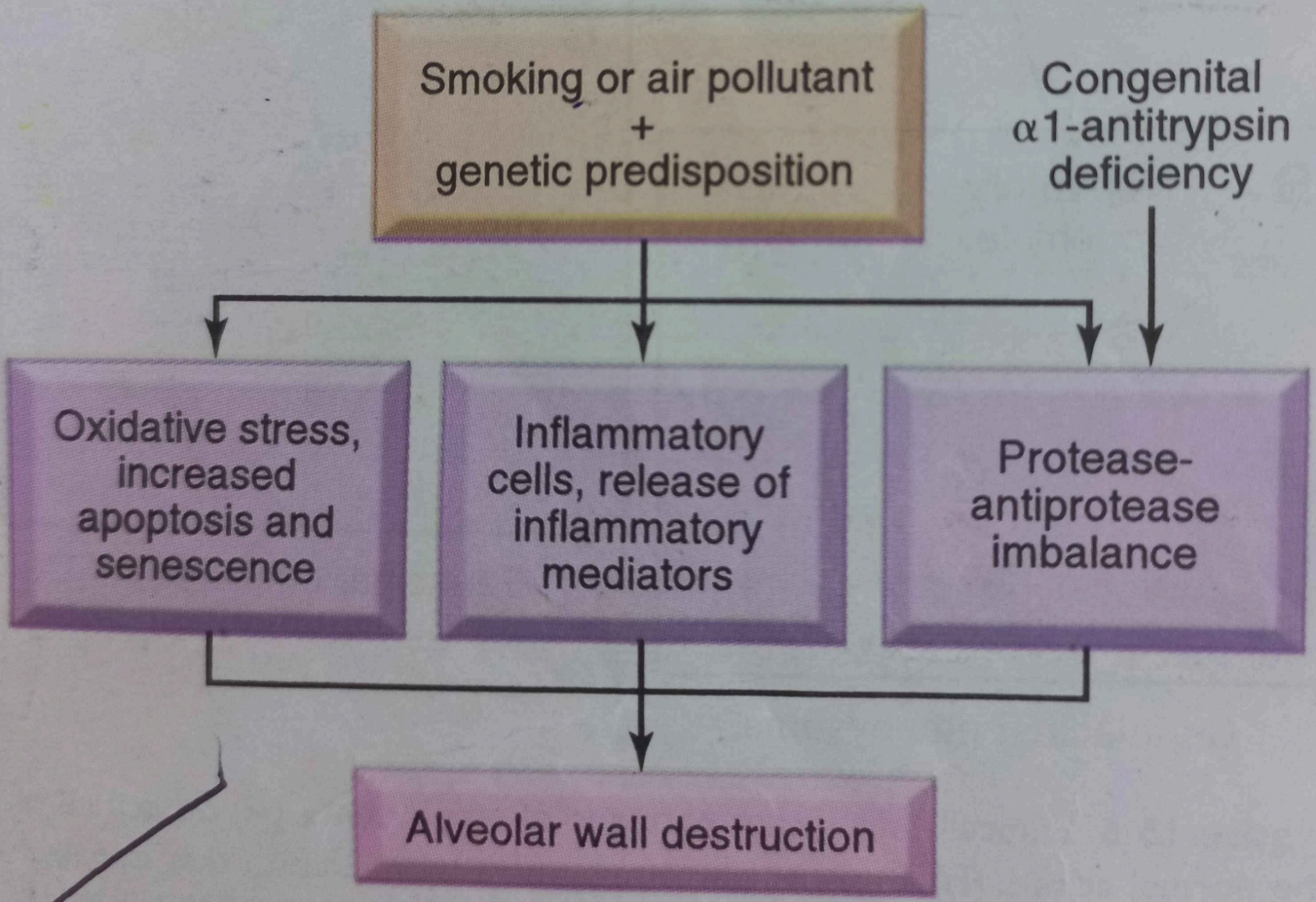

Figure 15.8 Pathogenesis of emphysema. See text for details.

MORPHOLOGY

Advanced emphysema produces voluminous lungs, often overlapping the heart anteriorly. Generally, in patients with smoking-related disease, the upper two-thirds of the lungs are more severely affected. Large alveoli can easily be seen on the cut surface of fixed lungs (see Fig. 15.7). Apical blebs or bullae characteristic of irregular emphysema may appear in patients with advanced disease.

Microscopically, abnormally large alveoli are separated by thin septa with focal centriacinar fibrosis. There is loss of attachments between alveoli and the outer wall of small airways. The pores of Kohn are so large that septa appear to be floating or protrude blindly into alveolar spaces with a club-shaped end. As alveolar walls are destroyed, there is a decrease in the capillary bed area. With advanced disease, there are even larger abnormal airspaces and possibly blebs or bullae, which often deform and compress the respiratory bronchioles and vasculature of the lung. Inflammatory changes in small airways are often superimposed (described next under chronic bronchitis), as are vascular changes related to pulmonary hypertension stemming from local hypoxemia and loss of capillary beds.

decreased breath sounds. hyper resonant lung fields. lucency. barrel chest

Chronic Bronchitis

Chronic bronchitis is defined clinically as persistent cough with sputum production for at least 3 months in at least 2 consecutive years in the absence of any other identifiable cause. Longstanding chronic bronchitis is associated with progressive lung

Granulomatous Diseases

Sarcoidosis

Sarcoidosis is a systemic granulomatous disease of unknown cause that may involve many tissues and organs.

Sarcoidosis = granu

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composed of aggr
phages, often with
chronicity the gra
rims or may evel

Non-ca

Its various clinical presentations are protean, but the most common are bilateral hilar lymphadenopathy or parenchymal lung involvement, occurring in 90% of cases. Eye and skin lesions are next in frequency. Since other diseases, including mycobacterial and fungal infections and berylliosis, can also produce noncaseating granulomas, the diagnosis is one of exclusion.

Sarcoidosis usually occurs in adults younger than 40 years of age but can affect any age group. The prevalence is higher in women but varies widely in different countries and populations. In the United States the rates are highest in the Southeast and are 10 times higher in African-Americans than in Caucasians. In contrast, the disease is rare among the Chinese and Southeast Asians. Patterns of organ involvement also vary with race.

Pathogenesis

Although several lines of evidence suggest that sarcoidosis is a disease of disordered immune regulation in genetically predisposed individuals, its etiology is unknown. There are several immunologic abnormalities in the local milieu of sarcoid granulomas that suggest a cell-mediated immune response to an unidentified antigen. These abnormalities include:

- Intra-alveolar and interstitial accumulation of CD4+ T cells, resulting in CD4/CD8 T-cell ratios ranging from 5:1 to 15:1, suggesting pathogenic involvement of CD4+ helper T cells. There is oligoclonal expansion of T-cell subsets as determined by analysis of T-cell receptor rearrangement, consistent with an antigen-driven proliferation.
- Increased levels of T cell–derived Th1 cytokines such as IL-2 and interferon (IFN)-γ, which may be responsible for T-cell expansion and macrophage activation, respectively.
- Increased levels of several cytokines in the local environment (IL-8, TNF, macrophage inflammatory protein 1α) that favor recruitment of additional T cells and monocytes and contribute to the formation of granulomas. TNF in particular is released at high levels by activated alveolar macrophages, and the TNF concentration in the bronchoalveolar fluid is a marker of disease activity.
- Impaired dendritic cell function.

Additionally, there are systemic immunologic abnormalities in individuals with sarcoidosis. Both anergy to common skin test antigens, such as *Candida* or tuberculosis purified protein derivative (PPD), and polyclonal hypergammaglobulinemia, another manifestation of helper T-cell dysregulation, are frequently observed. Evidence of genetic influences includes familial and racial clustering of cases and the association with certain human leukocyte antigen (HLA) genotypes (e.g., HLA-A1 and HLA-B8).

MORPHOLOGY

Virtually every organ in the body has been described as being affected by sarcoidosis at least on rare occasions. Involved tissues contain well-formed **non-necrotizing granulomas** (Fig. 15.22) composed of aggregates of tightly clustered epithelioid macrophages, often with giant cells. Central necrosis is unusual. With chronicity the granulomas may become enclosed within fibrous rims or may eventually be replaced by hyaline fibrous scars.

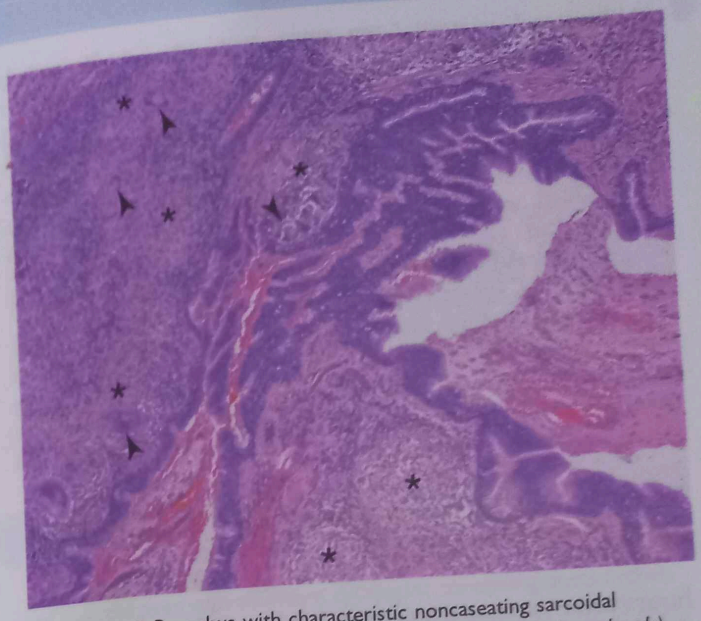

Figure 15.22 Bronchus with characteristic noncaseating sarcoidal granulomas *(asterisks)*, with many multinucleated giant cells *(arrowheads)*. Note subepithelial location of granulomas.

Laminated concretions composed of calcium and proteins known as **Schaumann bodies** and stellate inclusions known as **asteroid bodies** are found within giant cells in approximately 60% of the granulomas. Though characteristic, these microscopic features are not pathognomonic of sarcoidosis because asteroid and Schaumann bodies may be encountered in other granulomatous diseases (e.g., tuberculosis).

The **lung** is a common site of involvement. Macroscopically, there is usually no demonstrable alteration, although in advanced cases coalescence of granulomas produces small nodules that are palpable or visible as 1 to 2 cm, noncaseating, noncavitated consolidations. The lesions are distributed primarily along the lymphatics around bronchi and blood vessels, although alveolar lesions and pleural involvement are also seen. The relatively high frequency of granulomas in the bronchial submucosa accounts for the high diagnostic yield of bronchoscopic biopsies. There seems to be a strong tendency for lesions to heal in the lungs, so varying stages of fibrosis and hyalinization are often found.

Lymph nodes are involved in almost all cases, particularly the hilar and mediastinal nodes, but any node in the body may be affected. Nodes are characteristically enlarged, discrete, and sometimes calcified. Tonsillar granulomas are seen in about one-fourth to one-third of cases. The **spleen** is involved in about 75% of cases, but overt splenomegaly is seen in only 20% of cases. On occasion, granulomas may coalesce to form small nodules that are visible macroscopically. The **liver** is affected slightly less often than the spleen. It may be moderately enlarged and typically contains scattered granulomas, more in portal triads than in the lobular parenchyma.

The **bone marrow** is involved in about 20% of cases. Radiologically, visible bone lesions have a particular tendency to involve phalangeal bones of the hands and feet, creating small circumscribed areas of bone resorption within the marrow cavity and a diffuse reticulated pattern throughout the cavity, with widening of the bony shafts or new bone formation on the outer surfaces.

Skin lesions, encountered in 25% of cases, assume a variety of appearances, including discrete subcutaneous nodules; focal, slightly elevated, erythematous plaques; or flat lesions that are

slightly reddened and scaling, resembling those of systemic lupus erythematosus. Lesions may also appear on the mucous membranes of the oral cavity, larynx, and upper respiratory tract. Other patients present with **erythema nodosum**, painful erythematous nodules on the shins that stem from septal panniculitis.

Ocular involvement, seen in 25% of cases, takes the form of iritis or iridocyclitis and may be bilateral or unilateral. Consequently, corneal opacities, glaucoma, and total loss of vision may occur. These ocular lesions are frequently accompanied by inflammation of the lacrimal glands and suppression of lacrimation (**sicca syndrome**). Bilateral sarcoidosis of the parotid, submaxillary, and sublingual glands constitutes the combined uveoparotid involvement designated as Mikulicz syndrome (Chapter 16).

Muscle involvement is underdiagnosed, since it may be asymptomatic. Muscle weakness, aches, tenderness, and fatigue should prompt consideration of occult sarcoid myositis, which can be diagnosed by muscle biopsy. Sarcoid granulomas occasionally occur in the heart, kidneys, central nervous system (neurosarcoidosis, seen in 5% to 15% of cases), and endocrine glands, particularly in the pituitary, as well as in other body tissues.

Clinical Features

Because of its varying severity and inconstant tissue distribution, sarcoidosis may present with diverse features. It may be discovered unexpectedly on routine chest films as bilateral hilar adenopathy or may present with peripheral lymphadenopathy, cutaneous lesions, eye involvement, splenomegaly, or hepatomegaly. In the great majority of

Hospital-Acquired Pneumonia Nosocomial

Hospital-acquired pneumonias are defined as pulmonary infections acquired in the course of a hospital stay. They are common in patients with severe underlying disease, immunosuppression, prolonged antibiotic therapy, or invasive access devices such as intravascular catheters. Patients on mechanical ventilation are at particularly high risk. Superimposed on an underlying disease (that caused hospitalization), hospital-acquired infections are serious and often life-threatening. Gram-positive cocci (mainly *S. aureus*) and gram-negative rods (Enterobacteriaceae and *Pseudomonas* species) are the most common isolates. The same organisms predominate in ventilator-associated pneumonia, with gram-negative bacilli being somewhat more common in this setting.

Hepatitis B Virus

Hepatitis B virus (HBV) infection has varied clinical outcomes, which depend on the age of exposure, comorbid conditions (including exposure to other infectious agents), and host immunity. The major clinical presentations include: (1) acute hepatitis followed by recovery and clearance of the virus, (2) acute hepatic failure with massive liver necrosis, (3) chronic hepatitis with or without progression to cirrhosis, and (4) an asymptomatic, "healthy" carrier state (Fig. 18.9).

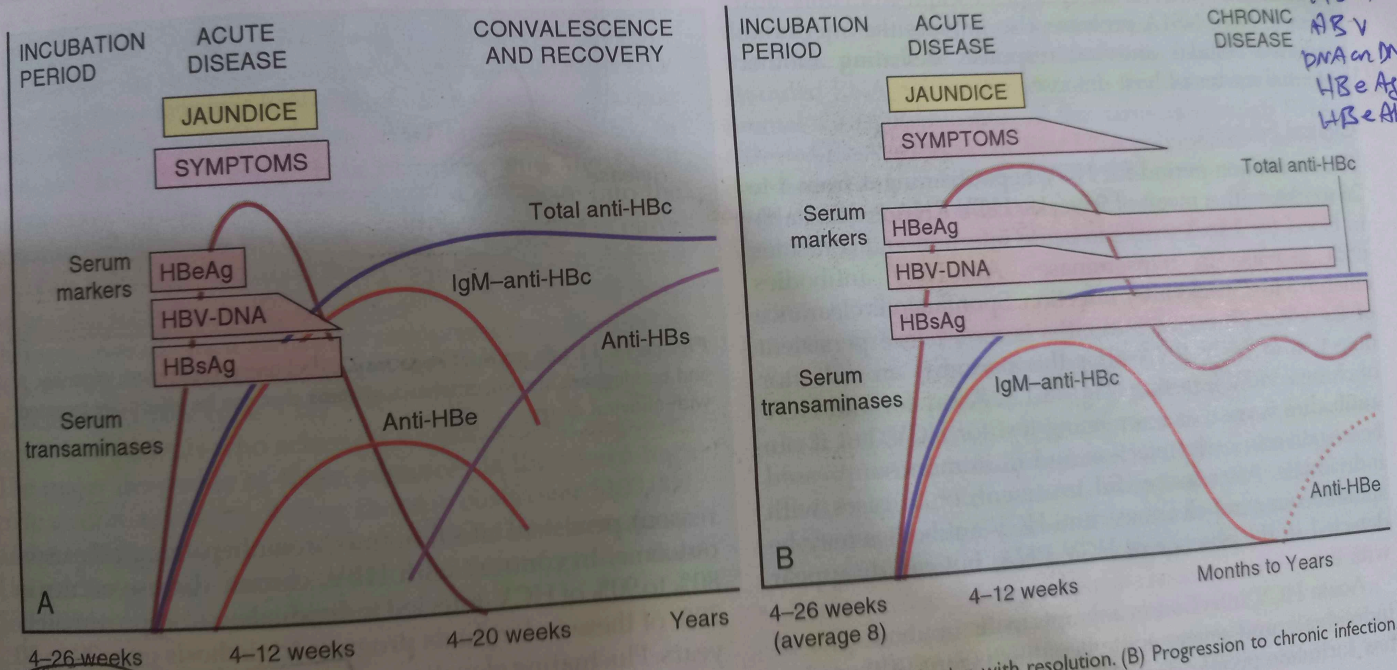

Figure 18.10 Temporal changes in serologic markers in hepatitis B viral infection. (A) Acute infection with resolution. (B) Progression to chronic infection. In some cases of chronic hepatitis B virus, serum transaminases may become normal.

Table 18.3 Hepatitis Viruses

Virus	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Type of virus	ssRNA	Partially dsDNA	ssRNA	Circular defective ssRNA	ssRNA
Route of transmission	Fecal-oral (contaminated food or water)	Parenteral, sexual contact, perinatal	Parenteral; intranasal cocaine use	Parenteral	Fecal-oral
Mean incubation period	2–6 weeks	2–26 weeks	4–26 weeks	Same as HBV	4–5 weeks
Frequency of chronic liver disease	Never	5%–10%	>80%	10% (co-infection); 90%-100% for superinfection	In immunocompromised hosts only
Diagnosis	Serum IgM antibodies	HBsAg or HBcAg antibodies; PCR for HBV DNA	ELISA for HCV antibodies; PCR for HCV RNA	Serum IgM and IgG antibodies; PCR for HDV RNA	Serum IgM and IgG antibodies; PCR for HEV RNA

dsDNA, Double-stranded DNA; *ELISA*, enzyme-linked immunosorbent assay; *HBcAg*, hepatitis B core antigen; *HBsAg*, hepatitis B surface antigen; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *HDAg*, hepatitis D antigen; *HDV*, hepatitis D virus; *HEV*, hepatitis E virus; *IgG*, immunoglobulin G; *IgM*, immunoglobulin M; *IV*, intravenous; *PCR*, chain reaction; *ssRNA*, single-stranded RNA.

CHOLELITHIASIS (GALLSTONES)

More than 95% of biliary tract disease is attributable to gallstones. Gallstones afflict 10% to 20% of adult populations in high income countries. It is estimated that more than 20 million persons in the United States have gallstones, totaling some 25 to 50 tons in weight, leading to more than 700,000 cholecystectomies performed annually at a cost of approximately $6 billion.

The major risk factors associated with the development of gallstones are listed in Table 18.11 and are briefly described here:

- *Age and sex.* The prevalence of cholesterol gallstones increases throughout life, but they predominantly affect individuals of middle to older age. Prevalence is higher in females in any region or ethnicity; in Caucasian women, it is about twice as high as in men. Hypersecretion of biliary cholesterol seems to play the major role in both age and gender differences. Significant associations are also seen with metabolic syndrome and obesity.
- *Environmental factors.* Estrogen exposure, including through oral contraceptive use and during pregnancy, increases expression of hepatic lipoprotein receptors and stimulates hepatic HMG-CoA reductase activity, enhancing both cholesterol uptake and biosynthesis, respectively.

4F's Fat Forty Female Fer

The net result is excess biliary secretion of cholesterol. Obesity and rapid weight loss are also strongly associated with increased biliary cholesterol secretion.

- *Acquired disorders.* Gallbladder stasis, either neurogenic or hormonal, fosters a local environment that is favorable for both cholesterol and pigment gallstone formation.
- *Hereditary factors.* Genes encoding hepatocyte proteins that transport biliary lipids, known as ATP-binding cassette (ABC) transporters, have associations with gallstone formation. In particular, a common variant of the sterol transporter encoded by the *ABCG8* gene is associated with an increased risk of cholesterol gallstones.

Pathogenesis of Cholesterol Stones

Cholesterol is rendered soluble in bile by forming micelles with bile salts and lecithins, both of which act as detergents. When cholesterol concentrations exceed the solubilizing capacity of bile (supersaturation), cholesterol can no longer remain dispersed and nucleates into solid cholesterol monohydrate crystals. Four conditions appear to contribute to formation of cholesterol gallstones: (1) supersaturation of bile with cholesterol; (2) hypomotility of the gallbladder; (3) accelerated cholesterol crystal nucleation; and (4) hypersecretion of mucus in the gallbladder, which traps the nucleated crystals, leading to accretion of more cholesterol and the appearance of macroscopic stones.

Pathogenesis of Pigment Stones

Pigment gallstones are complex mixtures of insoluble calcium salts of unconjugated bilirubin and inorganic calcium salts. Disorders that are associated with elevated levels of unconjugated bilirubin in bile increase the risk of developing pigment stones. These include chronic hemolytic anemia, severe ileal dysfunction or bypass, and bacterial contamination of the biliary tree. Unconjugated bilirubin is normally a minor component of bile, but it increases when infection of the biliary tract leads to release of microbial β-glucuronidases, which hydrolyze bilirubin glucuronides. Thus, infection of the biliary tract with *Escherichia coli*, *Ascaris lumbricoides*, or the liver fluke *C. sinensis* increases the

Table 18.11 Risk Factors for Gallstones

Cholesterol Stones
Demography: northern Europeans, North and South Americans, Native Americans, Mexican Americans
Advancing age
Female sex hormones
Female gender
Oral contraceptives
Pregnancy
Obesity and metabolic syndrome
Rapid weight reduction
Gallbladder stasis
Inborn disorders of bile acid metabolism
Hyperlipidemia syndromes
Pigment Stones
Demography: Asians more than Westerners, rural more than urban
Chronic hemolytic anemias
Biliary infection
Gastrointestinal disorders: ileal disease (e.g., Crohn disease), ileal resection or bypass, cystic fibrosis with pancreatic insufficiency

urothelial neoplasms being by far the most common type followed by squamous and glandular neoplasms.

Urothelial Neoplasms

Urothelial neoplasms represent about 90% of all bladder tumors and run the gamut from small benign lesions that do not recur to aggressive cancers that are often fatal. Many of these tumors are multifocal at presentation. Though most common in the bladder, all of the urothelial lesions described here may be seen at any site where there is urothelium, from the renal pelvis to the distal urethra.

There are two distinct precursor lesions to invasive urothelial carcinoma: noninvasive papillary tumors and flat noninvasive urothelial carcinoma in situ (CIS) (Fig. 21.4). The most common precursor lesions are the noninvasive

Table 21.3 Tumors of the Urinary Bladder

Urothelial (transitional) tumors
• Noninvasive urothelial (transitional cell) tumors
• Infiltrating urothelial carcinoma
• Variants: nested, microcystic, micropapillary, plasmacytoid, sarcomatoid, giant cell, poorly differentiated, lipid-rich, and clear cell
Adenocarcinoma
Squamous cell carcinoma
Mixed carcinoma
Small-cell carcinoma
Sarcomas

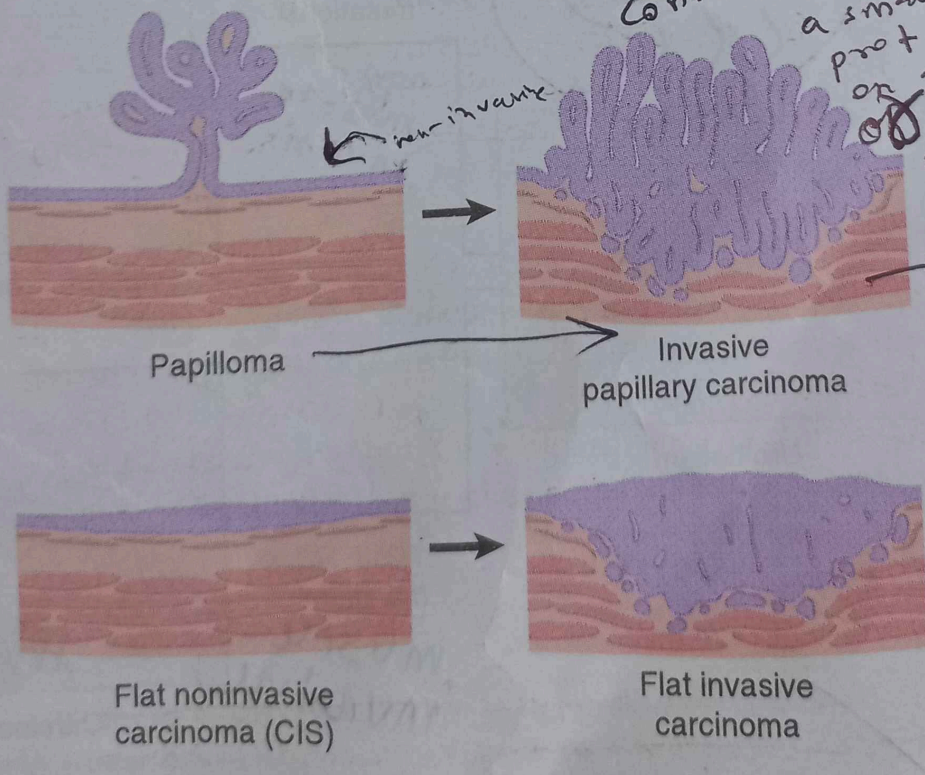

Figure 21.4 Four morphologic patterns of bladder tumors. *CIS*, Carcinoma in situ.

(Chapter 7). Cancer appears 15 to 40 years after the first exposure.

other carcinogen-induced cancers, such as lung cancer and melanoma. As in other cancers, recurrently mutated

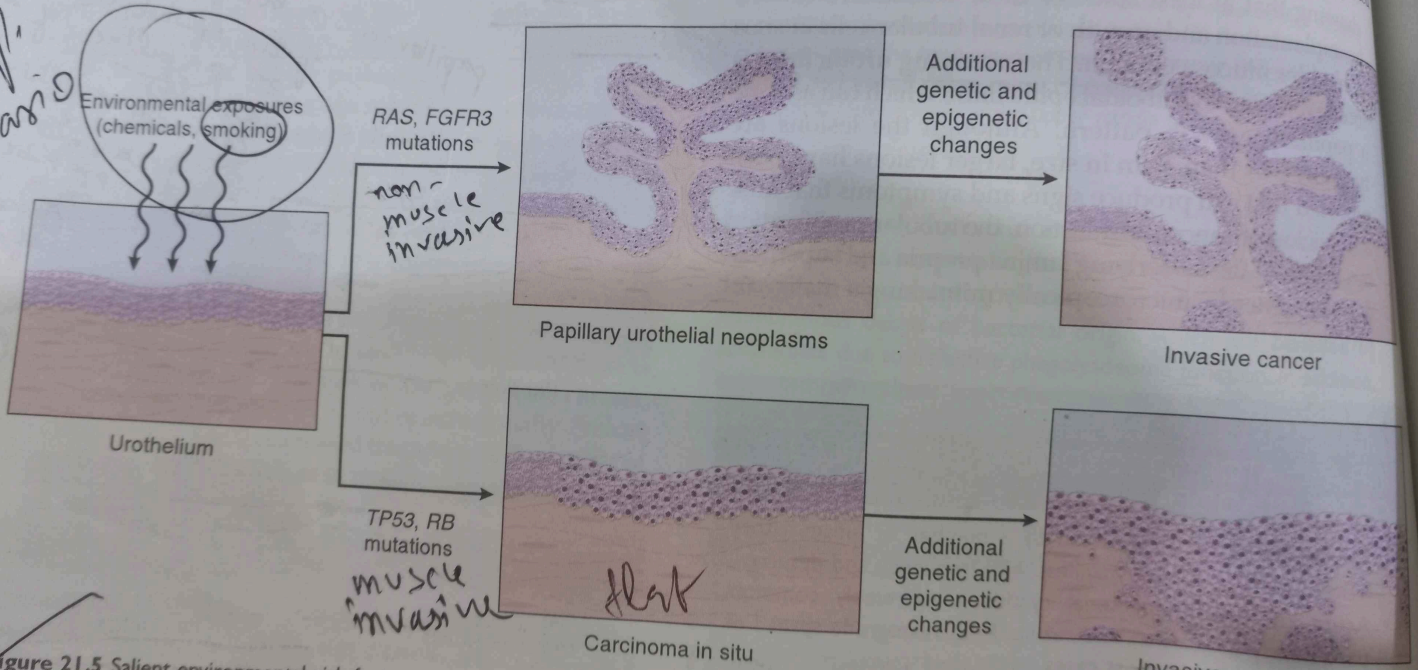

Figure 21.5 Salient environmental risk factors and major molecular pathways of bladder cancer development from carcinoma in situ and papillary bladder neoplasms. See text for details.

understand their [illegible] clinical significance.

MORPHOLOGY

The appearance of urothelial tumors varies from purely papillary to nodular or flat. Papillary lesions are red, elevated excrescences ranging in size from less than 1 cm in diameter to large masses up to 5 cm in diameter (Fig. 21.6). Multiple discrete tumors are often present.

Table 21.3 lists the grading system of urothelial tumors. **Papillomas** represent 1% or less of bladder tumors and are often seen in younger patients. These tumors typically arise singly as small (0.5 to 2 cm), delicate structures superficially attached to the mucosa by a stalk and are referred to as **exophytic papillomas.** The individual finger-like papillae have a central core of loose fibrovascular tissue covered by epithelium that is histologically identical to normal urothelium (Fig. 21.7A). Recurrences and progression are rare but

Figure 21.8 Bladder
a disorganized urothelium containing

may occur. In contrast to exophytic papillomas, **inverted papillomas** are completely benign lesions consisting of inter-anastomosing cords of cytologically bland urothelium that extend down into the lamina propria; they simulate an invasive process.

Papillary urothelial neoplasms of low malignant potential (PUNLMP) share many histologic features with papillomas, differing only in having thicker urothelium with greater density of cells (Fig. 21.7B) At cystoscopy, these tumors tend to be larger than papillomas and may be indistinguishable from papillary cancers. Recurrent tumors usually show the same morphology; progression to tumors of higher grade may occur but is rare.

Low-grade papillary urothelial carcinomas have an orderly architectural appearance and low-grade cytologic atypia. The cells are evenly spaced (i.e., maintain polarity) and cohesive. There are scattered hyperchromatic nuclei, infrequent mitotic figures predominantly toward the base, and slight variation in nuclear size and shape (Fig. 21.7C). These low-grade cancers may recur and, infrequently, may also invade. Only rarely do these tumors pose a threat to life.

High-grade papillary urothelial carcinomas contain dyscohesive cells with large hyperchromatic nuclei, irregular nuclear chromatin, and prominent nucleoli. Some of the tumor cells are highly anaplastic (Fig. 21.7D). Mitotic figures, including atypical ones, are frequent. Architecturally, there is disarray and loss of polarity. As compared to low-grade lesions, these tumors have a much higher incidence of progression to muscle-invasive bladder cancer and have a significant potential for metastasis to regional lymph nodes and systemic spread (e.g., to liver and lung).

CIS (or flat urothelial carcinoma) is defined by the presence of cytologically malignant cells within a flat urothelium (Fig. 21.8). CIS may range from full-thickness cytologic atypia to scattered malignant cells in an otherwise normal urothelium, the latter termed **pagetoid spread.** A common feature shared with high-grade papillary urothelial carcinoma is a lack of cohesiveness, which leads to shedding of malignant cells into the urine. When shedding is extensive, only a few CIS cells may be left clinging to a largely denuded basement membrane. On cystoscopy CIS usually appears as an area of mucosal reddening, granularity, or thickening without an evident intraluminal mass. It is commonly multifocal and may involve most of the bladder surface and extend into the ureters and urethra. **If untreated, 50% to 75% of CIS progresses to invasive cancer.**

Invasive urothelial carcinoma (Fig. 21.9) may be associated with papillary urothelial cancer, usually high grade, or adjacent

testis.

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 a complete or partial failure of the intra-abdominal testes to descend into the scrotal sac and is associated with testicular dysfunction and an increased risk of testicular cancer. It is found in approximately 1% of 1-year-old boys. 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 phases. During the first transabdominal phase, the testis comes to lie within the lower abdomen or brim of the pelvis. This phase is controlled by the hormone müllerian-inhibiting substance. In the second inguinoscrotal phase, the testes descend through the inguinal canal into the scrotal sac. This phase is androgen-dependent and is thought to be mediated by androgen-induced release of calcitonin gene–related peptide from the genitofemoral nerve. The testes may arrest anywhere along their pathway of descent; the most common site is in the inguinal canal, while arrest within the abdomen is uncommon, accounting for approximately 5% to 10% of cases. Even though testicular descent is controlled by hormonal factors, cryptorchidism is only rarely associated with a well-defined hormonal disorder.

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Cryptorchidism is usually unilateral, being bilateral in 25% of patients. Cryptorchid testes are small and firm. The histologic changes in the malpositioned testis begin as early as 2 years of age. Early on, **thickening of the basement membrane** of the spermatic tubules is seen (Fig. 21.15). Subsequent loss of spermatogonia leaves the tubules with only Sertoli cells. The scarred tubules may appear as dense cords of hyaline connective tissue associated with a concomitant increase in interstitial stroma. Leydig cells are spared and therefore appear relatively prominent. Similar histologic changes may also be seen in the contralateral (descended) testis in males with unilateral cryptorchidism, suggesting that cryptorchidism is a marker of an intrinsic defect in gonadal development.

Figure 21.15 Cryptorchi... shows tubules with active spermatogenesis Sertoli cells but no spermatogenesis. There is thickening of basement membranes and an app

Clinical Features

Cryptorchidism is asymptomatic and comes to attention when the scrotal sac is discovered to be empty by the patient, a parent, or a physician. In addition to sterility, cryptorchidism may be associated with other morbidity such as crushing injuries due to trauma to the inguinal region and inguinal hernia (10% to 20% of cases).

During the first year of life the majority of inguinal cryptorchid testes descend spontaneously into the scrotum. If it remains undescended, surgical correction by orchiopexy (placement in the scrotal sac) is required, preferably prior to development of histologic changes. Current recommendations are for orchiopexy to be performed at 6 to 12 months of age. Even with this corrective procedure, deficient spermatogenesis has been reported in 10% to 60% of patients, and repositioning has not been proven to completely eliminate the risk of cancer. Since the contralateral normally descended testis is also at higher risk for malignancy, it is believed that cryptorchidism and the associated risk for germ cell neoplasm is linked to an in utero defect in gonadal cell development (see discussion of testicular dysgenesis syndrome later), rather than the abnormal anatomic position.

KEY CONCEPTS

CRYPTORCHIDISM

- Cryptorchidism refers to incomplete descent of the testis from the abdomen to the scrotum and is present in about 1% of 1-year-old male infants.
- Bilateral or, in some cases, even unilateral cryptorchidism is associated with tubular atrophy and sterility.
- The cryptorchid testis carries a three- to fivefold higher risk for testicular cancer.
- Orchiopexy reduces but does not completely eliminate the risk of sterility and cancer.

Regressive Changes

Atrophy and Decreased Fertility

Testicular atrophy may be caused by one of several conditions, including (1) progressive

Seminoma

Seminoma is the most common type of GCT, making up about 50% of these tumors overall. The peak incidence is in the fourth decade. An identical tumor arises in the ovary, where it is called *dysgerminoma* (Chapter 22), and in the central nervous system, usually in midline structures such as the pineal gland, where it is referred to as *germinoma*.

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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 (Fig. 21.19). Generally the tunica albuginea is not penetrated, but occasionally extension to the epididymis, spermatic cord, or scrotal sac occurs.

The lesion is composed of sheets of uniform cells divided into poorly demarcated lobules by delicate fibrous septa containing a lymphocytic infiltrate (Fig. 21.20A); in some tumors, ill-defined granulomas also are present, presumably as part of a host response to the neoplasm. **The classic seminoma cell is round to polyhedral and has a distinct cell membrane; clear or watery-appearing cytoplasm; and a large, central nucleus with one or two prominent nucleoli** (Fig. 21.20B). The cytoplasm contains varying amounts of glycogen. By immunohistochemistry, the tumor cells are typically positive for KIT, OCT3/4, and podoplanin and negative for cytokeratin. 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.

(Fig. 21.27). Testicular androgens control the growth and survival of prostatic cells, and castration leads to widespread apoptosis of prostatic epithelium and atrophy of the prostate.

Only three pathologic processes affect the prostate gland with sufficient frequency to merit discussion: inflammation, benign prostatic hypertrophy (BPH), and tumors. Of these, BPH is the most common and occurs so often in older males that it can almost be viewed as a "normal" part of aging. Prostatic carcinoma is also extremely common in older men and is an important cause of morbidity and mortality. We begin our discussion with consideration of inflammatory processes.

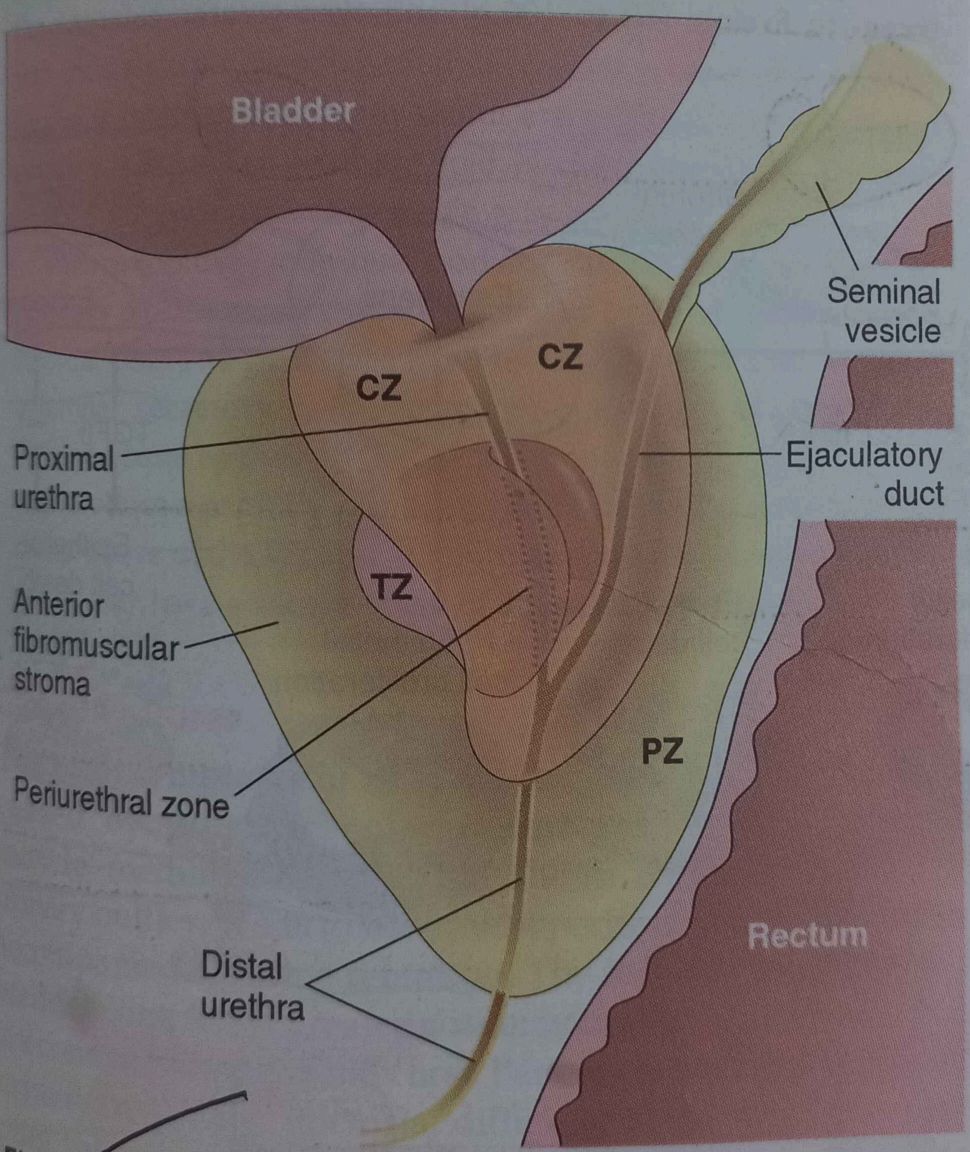


Figure 21.26 Adult prostate. The normal prostate contains several distinct regions, including a central zone *(CZ)*, a peripheral zone *(PZ)*, a transitional zone *(TZ)*, and a periurethral zone. Most carcinomas arise from the peripheral zone and may be palpable during digital examination of the rectum. Benign prostatic hyperplasia, in contrast, arises from the more centrally situated transitional zone and often produces urinary obstruction.

Benign Prostatic Hyperplasia

BPH (also referred to as nodular hyperplasia) is the most common benign prostatic disease in men older than age 50 years. Approximately 30% of white American men in that age group have moderate to severe symptoms of BPH, and histologic evidence of BPH is found in up to 90% of men by age 80. It is not a premalignant lesion.

Etiology and Pathogenesis

Dihydrotestosterone (DHT) is the main androgen in the prostate, where it is formed from testosterone through the action of type 2 5α-reductase (Fig. 21.28A). This enzyme is expressed primarily in stromal cells and is not expressed in prostatic epithelial cells. Type 1 5α-reductase is another enzyme that mediates DHT production from testosterone in extraprostatic locations (e.g., liver and skin) and provides an additional source of DHT that reaches the prostate through the blood.

DHT binds to and activates androgen receptors (ARs) found in both stromal and epithelial prostate cells. It is more inhibits epithelial 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.

While it is recognized that androgens play a permissive role in BPH pathogenesis, multiple lines of evidence support a role for estrogens as well. Two different forms of estrogen receptor (ER), ERα and ERβ, have opposing proliferative and antiproliferative effects on prostate cells, respectively. Effects of estrogens on the prostate are associated with multiple mechanisms including apoptosis, aromatase expression, and paracrine regulation via prostaglandin E_2. Estrogens thus contribute to BPH pathogenesis by tipping the balance toward proliferation (Fig. 21.28B).

MORPHOLOGY

In BPH, the weight of the enlarged prostate often increases three- to fivefold (60 to 100 g), and even greater enlargement

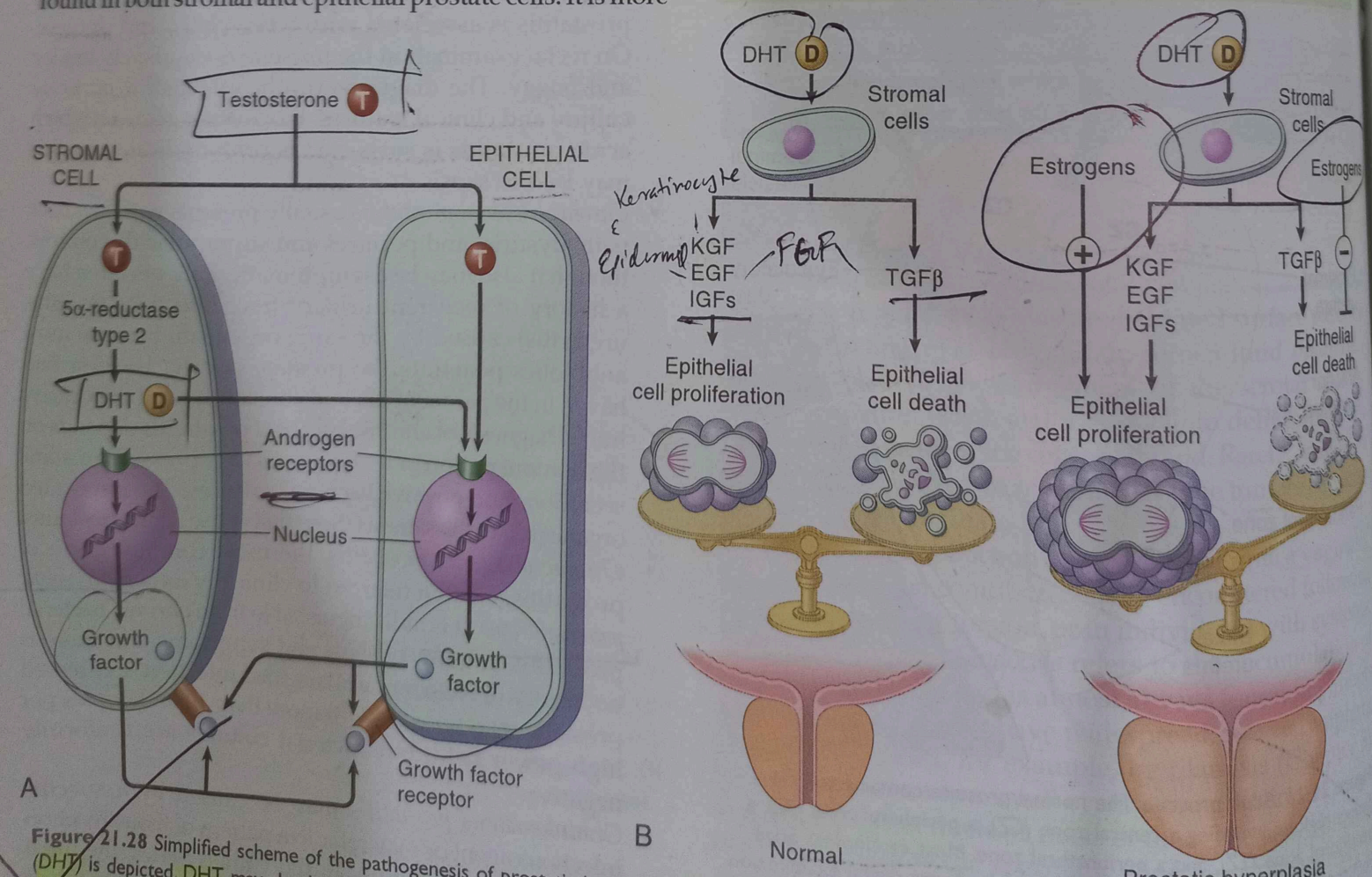


Figure 21.28 Simplified scheme of the pathogenesis of prostatic hyperplasia. (A) The central role of the stromal cells in generating dihydrotestosterone (DHT) is depicted. DHT may also be produced in skin and liver by both type 1 and type 2 5α-reductase. (B) The contribution of estrogen in tipping the balance of cell proliferation and cell death toward the former is illustrated. *EGF*, Epidermal growth factor; *IGFs*, insulin-like growth factors; *KGF*, keratinocyte growth factor; *TGFβ*, transforming growth factor β.

may be seen. BPH affects the transition zone and thus may encroach on the urethra, compressing it to a slit-like orifice (Fig. 21.29A). On cross-section, hyperplastic nodules are seen that vary in color and consistency depending on their cellular content (Fig. 21.29B). Nodules that contain mostly glands are yellow-pink and soft and exude a milky white prostatic fluid. Nodules composed primarily of fibromuscular stroma are pale gray and firm.

Microscopically, individual nodules contain small to large to cystically dilated glands that are separated by bland spindle-shaped stromal cells. The glands are lined by two layers of cells, an inner columnar secretory cell layer and an outer layer of cuboidal or flattened basal epithelium (Fig. 21.29C), and infolding of the glands may produce a papillary architecture. In markedly enlarged glands, compromise of the vascular supply may produce prostatic infarcts, which may have adjacent areas of squamous metaplasia.

Clinical Features

The main symptoms of BPH are due to urinary obstruction caused by prostatic enlargement and stromal smooth muscle–mediated contraction. The increased resistance to urinary outflow leads to bladder hypertrophy and distention, accompanied by urine retention. The inability to empty the bladder completely creates a reservoir of residual urine that is a common source of infection. Patients experience increased urinary frequency, nocturia, difficulty in starting and stopping the stream of urine, overflow dribbling, and dysuria (painful micturition) and have an increased risk of developing bacterial infections of the bladder and kidney. In many cases, sudden, acute urinary retention occurs that requires emergency catheterization for relief.

Symptomatic BPH is usually managed medically with α-adrenergic blockers and 5α-reductase inhibitors. The former decrease prostate smooth muscle tone via inhibition of α_1-adrenergic receptors, while the latter physically shrink the prostate by decreasing DHT synthesis. For moderate to severe cases recalcitrant to medical therapy, a wide range of invasive procedures exist. Transurethral resection of the prostate (TURP) was for long the gold standard, but alternative procedures to destroy excessive prostatic tissue have been developed with lower morbidity and lower costs. These procedures include high-intensity focused ultrasound (HIFU), laser therapy, hyperthermia, transurethral electrovaporization, and radiofrequency ablation.

KEY CONCEPTS

BENIGN PROSTATIC HYPERPLASIA

- BPH is characterized by proliferation of benign stromal and glandular elements. DHT, an androgen derived from testosterone, is the major hormonal stimulus for proliferation.
- BPH most commonly affects the inner periurethral zone and transition zone of the prostate, producing nodules that compress the prostatic urethra.
- Clinical symptoms and signs are related to urinary obstruction that also predisposes to recurrent urinary tract infections.
- Medical management is based on α-adrenergic blockers and 5α-reductase inhibitors, which decrease prostatic smooth muscle tone and inhibit DHT production, respectively.

Neoplasms

Adenocarcinoma

In the United States, adenocarcinoma of the prostate is the most common form of cancer in men, with an expected 174,650 new cases in 2019, accounting for 20% of all male cancers. Prostate cancer is the second cause of cancer-related

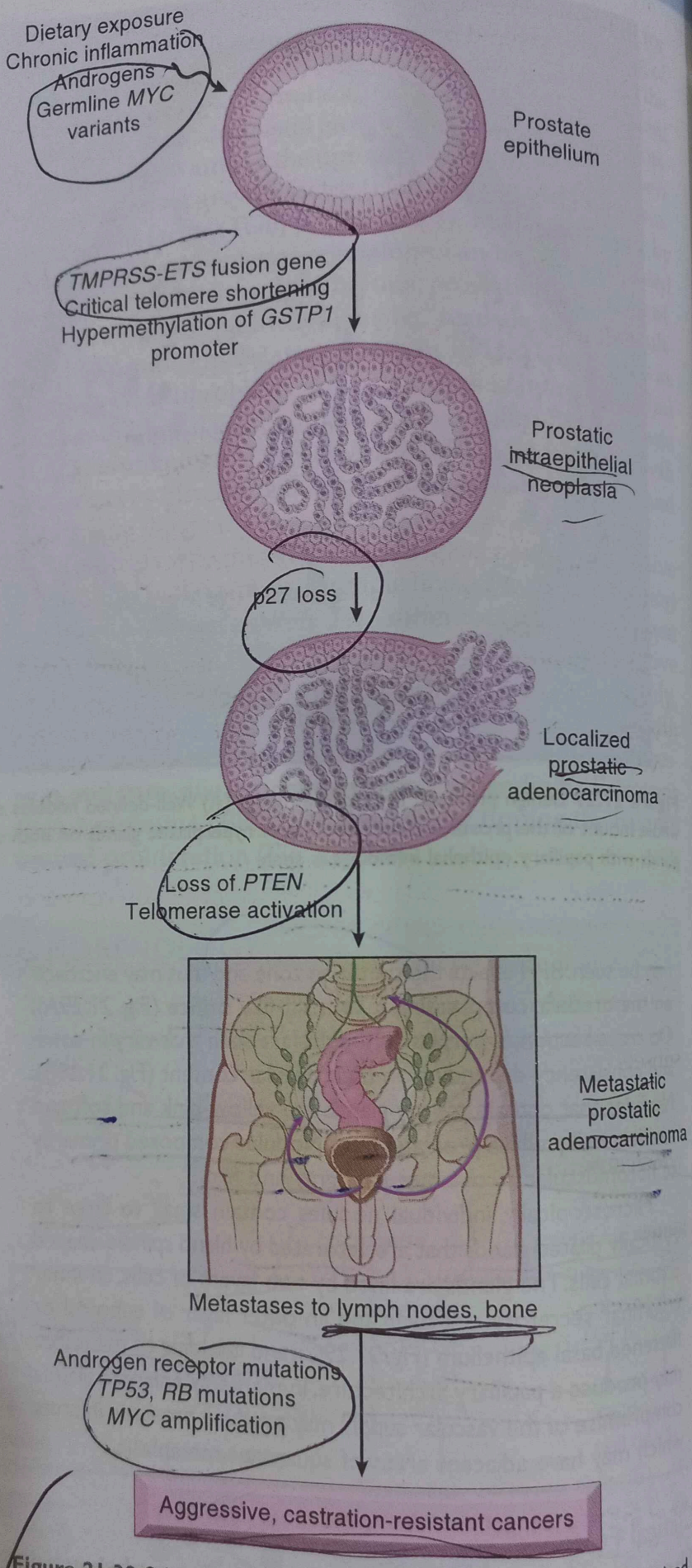


Figure 21.30 Salient environmental and genetic risk factors and acquired genetic and epigenetic alterations leading to prostate cancer development and progression. See text for details.

Androgens. **Like their normal counterparts, the growth and survival of prostate cancer cells depend on androgens, which bind to the AR and induce the expression of pro-growth and pro-survival genes. The** *importance* **of androgens in**

approximately 70% of cases, carcinoma of the prostate arises in the peripheral zone of the gland, classically in a posterior location, where it may be palpable on rectal examination. Characteristically, on cross-section the neoplastic tissue is gritty and firm to palpation, but it is sometimes extremely difficult to visualize by eye (Fig. 21.31). Histologically, most adenocarcinomas consist of glands arranged in well-defined, easily recognized patterns, which are used to grade these tumors (discussed later). The glands are typically smaller than benign glands and are lined by a single uniform layer of cuboidal or low columnar epithelium. In contrast to benign glands, malignant glands have tightly packed cells and characteristically lack branching and papillary infoldings. **The outer basal cell layer typical of benign glands is absent.** The cytoplasm of the tumor cells ranges from pale-clear to a distinctive amphophilic appearance. Nuclei are enlarged and often contain one or more large nucleoli. There is some variation in nuclear size and shape, but in general pleomorphism is not marked. Mitotic figures are uncommon.

When prostate cancer invades locally, it most commonly involves periprostatic tissue, seminal vesicles, and the base of the urinary bladder, which in advanced disease may produce ureteral obstruction. Metastases spread via lymphatics to the obturator nodes and eventually to the para-aortic nodes. **Hematogenous spread occurs chiefly to the bones,** particularly the axial skeleton. Bony metastases are typically osteoblastic, a feature that in men points strongly to a prostatic origin (Fig. 21.32). The bones that are most commonly involved, in descending order of frequency, are lumbar spine, proximal femur, pelvis, thoracic spine, and ribs. Tumors may also spread to viscera, but extensive visceral dissemination is the exception rather than the rule.

The diagnosis of prostate cancer on biopsy specimens can be challenging due to several factors. There is often only a scant amount of tissue available for histologic examination in needle biopsies, and malignant glands may be admixed with numerous benign glands (Fig. 21.33). Moreover, the histologic findings may be subtle (leading to underdiagnosis), and there are benign mimickers of cancer that can lead to a misdiagnosis. A few findings are specific, such as perineural invasion (Fig. 21.34), but in general the diagnosis is made based on a constellation of architectural, cytologic, and ancillary findings. As discussed earlier, one distinguishing feature

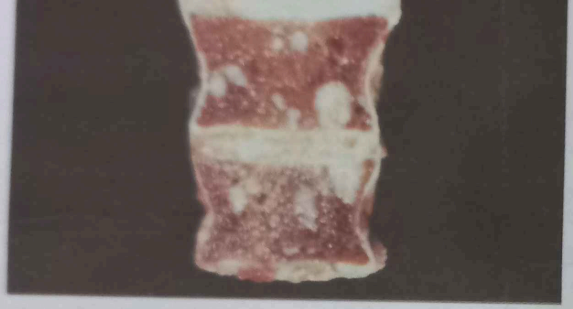


Figure 21.32 Metastatic osteoblastic prostatic carcinoma within vertebral bodies.

is that benign glands contain basal cells, which are absent in cancer (compare benign normal glands in Fig. 21.33A and benign hyperplastic glands in Fig. 21.29C with cancerous glands in Fig. 21.33B). This distinction can be brought out by using various immunohistologic markers that stain basal cells. Another useful marker is α-methylacyl coenzyme A racemase (AMACR), which is upregulated in prostate cancer. Most prostate cancers are positive for AMACR, the sensitivity varying among studies from 82% to 100%. Such markers, while improving diagnostic accuracy, are still prone to false-positive and false-negative results and must be used in conjunction with the routine hematoxylin and eosin–stained sections.

As already discussed, in approximately 80% of cases prostatic tissue removed for carcinoma also harbors **prostatic intraepithelial neoplasia (PIN)**. PIN consists of architecturally benign large, branching prostatic acini lined by atypical cells with prominent nucleoli that may be cytologically identical to carcinoma. Unlike malignant glands, glands involved by PIN retain, at least partially, a layer of basal cells and have an intact basement membrane.

Grading and Staging. **Grade and stage are the most important prognostic factors in prostate cancer.** Grading is performed using the Gleason system, which stratifies prostate cancer into five grades on the basis of glandular patterns of growth. Grade 1 corresponds to well-differentiated tumors in which the neoplastic glands are uniform and round in appearance and are packed into well-circumscribed nodules (Fig. 21.35A). In contrast, grade 5 tumors do not form glands, with tumor cells infiltrating the stroma in cords, sheets, and solid nests (Fig. 21.35C). Other grades fall between

location, but suffers from both low sensitivity and specificity. Patients with clinically advanced prostatic cancer may present with symptoms of urinary obstruction. Typically, a transrectal needle biopsy is required to confirm the diagnosis.

Measurement of serum PSA levels is widely used to assist with the diagnosis and management of prostate cancer but is controversial. PSA is a product of prostatic epithelium and is normally secreted in the semen. It is an androgen-regulated serine protease whose function is to cleave and liquefy the seminal coagulum formed after ejaculation. In normal men, only minute amounts of PSA circulate in the serum. Elevated blood levels of PSA occur in association with localized as well as advanced cancer. However, as a screening test for prostate cancer, PSA measurement has suboptimal sensitivity and specificity.

Table 21.8 Prostate Cancer Gleason Grade Groups

- Grade Group 1 (≤6)
  Only individual discrete well-formed glands
- Grade Group 2 (3 + 4)
  Predominantly well-formed glands with a lesser component of poorly formed, fused or cribriform glands
- Grade Group 3 (4 + 3)
  Predominantly poorly formed/fused/cribriform glands with a lesser component of well-formed glands
- Grade Group 4 (4 + 4/3 + 5/5 + 3)
  Only poorly formed/fused/cribriform glands or predominantly mix of well-formed glands and lack of glands
- Grade Group 5 (4 + 5/5 + 4/5 + 5)
  Lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands

Table 21.9 Pathologic Staging of Prostatic Adenocarcinoma Using the pTNM System

pTNM, AJCC 8th Edition	
pTNM Designation	**Anatomic Findings**
Extent of Primary Tumor (T)	
pT2	Organ confined
pT3	Extraprostatic extension
pT3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
pT3b	Tumor invades seminal vesicles
pT4	Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, or pelvic wall
Definition of Regional Lymph Nodes (N)	
Nx	Regional nodes not accessed
N0	No regional nodal metastases
N1	Metastasis in regional lymph nodes
Definition of Distant Metastases (M)	
M0	No distant metastases
M1	Distant metastases present
M1a	Metastases to distant lymph nodes
M1b	Bone metastases
M1c	Other distant sites

AJCC, American Joint Commission on Cancer.

Pathogenesis

IBD results from a combination of abnormalities in immune regulation, host-microbe interactions, and epithelial barrier functions in genetically susceptible individuals. Over 200 IBD-associated genetic polymorphisms have been identified, but these account for less than 50% of disease risk in Crohn disease and make even smaller contributions to ulcerative colitis. For example, polymorphisms of *NOD2*, the strongest risk gene for Crohn disease, are associated with only a 10-fold increased risk of disease. Further, risk-associated *NOD2* alleles are found in about 35% of Caucasians with Crohn disease, or twice as often as in healthy Caucasians. Thus, while genetic predisposition is important, environmental factors are also critical to pathogenesis. The genetic and environmental elements that contribute to disease can be thought of in terms of immunity, autophagy and cellular stress responses, and host-microbial interactions.

- *Mucosal immunity*. A plethora of immune signaling and regulatory genes including those encoding HLA molecules and cytokines have been associated with IBD. In the case of the latter, polymorphisms in genetic loci that include genes in both proinflammatory, e.g., interferon-γ, and

Ulcerative colitis

cases of pancolitis. Skip lesions are not seen (although
appendiceal or cecal inflammation may occasionally be
in ulcerative colitis that is otherwise limited to the distal

Grossly, involved colonic mucosa may be slightly red
granular or have extensive, broad-based ulcers. There can
abrupt transition between diseased and uninvolved colon
17.36B). Ulcers are aligned along the long axis of the colon
do not typically replicate the serpentine ulcers of Crohn
Isolated islands of regenerating mucosa often bulge into the
to create **pseudopolyps** (Fig. 17.36C), and the tips of
polyps may fuse to create **mucosal bridges** (Fig. 17.36D). Chr
disease may lead to **mucosal atrophy** with a smooth muc
surface that lacks normal folds. Unlike Crohn disease, ulcer
colitis is not transmural. As a result **the colon wall is**
thickened, the serosal surface is normal, and strictu
do not occur. Uncommonly, severe cases are associated
inflammation of the muscularis propria and neuromuscular
tion leading to colonic dilation and **toxic megacolon,**
carries a significant risk of perforation.

Histologic features of mucosal disease in ulcerative colitis
similar to colonic Crohn disease and include inflamma
infiltrates, crypt abscesses (Fig. 17.37A), crypt distortion,
pseudopyloric epithelial metaplasia (Fig. 17.37B). In contra

(C) Inflammatory polyps. (D) Mucosal bridges can join inflammatory polyps.

cryptitis + abscess + pyloric metaplasia

Crohn disease, granulomas are not present, and the diffuse inflammation is generally limited to the mucosa and superficial submucosa (Fig. 17.37C). In severe cases, extensive mucosal destruction may be accompanied by ulcers that extend into the submucosa, but the muscularis propria is rarely involved. Submucosal fibrosis, mucosal atrophy, and distorted mucosal architecture remain as residua of healed disease, but histology may also revert to near normal after prolonged remission. -/s Skip lesions in Crohn's disease

Clinical Features

Ulcerative colitis is a relapsing disorder characterized by attacks of bloody diarrhea with stringy mucoid material, lower abdominal pain, and cramps that are temporarily relieved by defecation. These symptoms may persist for days, weeks, or months before they subside. The initial attack may, in some cases, be severe enough to constitute a medical or surgical emergency. More than half of patients have clinically mild disease, although almost all experience at least one relapse during a 10-year period. Historically, up to 30% of those affected required colectomy within the first 3 years after presentation because of uncontrollable symptoms, but the incidence of colectomy has fallen sharply with improvements in medical management. Colectomy effectively cures intestinal disease in ulcerative colitis, but extraintestinal manifestations may persist.

Before endoscopy → P/D long lasting + not settling
↳ erythematous mucosa

The factors that trigger development of ulcerative colitis in previously healthy individuals are not known. However, infectious enteritis precedes disease onset in some cases. It has been hypothesized that enteritis triggers mucosal immune activation and microbial changes that lead to disease in susceptible individuals. In other patients the first episode of disease is preceded by psychologic stress, which may also be linked to relapse during remission. The initial onset of symptoms has also been reported to occur shortly after smoking cessation in some patients; in these smoking may partially relieve symptoms. Uveitis. Migratory polyarth
erythmatus nodusum

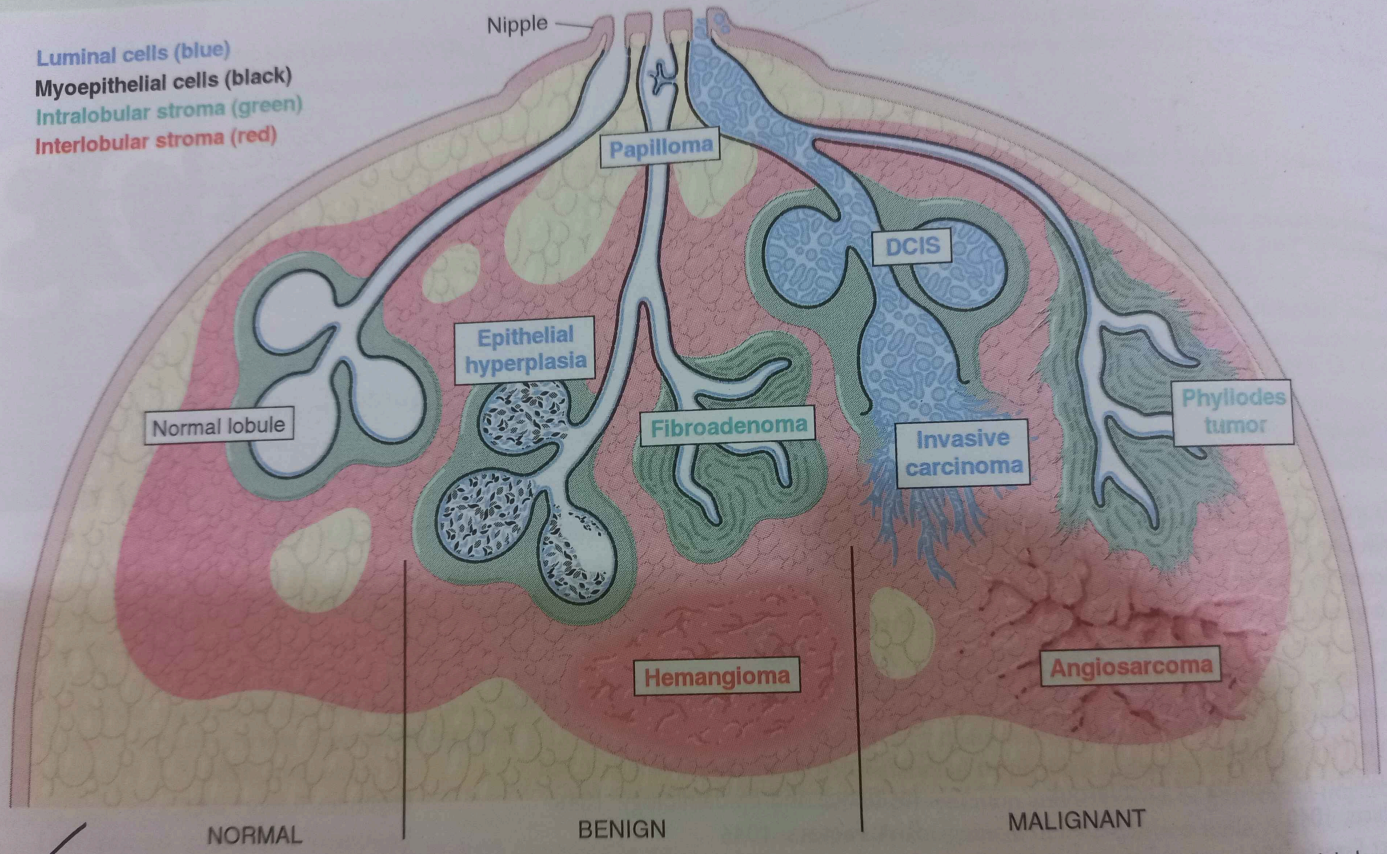


Figure 23.1 The normal cells and structures of the breast, including epithelial cells and myoepithelial cells, intralobular stromal cells and interlobular stromal cells, and large ducts and terminal duct lobular units, can give rise to both benign and malignant tumors. *DCIS*, Ductal carcinoma in situ.

findings in

Nonproliferative Breast Changes (Fibrocystic Changes)

This group includes common morphologic alterations that are often grouped under the term *fibrocystic changes*. To the clinician, the term might mean "lumpy bumpy" breasts on palpation; to the radiologist, a dense breast with cysts, and to the pathologist, benign histologic findings. These lesions are termed nonproliferative to indicate that they are not associated with an increased risk of breast cancer; this name is somewhat unfortunate because some of these changes do involve increased proliferation and may even be associated with clonal genetic aberrations.

MORPHOLOGY

There are three principal nonproliferative morphologic changes: (1) cystic change, often with apocrine metaplasia; (2) fibrosis; and (3) adenosis.

- **Cysts.** Small cysts form by the dilation of lobules and in turn may coalesce to form larger cysts. Unopened cysts contain turbid, semitranslucent brown- or blue-colored fluid (blue-dome cysts) (Fig. 23.5B). Cysts are lined either by a flattened atrophic epithelium or by metaplastic apocrine cells. The latter cells have abundant granular, eosinophilic cytoplasm and closely resemble the normal apocrine epithelium of sweat glands (Fig. 23.5C). Calcifications are common (Fig. 23.5A). Cysts may cause concern when they are solitary and firm. The diagnosis is confirmed by the disappearance of the mass after fine-needle aspiration of its contents.
- **Fibrosis.** Cysts frequently rupture, releasing secretory material into the adjacent stroma. The resulting chronic inflammation and fibrosis contribute to palpable nodularity of the breast.
- **Adenosis.** Adenosis is defined as an increase in the number of acini per lobule. It is a normal feature of pregnancy. In nonpregnant women, adenosis can occur as a focal change. The

acini are lined by columnar epithelial cells, and calcifications are occasionally present within the lumens.

Several other morphologic alterations fall into the category of "nonproliferative" changes. **Lactational adenomas** present as palpable masses in pregnant or lactating women and regress after cessation of breastfeeding. They consist of normal-appearing breast tissue with lactational changes. Their name may be a misnomer, as these lesions may be an exaggerated local response to gestational hormones rather than true neoplasms. **Flat epithelial atypia** is a clonal process characterized by the presence of dilated acini and cysts lined by epithelial cells that display mild cytologic atypia. It is associated with deletions of chromosome 16q and is the earliest morphologically recognizable clonal lesion of the breast. Flat epithelial atypia is often associated with lesions that increase the risk of cancer (e.g., atypical hyperplasia, described later) but has not been shown to increase risk in isolation.

CARCINOMA OF THE BREAST

Breast carcinoma is the most common and deadly malignancy of women globally; each year, 1.7 million women are diagnosed, and one in three of those afflicted die of disease. Although the incidence of breast cancer is four to seven times higher in the United States and Europe than elsewhere, the worldwide incidence and mortality is increasing at an alarming rate, and by 2020 it is estimated that 70% of cases will be in lower income countries. The factors underlying this trend are thought to be social changes that increase breast cancer risk—specifically delayed childbearing, fewer pregnancies, and reduced breastfeeding—combined with a lack of access to optimal health care.

The lifetime risk of breast cancer is 1 in 8 for women living to age 90 in the United States. In 2019, over 260,000 women in the United States were diagnosed with invasive breast cancer, and more than 40,000 women died of the disease—a toll among cancers second only to lung cancer. It is both ironic and tragic that a neoplasm arising in an exposed organ, readily accessible to self-examination and clinical surveillance, continues to exact such a heavy toll.

All breast cancers can be separated into three major groups defined by the expression of two proteins, ER and HER2 (also known as ERBB2). In this chapter, "luminal" cancers are defined as being positive for ER and negative for HER2. "HER2" cancers are defined as cancers overexpressing HER2 and can be either ER-positive or ER-negative. "Triple negative breast cancers" (TNBCs) are cancers that are negative for ER and HER2. These cancers are termed "triple negative" because they also fail to express progesterone receptor (PR), which is under the control of ER. These three groups of cancers differ with regard to patient characteristics, pathologic features, treatment response, metastatic patterns, time to relapse, and outcome and will be discussed in more detail later. However, it is important to note that breast cancer is biologically heterogeneous and that each of these three groups is comprised of numerous clinically important subtypes.

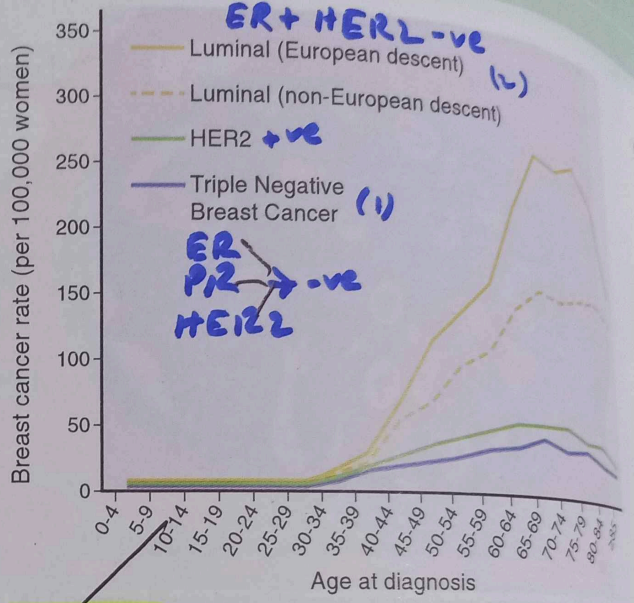


Figure 23.12 Incidence of luminal (ER-positive/HER2-negative), HER2 (HER2-positive), and triple negative (ER-negative/HER2-negative) breast cancers according to age. Rates are per 100,000 women. Triple negative *(solid blue line)* and HER2 *(solid green line)* cancers have a relatively constant incidence after age 40 years. In contrast, luminal cancers show a marked increase in incidence with age. This increase is greatest for women of European descent *(solid yellow line)* and less pronounced for women of other ethnic backgrounds (African, Hispanic, and Asian) *(broken yellow line)*. TNBC, Triple negative breast cancer.

Breast cancer incidence and biology vary with ethnicity. The incidence of breast cancer is highest in women of European descent; in this group, the average age at diagnosis is 63 years, and only 20% of cases are diagnosed at an age younger than 50 years. In contrast, the average age at diagnosis for women of African descent is 59 years, and 35% of cancers are diagnosed at ages below 50. For Hispanic women, the average age at diagnosis is 56, and 20% are diagnosed at ages below 50. The "excess" cancers in women of European descent are mostly of luminal type (Fig. 23.12). Thus, TNBCs and HER2 cancers make up a greater proportion of cancers occurring in other ethnic groups.

The risk of death in those who develop invasive breast cancer has gradually declined in both younger and older

Molecular Classification and Pathogenesis

Several different approaches have been used to subclassify breast cancer into clinically meaningful subtypes. Based on gene expression profiling, breast cancers cluster into three main groups: "luminal" (predominantly ER-positive/HER2-negative), "HER2-enriched" (predominantly HER2-positive), and "basal-like" (predominantly ER-negative/HER2-negative). Because these molecular subtypes correlate reasonably well with ER and HER2 protein expression (Fig. 23.13), which is easily assessed by standard clinical assays, molecular subtyping by expression profiling is not a routine part of breast cancer classification.

of-function mutations in the single normal copy of the gene.

Mutations in *BRCA1* and *BRCA2* are responsible for 80% to 90% of single gene familial breast cancers and about 3% to 6% of all breast cancers. Penetrance, age of onset, and susceptibility to other types of cancers vary according to the specific *BRCA1* and *BRCA2* mutation that is inherited, but most carriers develop breast cancer by the age of 70 years. Mutations in *BRCA1* also markedly increase the risk of ovarian carcinoma, which occurs in 20% to 40% of carriers. *BRCA2* confers a smaller risk for ovarian carcinoma (10% to 20%) but is associated more frequently with male breast cancer. *BRCA1* and *BRCA2* carriers also are at higher risk for other epithelial cancers, such as prostatic and pancreatic carcinoma.

BRCA1 (on chromosome 17q21) and *BRCA2* (on chromosome 13q12.3) are both large genes, and hundreds of different

Table 23.2 Risk Factors for Developing Breast Cancer

Risk Factors	Relative Risk[a]
Female gender Increasing age Germline mutations of high penetrance Strong family history (>1 first-degree relative, young age, multiple cancers) Personal history of breast cancer High breast density	>4.0
Germline mutations of moderate penetrance High-dose radiation to chest at young age Family history (1 first-degree relative)	2.1–4.0
Early menarche (age <12 years) Late menopause (age >55 years) Late first pregnancy (age >35 years) Nulliparity Absence of breastfeeding Exogenous hormone therapy Postmenopausal obesity Physical inactivity High alcohol consumption	1.1–2.0

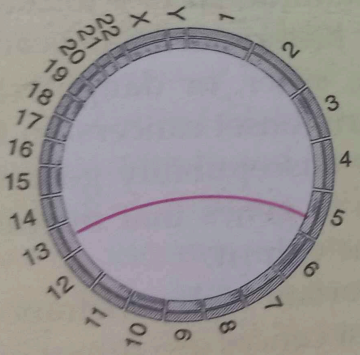
[a]Relative risk is the likelihood of developing invasive carcinoma compared to women without any risk factors.

Molecular Classification

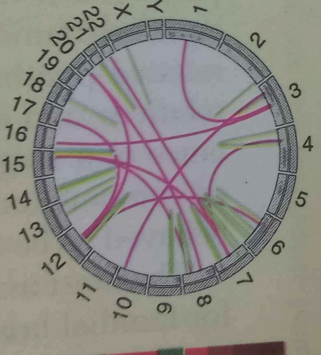
most common

Luminal
(ER-positive, HER2-negative)

Low proliferation

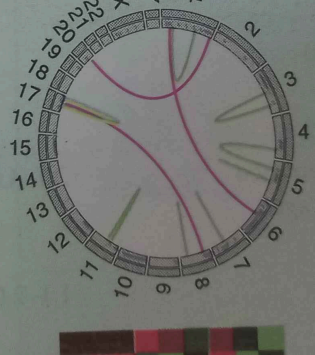


High proliferation



HER2
(HER2-positive)

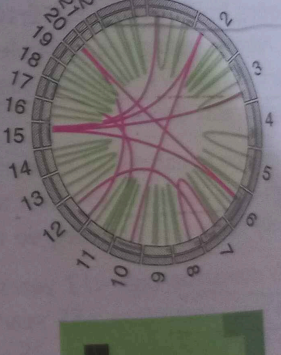
High proliferation



Basal like

Triple Negative Breast Cancer
(ER-negative, HER2-negative)

High proliferation



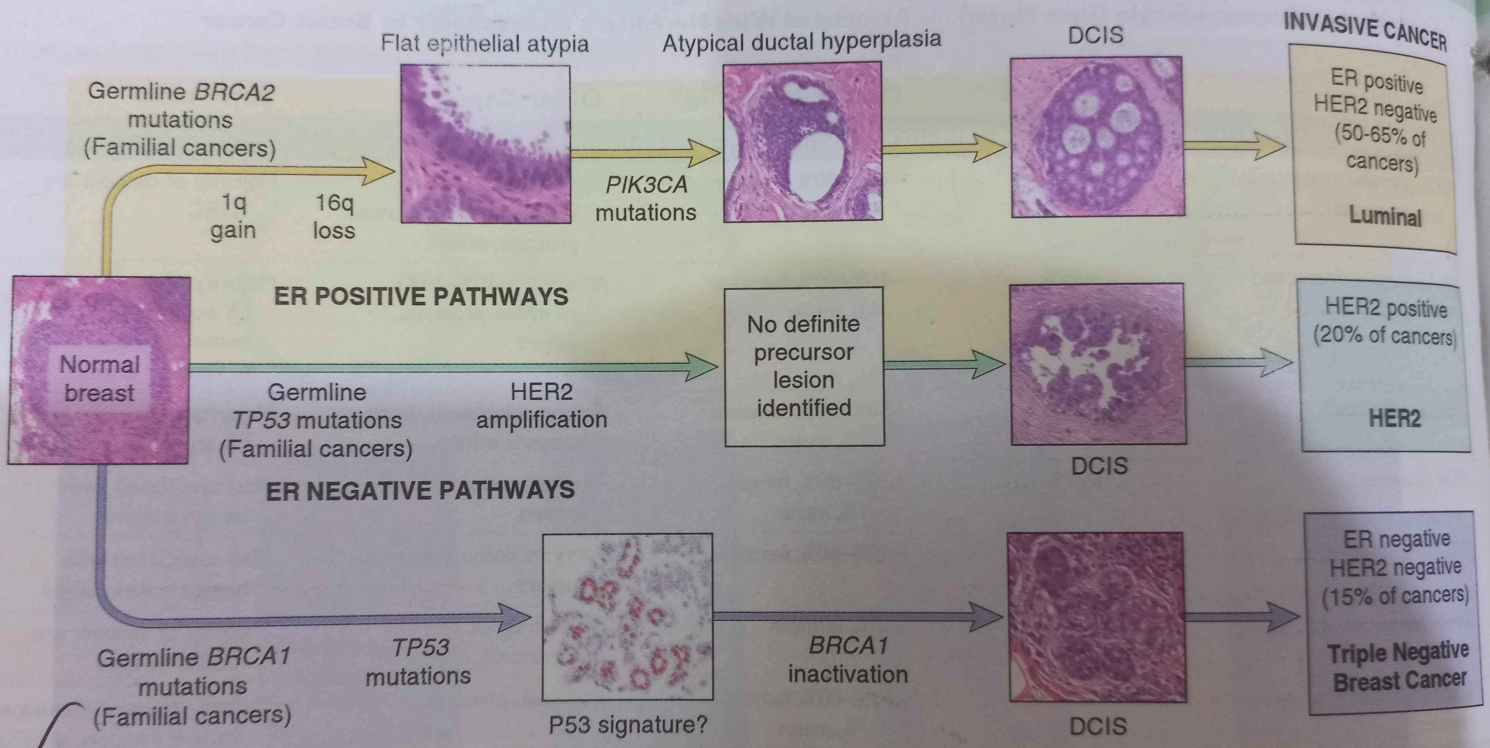


Figure 23.14 Major pathways of breast cancer development. Three main pathways have been identified. The most common pathway *(yellow arrow)* leads to luminal (ER-positive) carcinomas. Recognizable non-obligate precursor lesions include flat epithelial atypia and atypical hyperplasia. A less common pathway *(blue arrow)* leads to triple negative breast cancer (ER-negative/HER2-negative). A possible precursor lesion consisting of morphologically normal cells that overexpress p53 has been identified (analogous to the "p53 signature lesions" for ovarian carcinoma). The third pathway *(green arrow)* consists of HER2-positive cancers. Amplification of HER2 can occur in either ER-positive or ER-negative lesions. A definite HER2-positive precursor lesion has not been identified. See text for other details. *DCIS*, Ductal carcinoma in situ.

the pathology

KEY CONCEPTS

CARCINOMA OF THE BREAST

- Breast cancer is the most common non-skin malignancy in women and the second most common cause of cancer deaths in the United States.
- The most important risk factors for sporadic cancers in women are estrogenic stimulation and age.
- Approximately a quarter to a third of breast cancers are familial, being related to inheritance of genetic variants that increase breast cancer risk.
- High-risk genes associated with familial breast cancer include several involved with DNA repair and genomic stability, most notably *BRCA1*, *BRCA2*, and *TP53*.
- Breast cancers cluster into three major molecular groups, luminal (ER-positive), HER2, and triple negative, each with distinctive biologic and clinical features.
- Luminal cancers are further divided into two groups, A and B, that differ mainly in terms of proliferation, which is low in group A and high in group B.
- HER2 cancers are defined by overexpression of the HER2 receptor, usually due to *HER2* gene amplification, and respond well to HER2 inhibitors.
- TNBCs lack ER and HER2 expression, are often associated with defects in DNA repair or genomic stability (e.g., due to silencing of *BRCA1* or *TP53* mutation), and carry a relatively poor prognosis.

Types of Br

Ductal Carcinoma in Situ. DCIS is a clonal proliferation of epithelial cells limited to ducts and lobules by the basement membrane. Myoepithelial cells are preserved in involved ducts/lobules, although they may be diminished in number. DCIS can spread throughout the ductal system and produce extensive lesions involving an entire sector of a breast.

DCIS is almost always detected by mammography. Without mammography, fewer than 5% of carcinomas detected are in situ lesions, but this rises to 15% to 30% in screened populations. Most are identified as a result of calcifications associated with secretory material or necrosis; less commonly, periductal fibrosis surrounding DCIS results in a mammographic density or creates a vaguely palpable mass. Rarely, DCIS (often of micropapillary or papillary types) produces a nipple discharge or is detected as an incidental finding upon biopsy for another lesion.

MORPHOLOGY

DCIS grows in several architectural patterns, which vary in nuclear grade and the presence and extent of necrosis (Fig. 23.17). Some cases of DCIS have a single growth pattern, but most are comprised of a mixture of patterns. **Comedo DCIS** may occasionally produce a vague nodularity, but more often is detected as clustered or linear and branching areas of calcification (Fig. 23.17A). It is defined by two features: (1) tumor cells with pleomorphic, high-grade nuclei and (2) areas of central necrosis (Fig. 23.17B). **Cribriform DCIS** has rounded (cookie cutter–like) spaces, often filled with calcified secretory material (Fig. 23.17C). **Micropapillary DCIS** produces complex bulbous protrusions without fibrovascular cores (Fig. 23.17D). **Papillary DCIS** produces true papillae with fibrovascular cores that lack a myoepithelial cell layer. Varying degrees of necrosis can be associated with each architectural pattern as well as calcifications, which develop in association with intraluminal secretions or necrosis.

Paget disease of the nipple is a rare manifestation of breast cancer (1% to 4% of cases) that presents as a unilateral erythematous eruption with a scale crust. Pruritus is common, and the lesion may be mistaken for eczema. Malignant cells (Paget cells) extend from DCIS within the ductal system via the lactiferous

LCIS is a risk factor for developing invasive carcinoma in either breast, with a slightly higher risk to the ipsilateral breast. Invasive carcinoma develops at a rate of about 1% per year, similar to that observed for untreated DCIS. However, unlike DCIS, it is unclear if surgical removal of the identified lesion lowers risk. Invasive carcinomas developing in women after LCIS are three-fold more likely to be lobular carcinoma; however, most are of other morphologies. Treatment choices include bilateral prophylactic mastectomy, tamoxifen, or, more typically, close clinical follow-up and mammographic screening.

Invasive (Infiltrating) Carcinoma

Breast carcinoma has a wide variety of morphologic appearances. About one-third can be classified into special histologic types that merit discussion because they have important biologic and clinical associations. We will first cover infiltrating carcinomas of "no special type" (typical ductal carcinomas) and will then discuss those that fall into special categories.

MORPHOLOGY

The majority of invasive breast cancers are ductal adenocarcinomas that are not classified further into a special type. In the absence of mammographic screening, these carcinomas usually present as a mass of at least 2 to 3 cm in size. The mammographic and gross appearance varies widely depending on the stromal reaction to the tumor (Fig. 23.20). They most commonly present as a hard, irregular radiodense mass (Fig. 23.20A, B) associated with a desmoplastic stromal reaction (Fig. 23.20C). When cut or scraped, such tumors typically produce a characteristic grating sound (similar to cutting a water chestnut) due to small, central pinpoint foci or streaks of chalky-white desmoplastic stroma and

occasional foci of calcification. Less commonly, tumors present as deceptively well-circumscribed (Fig. 23.20D, E) masses composed of sheets of tumor cells with scant stromal reaction (Fig. 23.20F) or may be almost imperceptible (Fig. 23.20G, H), being comprised of scattered neoplastic glands or single tumor cells infiltrating otherwise unremarkable fibrofatty tissue (Fig. 23.20I).

Larger carcinomas may invade the pectoralis muscle and become fixed to the chest wall or invade the dermis and cause retraction (dimpling) of the skin. When the tumor involves the central portion of the breast, retraction of the nipple may develop. Rarely, breast cancer presents as metastasis to an axillary lymph node or a distant site before cancer is detected in the breast. In such cases, the primary carcinoma may be small, may be obscured by dense breast tissue, or may fail to produce a desmoplastic response. In most cases, these "occult" primary tumors (which are easily missed by palpation or mammography) can be detected by imaging studies using ultrasound or MRI.

Invasive carcinoma is graded using the Nottingham Histologic Score. Carcinomas are scored for tubule formation, nuclear pleomorphism, and mitotic rate. Grade 1 (well differentiated) carcinomas grow in a tubular or cribriform pattern, have small uniform nuclei, and have a low proliferative rate (Fig. 23.21A). Grade 2 (moderately differentiated) carcinomas have areas where cells grow as solid clusters or single infiltrating cells and show greater nuclear pleomorphism and high numbers of mitotic figures (Fig. 23.21B). Grade 3 (poorly differentiated) carcinomas invade as ragged nests or solid sheets of cells and have enlarged irregular nuclei. A high proliferative rate and areas of tumor necrosis are common in high-grade tumors (Fig. 23.21C).

tion of small, [illegible] of a
s extend into the adjacent duct by pagetoid spread. (B) Immunoperoxidase study
d by E-cadherin–negative LCIS cells spreading along the basement membrane.

uncommon, study of these tumors has also provided important insights into breast cancer pathogenesis.

Lobular carcinoma is the subtype with the clearest association of phenotype and genotype. Like LCIS, most cases show biallelic loss of expression of *CDH1*, the gene that encodes E-cadherin. Lobular carcinomas are dyscohesive, typically infiltrate as single cells, and sometimes fail to produce a desmoplastic response, making it difficult to detect these cancers by palpation and imaging. They also have distinctive patterns of metastatic spread, often involving the peritoneum and retroperitoneum, the leptomeninges (carcinomatous meningitis), the gastrointestinal tract, and the ovaries and uterus. Males and females with heterozygous germline mutations in *CDH1* are at increased risk for developing lobular carcinoma and have a greatly increased risk for signet ring carcinoma of the stomach (Chapter 17).

Carcinomas with medullary pattern are of interest due to the finding that over half of *BRCA1*-associated carcinomas have this appearance (see Table 23.3). Although the majority of carcinomas with medullary pattern are not associated with germline *BRCA1* mutations, hypermethylation of the *BRCA1* promoter leading to downregulation of *BRCA1* expression is observed in 67% of these tumors. Of interest, this subtype has a better prognosis than other poorly differentiated carcinomas. Notably, these tumors also have unusually large number of infiltrating T lymphocytes, suggesting that improved outcomes may be related to a host immune response to tumor antigens.

Many other special histologic types of breast cancer (too numerous to list) have been described. There is much that remains to be learned about the biology and pathogenesis of these tumors, some of which are described below.

Table 21.4 Grading of Noninvasive Urothelial (Transitional Cell) Tumors

WHO/ISUP Grades (2016)
Flat Lesions
• Urothelial proliferation of uncertain malignant potential (flat hyperplasia)
• Urothelial dysplasia
• Urothelial carcinoma in situ
Exophytic Papillary Lesions
• Papilloma
• Urothelial proliferation of uncertain malignant potential (papillary hyperplasia)
• Papillary urothelial neoplasms of low malignant potential
• Papillary urothelial carcinoma, low grade
• Papillary urothelial carcinoma, high grade

ISUP, International Society of Urological Pathology; *WHO*, World Health Organization.