PART III

PATHOLOGY

Cellular injury and inflammation are basic processes underlying all cellular and tissue changes in health and disease. These disease states may result from neoplasms, genetic or metabolic disorders, or from the introduction of exogenous toxic materials. This chapter will focus on the underlying processes causing cellular disease states, as well as the mechanisms by which the cell adapts to its external stimuli.

CELLULAR INJURY AND ADAPTATION

Pathologic processes are manifested at the cellular, organ, and whole body levels. Cell survival depends on the maintenance of homeostasis, a stable internal environment, which requires a constant supply of metabolic energy and active transport processes. Prior to the microscopic appearance of cell injury, critical alterations of basic biochemical pathways must occur. When this homeostatic state is disrupted sublethally, the cell first adapts to the change. If the cell is unable to fully adapt, cell injury ensues. Injury at first causes reversible changes but may progress ultimately to irreversible injury and cell death. The ability of the cell or organ to tolerate injury depends on the severity, duration, and type of insult, as well as the adaptive capacity of the tissue.

A. Causes of cellular injury

1. **Hypoxia**, a lack of oxygen, leads to the inability of the cell to synthesize sufficient ATP. The loss of ATP production results in a failure of the membrane sodium pump, increased glycolysis, and progressive detachment of the ribosomes from the rough endoplasmic reticulum. Hypoxia can result from:
   a. Loss of blood supply (ischemia) due to decreased arterial flow.
   b. A decrease in the oxygen-carrying capacity of the blood due to anemia or carbon monoxide poisoning; CO produces a stable complex with hemoglobin, blocking O_2 transport.

In a Nutshell

   i. Poisoning of the enzymes of oxidative phosphorylation by toxins such as cyanide, rotenone, and antimycin A.

2. **Chemical injury** can lead to a disruption of the physical structure of the cell or to a breakdown of the biochemical processes of the cell. For example, chemicals can alter membrane permeability or block the action of an enzyme by binding either to the enzyme or to its cofactor.
3. **Physical injury** such as crush injuries, gunshot wounds, burns, frostbite, radiation, and pressure changes can lead to cell death and inflammation.
4. **Infections.** Virtually all aspects of cellular metabolism are affected by biologic agents infecting the cell.
   a. **Viruses** invade cells, commandeer synthetic machinery, and may release proteins that are toxic to host cells and cellular metabolism.
   b. **Bacteria** release exotoxins (e.g., phospholipases) or produce endotoxins (e.g., lipopolysaccharides) from their cell walls. Both cause cell injury and possibly death.
   c. Viruses, bacteria, parasites, and fungi can cause the host to initiate a cellular (e.g., macrophages, T cells) or humoral (e.g., IgG, IgM) immunologic reaction to the invader.
5. **Immunologic reactions.** Although the immune response is tightly regulated, it can result in injury as manifested by an anaphylactic reaction, or autoimmune diseases. Direct injury to an organism can result from the absence of an immune reaction.
6. **Genetic disorders,** which can present as biochemical abnormalities, can lead to the accumulation of toxic products or the inability to metabolize various compounds due to enzyme defects, such as cystic fibrosis, sickle cell anemia, and Tay-Sachs disease. Acquired genetic defects (mutations) in genes that govern cell growth and differentiation (oncogenes) may lead to the development of cancer.
7. **Nutritional or vitamin deficiencies,** hypervitaminosis, inadequate calorie intake, or inadequate protein intake may all lead to cellular atrophy or even death.
8. **Aging** can lead to the breakdown of normal cellular machinery, ultimately leading to death of the cell. Some cells, such as gut epithelium or bone-marrow stem cells, continuously renew, whereas others, such as neurons and skeletal muscle, may age and die.

B. Cellular changes during injury

1. **Cloudy swelling** results from disruption of the integrity of the plasma membrane. By inhibiting oxidative phosphorylation, hypoxia results in decreased ATP production. The loss of ATP affects the ouabain-ATPase, causing a failure of the membrane Na^+ pump. Disruption of the cells' osmotic pumps leads to an influx of Ca^{2+} and water and an

efflux of K^+. The cells swell and the endoplasmic reticulum becomes dilated. Although initially reversible, ultimately injury to the cell becomes irreversible if ATP is not restored.

2. **Membrane damage** plays a central role in the pathogenesis of irreversible injury. The membrane can be damaged from the loss of membrane phospholipids, breakdown of the cytoskeleton, production of toxic oxygen intermediates, and the production of lipid products, which by themselves can have a detergent-like effect on the plasma membrane.
3. **Dilation and swelling** of the endoplasmic reticulum lead to detachment of ribosomes, which leads to a decrease in protein synthesis.
4. **Mitochondrial swelling** results in an accumulation of Ca^{2+}, which uncouples oxidative phosphorylation.
5. **Lysosomes rupture,** releasing their digestive enzymes into autophagic vacuoles or into the cytosol.
6. **Nuclear changes** proceed from chromatin clumping to pyknosis with degeneration and condensation of nuclear chromatin. This can be followed by karyorrhexis (i.e., nuclear fragmentation) or karyolysis (i.e., dissolution of the nucleus).

C. **Expected pathologic changes in cell death and injury**

1. **Coagulative necrosis** is the most common form of necrosis in cells without large numbers of lysosomes. The cell is converted into a homogeneous, eosinophilic mass with loss of the nucleus but preservation of cellular shape. Coagulative necrosis typically occurs after sudden ischemia, thermal injury, or toxin injury. The heart is the most common example of an organ undergoing coagulative necrosis following an injury.
2. **Liquefaction necrosis** results from cellular destruction by hydrolytic enzymes involved in autolysis and heterolysis. Typically, liquefaction necrosis occurs in brain infarcts and pancreatic necrosis. Liquefaction by leukocytic enzymes is called suppuration, and the resultant fluid is called pus.
3. **Caseous necrosis** is a combination of coagulation and liquefaction necrosis, which produces tissue that is grossly soft, friable, and "cheese-like." Caseous necrosis is characteristic of tuberculosis, some granulomas and fungal infections, and the center of certain malignancies.
4. **Enzymatic fat necrosis** is caused by the action of lipases on fatty tissue. It is characteristic of tissues adjacent to acute pancreatic necrosis.

In a Nutshell

Cellular changes during injury:

- *Cloudy swelling from cell membrane disruption*
- *Membrane damage*
- *Endoplasmic reticulum swelling*
- *Mitochondrial swelling*
- *Lysosomal swelling*
- *Nuclear changes*
- *Apoptosis*

Note

Squamous carcinomas often necrose in the center of invasive nodules due to their rapid growth.

5. **Gummatous necrosis** is seen in the late stage of syphilis; grossly, it differs from coagulative and liquefactive necrosis by its gelatinous appearance.
6. **Apoptosis** is a specialized form of programmed cell death characterized by:
   a. Chromatin condensation and formation of cytoplasmic membrane blebs (cell surface deformities caused by cytoskeletal disruption)
   b. Breakdown of DNA into nucleosome-sized fragments
   c. RNA and protein synthesis
   d. A minimal inflammatory response

D. **Other cellular alterations during injury**

1. **Intracellular accumulations**
   a. **Lipids**
      (1) Triglycerides (e.g., fatty change in liver cells)
      (2) Cholesterol (e.g., atherosclerosis)
      (3) Complex lipids (e.g., sphingolipid accumulation)
   b. **Proteins** (e.g., renal epithelial cells in proteinuria)
   c. **Glycogen and complex carbohydrates** (e.g., glycogen storage diseases, mucopolysaccharidoses)
   d. **Pigments** are colored substances, either normal cellular constituents or abnormal constituents that lead to deposits.
      (1) **Exogenous pigments.** Anthracotic pigmentation of the lung is secondary to inhalation of carbon dust.
      (2) **Endogenous pigments.** Lipofuscin (wear and tear pigment), melanin, hemosiderin, and bilirubin may all accumulate either in the cells that make them or in macrophages.
2. **Calcification**
   a. Dystrophic calcification appears in areas of necrosis due to precipitation of calcium phosphate in low pH.
   b. Metastatic calcification caused by hypercalcemia (malignancy, hyperparathyroidism) is due to precipitation of supersaturated solutions of calcium phosphate.

E. **Adaptive cellular responses to injury**

1. **Atrophy** is a loss of cells or cell substances, resulting in a decrease in cell and organ size. The causes of atrophy are disuse, ischemia, aging, malnutrition, and lack of hormonal or neural stimulation. Atrophy of an organ may be due to loss of cells, a decrease in cell size, or both.
2. **Hypertrophy** is an increase in both cell and organ size. It is due to an increased mechanical demand, such as that seen in striated muscle of weight lifters or cardiac muscle in hypertension. It can also be seen with increased endocrine stimulation. Hypertrophy can be physiologic or pathologic. Hypertrophy of an organ may be due to an increase in

cell number (lactating breast), an increase in cell size (skeletal muscle), or both (many cancers).

3. **Hyperplasia** is an increase in the number of cells. It is often associated with hypertrophy. Some cell types are unable to exhibit hyperplasia (e.g., nerve, cardiac, skeletal muscle cells). It can be physiologic or pathologic. Physiologic causes include compensatory (e.g., after partial hepatectomy), hormonal stimulation (e.g., breast development at puberty), or antigenic stimulation (e.g., lymphoid hyperplasia).
4. **Metaplasia** is a reversible change of one cell type to another, usually in response to irritation. It has been suggested that the replacement cell is better able to tolerate the environmental stresses. For example, bronchoalveolar epithelium undergoes squamous metaplasia in response to chronic irritation of tobacco smoke.

INFLAMMATION AND REPAIR

Inflammation enables the body to resist infection. Inflammation occurs in response to injury, which can result from hypoxia, chemicals, drugs, physical agents, microbial agents, immunologic reactions, nutritional imbalances, genetic defects, or aging. The acute inflammatory response occurs over seconds, minutes, hours, and days after the initial insult, whereas the chronic inflammatory response can continue for weeks, months, and even years after the primary injury.

A. Acute Inflammation

1. **Cardinal signs of inflammation**
   a. Rubor (redness)
   b. Calor (heat)
   c. Tumor (swelling)
   d. Dolor (pain)
   e. Loss of function
2. **Pathophysiology.** The acute inflammatory response begins with changes in the vasculature. There is a transient vasoconstriction followed by vasodilatation of the affected area. Ultimately, the blood flow slows as the vasculature becomes leaky. First, there is a **transudate** of comparatively protein-free fluid into the extravascular space, followed by an **exudate** of proteins, cells, and plasma, depending on the severity of the injury.
   a. **Vascular changes**
      (1) There is a transient vasoconstriction of arterioles followed by vasodilatation with opening of supplementary capillary beds, which leads to an increased blood flow. Vasodilatation can be mediated by histamine, bradykinin, and prostaglandins.
      (2) Increased vascular permeability or vascular leakage is the result of endothelial cell and pericyte contraction, transiently affecting

Note

Transudate is a protein-free fluid buried to the extravascular space. **Exudate** is fluid containing proteins and cells buried to the extravascular space. Transudate is usually due to pressure differences between the vasculature and extracellular space (e.g., pulmonary edema in CHF). Exudate is usually due to increased permeability of endothelial cell barriers and chemotactic factors attracting white blood cells (e.g., lung cancer, infection, trauma).

venules; direct endothelial cell injury, affecting all microvessels; leukocyte-dependent injury to vessels; and regenerating endothelium.

(3) Chemical mediators of increased vascular permeability include the vasoactive amines, histamine and serotonin, which are stored in the granules of mast cells, basophils, and platelets. They act exclusively on venules (not capillaries). The complement components C3a and C5a are both anaphylatoxins and cause the release of more vasoactive amines. Bradykinin, an end product of the kinin cascade, can also cause pain. Leukotrienes (i.e., LTC_4, LTD_4, LTE_4) also individually produce increased vascular permeability.

(4) Slowing of the circulation, resulting from increased blood viscosity due to extravasation of fluid, allows leukocytes to marginate, roll, and then adhere to endothelium via specific receptors. These include the integrin family of glycoproteins (LFA-1) on the neutrophil and intercellular adhesion molecule (ICAM-1) on the endothelial cell. Adhesion is Ca^{2+}-dependent.

(5) Leukocytes emigrate from the vasculature. The marginated, adherent cells extend pseudopods between the endothelial cells. They then move between the endothelial cells, migrating through the basement membrane, toward the inflammatory stimulus.

(6) **Chemotaxis** is the attraction of cells toward a chemical mediator that is released in the area of inflammation. Important chemotactic factors include bacterial products, such as *N*-formylmethionine (a prokaryotic product), LTB_4, many factors liberated from leukocytes, and IL-8. The two most important chemotactic factors for neutrophils are C5a and IL-8.

(7) **Phagocytosis.** Neutrophils and macrophages engulf and destroy foreign material. The particle to be phagocytosed can be coated with serum opsonins, such as IgG and C3b. These facilitate phagocytosis by allowing the particle to bind to complement receptor 1 (CR1) and the Fc receptor on the surface of the cell. After the particle is engulfed, the phagocytic vacuole fuses with a lysosome, forming a phagolysosome complex. The lysosome disgorges its contents into the fused vacuole. The offending particle (e.g., a bacterium) is then broken down via the action of reactive oxygen species, acid hydrolases, neutral proteases, and lysozyme.

b. **Chemical mediators of inflammation.** Metabolites of arachidonic acid metabolism mediate many of the important aspects of the inflammatory response. The processing of arachidonic acid occurs via two pathways:

(1) **Cyclooxygenase pathway**, leading to prostaglandin formation: certain prostaglandins (i.e., PGI_2, PGD_2, PGE_2, $PGF_{2\alpha}$) mediate vasodilatation and pain.

(2) **Lipoxygenase pathway**, leading to leukotriene synthesis: certain leukotrienes (i.e., LTB_4) are involved in chemotaxis and increasing vascular permeability.

c. **Actions of anti-inflammatory drugs**

(1) **Aspirin and the NSAIDs** exert their anti-inflammatory effect by inhibiting prostaglandin synthesis (cyclooxygenase).

(2) **Corticosteroids** most likely act by preventing the transformation of phospholipid into arachidonic acid by inhibiting the membrane enzyme phospholipases. Therefore, they inhibit both prostaglandin and leukotriene synthesis. Corticosteroids also impair leukocyte migration toward an inflammatory focus and stabilize lysosomal membranes.

8. **Chronic inflammation.** Acute inflammation can be resolved completely or progress to chronic inflammation. The activated monocyte-macrophage plays a central role in chronic inflammation. It secretes enzymes such as neutral proteases (i.e., elastase, collagenase) and acid hydrolases (i.e., phospholipases), which can digest connective tissue. The activated monocyte-macrophage acquires the capability in a few days of secreting various plasma proteins, such as complement components C1 to C5, reactive metabolites of oxygen, leukotrienes, prostaglandins, cytokines (i.e., IL-1, tumor necrosis factor), as well as various growth factors (i.e., fibroblast growth factor, epidermal growth factor, platelet-derived growth factor). **Chronic inflammation occurs** if the offending agent cannot be removed (e.g., nondegradable foreign bodies, parasites) or if the tissue is subjected to repeated episodes of acute inflammation, such as recurrent cholecystitis.

a. **Composition of the cellular infiltrate**

i. Cellular infiltrate is primarily mononuclear with proliferation and maturation of monocytes into macrophages (e.g., interferon-γ).

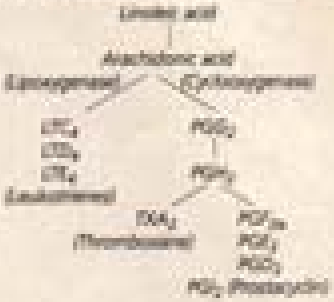
ii. Fibroblasts are recruited and proliferate; small vessels proliferate, and subsequent collagen deposition results in fibrosis and scarring.

iii. Lymphocytes, plasma cells, and eosinophils are also present in sites of chronic inflammation.

iv. Neutrophils are occasionally continuously attracted in chronic inflammation associated with pus.

2. **Chronic granulomatous inflammation** occurs if a substance cannot be completely removed (e.g., asbestos, silica, tuberculous bacilli) or if a cell-mediated reaction is initiated against an agent. It is most frequently seen in tuberculosis (caseating granulomas), sarcoid (non-caseating granulomas), or with foreign bodies. Granulomas are also

Bridge to Biochemistry



Note

The main cellular component in acute inflammation is the neutrophil; the main cellular component in chronic inflammation is the monocyte-macrophage.

seen in Gaucher's disease, gout, rheumatoid arthritis, and in fungal and parasitic infections.

a. **Granulomas** are small (0.5–2 mm) and consist of aggregations of macrophages, which can be transformed into epithelioid cells with occasional multinucleated giant cells. They are often surrounded by lymphocytes as well as plasma cells and fibroblasts.

b. Epithelioid cell-modified macrophages with abundant eosinophilic cytoplasm contain large amounts of endoplasmic reticulum, Golgi, and vesicles, which indicate a secretory rather than a digestive function.

C. **Repair.** Almost as soon as the inflammatory process begins, the repair of the damaged cells and tissues starts. Repair involves two separate processes: regeneration of the damaged tissue by cells of the same type and replacement by connective tissue. Together they constitute wound healing.

1. **Regeneration.** Different tissues have different regenerative capacities.
   a. **Labile cells** regenerate throughout life. This cell type includes surface epithelial cells (such as those lining the skin), oral cavity, vagina, cervix, hematopoietic, splenic, and lymphoid cells, and the mucosal cells of all excretory organs.
   b. **Stable cells** replicate at a low level throughout life but are dormant unless stimulated by some initiating event; these include the liver, pancreas, kidney, vascular endothelium, and smooth muscle.
   c. **Permanent cells** cannot replicate and include neurons, skeletal muscle, and cardiac muscle.

2. **Replacement** of a damaged area by connective tissue involves migration and proliferation of fibroblasts into the damaged area, deposition of extracellular matrix, formation of new blood vessels, and reorganization of the connective tissue into a scar. Macrophages are usually initially present as the area is being remodeled. Neutrophils, eosinophils, lymphocytes, and mast cells can also be present.

3. **Wound healing** involves collagen synthesis and degradation. Various growth factors (such as PDGF, transforming growth factors (TGF) α and β, FGF) and cytokines (such as tumor necrosis factor [TNF] and IL-1) stimulate collagen synthesis. Collagen can be broken down by various proteases such as collagenase, which can be secreted by macrophages and neutrophils migrating into the damaged area. Wound healing may be prolonged by foreign bodies, infection, ischemia, diabetes, malnutrition, or scurvy.
   a. **Primary union by first intention** occurs when there has been little surrounding tissue damage. The wound is clean, and the wound edges are closely approximated.
      (1) The wound fills with clotted blood, forming a scab.
      (2) Neutrophils line the wound edge within 24 hours.
      (3) A thin, continuous epithelial cover appears within 24–48 hours.

Clinical Correlate

Scurvy is caused by vitamin C deficiency since vitamin C is a necessary cofactor for the cross-linking of collagen. Scurvy can result in impaired wound healing because the cross-linking of collagen is essential for its tensile strength.

(4) Macrophages replace neutrophils, while granulation tissue fills in the wound; the epithelial covering thickens.

(5) By day 5, collagen fibers laid down by fibroblasts cross the incision following fibrin and fibronectin matrices.

(6) Collagen continues to be synthesized, and the scar becomes increasingly avascular.

(7) Full maturation of a scar requires up to one year.

b. **Secondary union by secondary intention** occurs when the two skin edges are not in contact. It requires larger amounts of granulation tissue to fill in the defect; it is characterized by significant wound contraction and is mediated by myofibroblasts.

CIRCULATORY DISTURBANCES

A. **Edema** is the presence of excess fluid in the interstitial space. It can be localized or generalized and is caused by:

1. Increased hydrostatic pressure due to venous thrombosis (local) or congestive heart failure (generalized).
2. Hypoalbuminemia, resulting in a decreased colloid osmotic pressure.
3. Lymphatic obstruction.
4. Renal retention of salt and water.

B. **Congestion** is an excessive amount of blood in an area secondary to diminished venous outflow. With increasing stasis, the area acquires a purplish hue.

C. **Thrombosis** is the solidification of a formed mass of blood components. It requires the interaction of all cells within the vasculature and endothelial cells, as well as circulating elements, such as platelets and the clotting cascade. Clotting is a balance between two opposing forces: those favoring the formation of a stable thrombus and those factors causing breakdown of the clot.

1. **Pathophysiology of thrombosis formation.** Injury to the vascular endothelium causes factors that paradoxically facilitate and inhibit thrombosis.
   a. **Facilitation**
      (1) Exposure of tissue factor from injured cells activates factor VII.
      (2) Exposure of thrombogenic subendothelial collagen activates factor XII.
      (3) Platelets deposit and aggregate due to collagen exposure and generation of thrombin.
   b. **Inhibition**
      (1) Increased prostacyclin (PGI_2) and nitryl (NO_2) inhibit platelet aggregation.
      (2) Synthesis of plasminogen activator promotes fibrinolytic activity.

CLINICAL CORRELATE

Congestion may be seen in purple-discolored legs with chronic venous stasis due to circulatory failure.

CLINICAL CORRELATE

Classic hemophilia (hemophilia A) is caused by a deficiency or reduced activity of factor VIII. It is characterized by excessive bleeding following trauma and bleeding into the joints (hemarthrosis). PTT is prolonged, but bleeding time and PT are normal.

A deficiency in von Willebrand's factor causes von Willebrand's disease, characterized by spontaneous bleeding from mucous membranes and excessive bleeding following trauma. Bleeding time is prolonged, but platelet count and PT are normal. PTT is also prolonged because von Willebrand's factor serves as a carrier for factor VIII; von Willebrand's disease therefore results in a functional factor VIII deficiency.

2. **Sequence of events in thrombogenesis**
   a. Endothelial injury exposes subendothelial collagen.
   b. Platelets adhere, requiring von Willebrand factor and factor VIII; stimulation of the clotting cascade requires thromboplastin release from the endothelium (tissue factor).
   c. Platelets degranulate, releasing ADP and fibrinogen, and synthesize thromboxane A_2.
   d. Platelets aggregate, forming a temporary hemostatic plug. Later, there is formation of a secondary plug enmeshed in fibrin, requiring ADP, thrombin, and thromboxane.
   e. The thrombus retracts and organizes with proliferation of capillaries, fibroblasts, and infiltration by neutrophils and macrophages.
   f. Canalization or formation of a new path for blood flow through the thrombus is accomplished by endothelial growth over the surface and through the thrombus, resulting in incorporation of the thrombus into the vessel.
3. **Additional factors favoring thrombogenesis**
   a. Endothelial injury releases abundant tissue factor.
   b. Changes in blood flow cause turbulence and stasis. Predisposing factors are sites of turbulence (i.e., vessel bifurcations, valves, past stenoses), atherosclerotic plaques, trauma, certain malignancies, and inflammation.
   c. States of hypercoagulability where there is increased thrombogenesis due to an alteration of the clotting mechanisms (e.g., nephrotic syndrome where more inhibitors than activators are lost).
4. **Morphology of the thrombus.** The head of the thrombus is composed of platelets and fibrin. The tail of the thrombus grows downstream. It consists of red blood cells and fibrin. Lines of Zahn are alternating layers of fibrin, platelets, and RBCs within the tail of the thrombus.
   a. **Mural thrombi** are adherent to the vessel wall. They are not occlusive and affect large vessels, such as the heart and aorta.
   b. **Occlusive thrombi** restrict blood flow most frequently in coronary, cerebral, femoral, iliac, popliteal, and mesenteric vessels. They often overlie an atherosclerotic plaque. Arterial thrombi are often occlusive and result in infarct (e.g., myocardial infarct, stroke), whereas venous thrombi rarely occlude vessels and tend to embolize.
   c. **Postmortem clot** can be differentiated from a thrombus by the absence of lines of Zahn and by its appearance as a rubbery coagulated mass that is not attached to the vessel wall but forms a cast of the wall.
5. **Disseminated intravascular coagulation (DIC)** begins with extensive formation of thrombi in the microcirculation, causing consumption of components necessary for hemostasis (i.e., platelets, fibrin, coagulation factors) and activation of the fibrinolytic pathways, leading to a bleeding diathesis. DIC is associated with a diverse array of clinical circ-

CLINICAL CORRELATE

DIC can be diagnosed by the presence of fibrin split products in the blood, low platelets, and prolonged PT and PTT.

conditions, such as amniotic fluid emboli, preeclampsia, Gram-negative sepsis, cancer, trauma, surgery, and burns.

D. **Embolism** is the occlusion of a vessel (either artery or vein) by a mass. Often they are thrombi that have dislodged from their site of formation and have lodged in a distal site occluding blood flow.

1. **Pulmonary emboli** often originate from deep vein thrombosis in the lower legs and less often from deep pelvic veins.
2. **Systemic emboli** are formed in the arterial circulation; most arise in the heart.
3. **Paradoxical emboli** cross over from the right side to the left side of the heart through septal defects and gain access to the systemic circulation.
4. **Other types of emboli** include gas emboli (e.g., Caisson's disease), fat emboli (e.g., associated with bone fractures), amniotic fluid emboli, bone chips, and tumor cells.

E. **Infarction.** If an artery or vein becomes occluded, then the acute loss of blood supply to the area can result in ischemic necrosis of the tissue. Most infarcts (99%) result from thrombosis or embolic occlusion of an artery or vein. Clinically, common sites of infarction are myocardial, pulmonary, brain, and intestinal tissue. Factors that affect the development of an infarct include:

1. Vascular supply, including collateral circulation
2. Rate of occlusion
3. Vulnerability of the tissue to hypoxia
4. Oxygen-carrying capacity of the blood

F. **Shock** is characterized by vascular collapse. There is a greatly decreased perfusion of both cells and tissue due to reduced blood volume, cardiac output, or vascular tone. Cellular injury is initially reversible, but if anoxia persists, cellular injury becomes progressive, leading to the death of cells and eventually the patient.

1. **Cardiogenic shock** results from myocardial infarction (pump failure).
2. **Hypovolemic shock** results from reduced blood volume from any cause (hemorrhage, fluid loss).
3. **Septic shock** results from bacterial infection, such as Gram-negative septicemia, which causes the release of vasodilatory mediators into the vasculature.
4. **Neurogenic shock** results from anesthesia or spinal cord injury.

NEOPLASMS

A neoplasm is a mass of abnormal tissue whose growth exceeds and is uncoordinated with that of the normal tissues and continues in the same excessive state after cessation of the stimuli that evoked the change.

Note

An embolus is most likely a thrombus that has dislodged from its site of formation and has travelled to another site.

A. **Definitions**

1. **Anaplasia** is loss of cell differentiation and tissue organization.
2. **Metaplasia** is replacement of one type of adult cell or tissue by another not normally present in that site.
3. **Desmoplasia** is excessive fibrous tissue formation in tumor stroma.
4. **Dysplasia** is abnormal atypical cellular proliferation.
5. **Carcinoma** is malignant tumor of epithelium.
6. **Carcinoma *in situ*** is malignant tumor of epithelium, which shows no invasion of underlying tissue.
7. **Sarcoma** is nonepithelial (mesenchymal) malignant tumor.
8. **Metastasis** is secondary, discontinuous malignant growth, such as a lung metastasis of a colon carcinoma.
9. **Grade** is an estimate of the cytologic malignancy of a tumor, including the degree of anaplasia and number of mitoses. Nuclear size, chromatin content, nucleoli, and nuclear-to-cytoplasmic ratio are all used.
10. **Stage** is the clinical estimate of the extent of spread of a malignant tumor. Low stage means a localized tumor. Stage rises as tumors spread locally then metastasize.

B. **Tumor markers**

1. **Alpha-fetoprotein (AFP)** is expressed in hepatoma, embryonal cell tumor of the testis, and malignant teratoma.
2. **Carcinoembryonic antigen (CEA)** can be seen in any tumor derived from gut epithelium or in intra-abdominal inflammation (e.g., ulcerative colitis). It is most often elevated in colon and pancreatic cancers. It is also elevated in smokers in the absence of tumor and may be elevated in some carcinomas of the lung.
3. **Beta human chorionic gonadotropin (hCG)** is elevated in choriocarcinoma, hydatidiform mole, and germinoma. It is also elevated in pregnancy, forming the basis of the common pregnancy test.
4. **Prostatic acid phosphatase** elevations are seen in prostate tumors extending outside the capsule of the prostate (stage C or D).
5. **Prostate-specific antigen (PSA)** is also elevated in prostate cancer and in some cases of benign prostatic hyperplasia.
6. **CA-125** is elevated in ovarian cancer.

C. **Ectopic hormone production** causes a paraneoplastic syndrome.

1. **Carcinoid tumors** may produce 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin.
2. **Oat cell tumors of the lung**, derived from neuroendocrine cells, may produce ectopic hormones, most frequently antidiuretic hormone (ADH) or adrenocorticotropic hormone (ACTH). Many other small

ON A NUTSHELL

- Carcinoid tumor → 5-HIAA
- Oat cell tumor → ADH, ACTH
- Squamous cell tumor → PTH

peptide hormones associated with oat cell carcinoma have been described.

3. **Squamous cell carcinoma of the lung** sometimes produces hypercalcemia by releasing a **PTH-like molecule**.

D. **Metastasis**

1. **Multiple routes to metastasis**
   a. **Body cavities and surfaces** (e.g., peritoneal, pleural, pericardial) may be directly seeded by tumor cells floating in fluid such as ascites or a pleural effusion.
   b. **Hematogenous spread** is also quite common for most neoplasms, making the lung a common site for metastases of all kinds of cancer.
   c. **Lymphatic spread** is the most common route of spread for epithelial carcinomas.
   d. **Transplantation via mechanical manipulation** (e.g., surgical incision, needle tracts) may occur but is relatively rare.

2. **Sequence of lymphohematogenous spread**
   a. Penetration of blood or lymphatic vessels requires detachment from neighboring cells, amoeboid movement, digestion of basement membranes, and crawling between endothelial cells.
   b. Release and embolization of tumor cells requires detachment from vessel walls and other tumor cells.
   c. Adherence of tumor cells, which become anchored in fibrin mesh, requires cell surface receptors that bind to extracellular matrix proteins.
   d. Penetration of vessel walls in the metastatic site (i.e., lung) also requires altered adhesion molecules and amoeboid movement.
   e. Once tumor cells have crawled out of blood vessels in a new organ, they must survive in a new environment of hormones dissimilar to the cell's original environment. Though millions of cells may be shed from a primary tumor, successful metastasis is relatively rare.

E. **Theories of carcinogenesis**

1. **Somatic mutation** refers to **structural changes in the gene or chromosomal level** that occur spontaneously or in response to carcinogens after germ cell line maturation. Somatic mutation produces neoplasms that are **more often monoclonal** than polyclonal.

2. **Aberrant differentiation** in cancer cells occurs in the **absence of structural changes indicating abnormalities of gene regulation** affecting growth and differentiation. This may occur regardless of the stimulus inciting malignant change: chemical, viral, radiation, or spontaneous.

3. **Viral infection** and **consequent integration of viral DNA into the host genome** may lead to malignant transformation (e.g., hepatitis B

genome has been found in hepatoma cells, and RNA retroviral DNA copies have been found in some lymphomas).

4. **Cell selection.** Carcinogens favor the expression of a pre-existing population of transformed cells that would not be clinically evident otherwise.

F. **Cytology** is the analysis of individual or clumps of cells to determine the degree of anaplasia. Cytology may be used to analyze cells from any source: uterine, cervix, sputum, pleural fluid, ascites, fine needle aspiration, joint fluid, and others. Besides staining cells on slides, cells may be analyzed by flow cytometry, a procedure in which fluorescent antibodies are reacted with cells to determine the surface markers they express. This is most often done in the case of lymphomas and leukemias. Karyotype analysis of tumors is also helpful in showing which chromosomal regions of tumors are abnormal. This helps in classification.

G. **Carcinogenic agents**

1. **Chemical carcinogens** may be divided into two broad groups:
   a. **Direct-acting chemical carcinogens** are mutagens that cause cancer directly, usually by modifying DNA (e.g., alkylating agents).
   b. **Procarcinogens** require metabolic conversion to form active carcinogens. Many strong chemical agents are procarcinogens.
      (1) They require an **initiating agent** and a **promoter**. Exposure to the initiating agent results in an irreversible cellular change, which allows the cells to produce a tumor. The promoter is an agent that increases the tumorigenic process in initiated cells. Cells may not be tumorigenic without previous exposure to an initiating agent. An initiator may cause a mutation, while a promoter causes increased growth rates.
      (2) Potential carcinogens are screened by the Ames test, which detects any mutagenic effects on bacterial cells in culture. Mutagenicity in vitro correlates well with carcinogenicity in vivo.
2. **Radiation**
   a. **Ultraviolet radiation** produces pyrimidine dimers in DNA, leading to transcriptional errors.
   b. **Ionizing radiation** by x-rays and gamma rays causes chain breaks in nucleic acids. When critical genes are mutated, cancer may result.
3. **Oncogenic viruses**
   a. **RNA oncogenic viruses** produce a viral-coded reverse transcriptase allowing synthesis of DNA from a viral RNA template. The DNA can then be integrated into the host genome.
   b. **DNA oncogenic viruses** include papovavirus, adenovirus, and herpesvirus. Infection does not necessarily result in the release of

infectious virus. For example, EBV is associated with Burkitt's lymphoma in Africa; HBV is associated with hepatocellular carcinoma. In both cases, viral DNA integrates into the host genome.

4. **Loss of immune regulation.** In patients with immune system dysfunction, an increased number of neoplasms develop, suggesting loss of the surveillance mechanism, which normally destroys neoplastic cells via recognition of "nonself" antigens.

TOXIC AND ENVIRONMENTAL CAUSES OF DISEASE

A. **Lead** (plumbism)

1. **Etiology.** Plumbism is most often due to **chronic gradual accumulation**; children absorb lead more readily than adults. In **children**, it may result from ingesting lead-based paint chips, chewing on painted furniture or painted lead pencils, and inhaling highway exhaust. Other sources of lead include improperly glazed ceramic dishes, home-fermented liquor, and contaminated drinking water. The use of lead-free paint and unleaded gasoline is reducing the incidence and severity of plumbism.
2. **Pathogenesis.** Lead **inhibits enzymes involved in hemoglobin synthesis** (including the inhibition of iron incorporation in tetrapyrrole ring) and **inhibits adenyl cyclase activity in the brain and pancreas.**
3. **Clinical features.** There is an insidious onset.
   a. **Anemia** is characterized by **increased hemolysis**, coarse basophilic stippling, and elevated free erythrocyte protoporphyrin. The anemia is hypochromic and microcytic.
   b. **Encephalopathy** is due to **diffuse edema**, demyelination, and neuronal degeneration, which causes delirium, seizures, and coma.
   c. **Peripheral neuropathy** is due to **myelin degeneration**, which predominantly affects motor neurons. The **radial nerve** is most often affected, leading to wrist drop.
   d. **Renal lesions** feature **proximal tubular dysfunction**, causing glycosuria, aminoaciduria, and hyperphosphaturia (Fanconi's syndrome). It is associated with mineral-containing intranuclear inclusions in proximal tubular cells.
   e. **Abdominal colic** is chronic and often severe.
   f. **Lead lines** refer to an **accumulation of lead sulfide on the gingival mucosa** and epiphyseal radiodensities on x-ray.

B. **Carbon monoxide**

1. **Pathogenesis.** Carbon monoxide combines with hemoglobin to form carboxyhemoglobin, which **cannot carry oxygen.** The affinity of carbon monoxide for hemoglobin is more than 200 times greater than that of oxygen. Once formed, carbon monoxide is displaced from hemoglobin very slowly.

IN A NUTSHELL

Key features of lead poisoning include:

- *Basophilic stippling of RBCs*
- *Peripheral neuropathy*
- *Lead lines in bones*
- *Abdominal colic*

Note

Cigarette smoke contains carbon monoxide; the percentage of carboxyhemoglobin in smokers is proportionate to the number of cigarettes smoked per day.

2. **Types**
   a. **Acute toxicity.** Symptoms of hypoxia are apparent when 30% of hemoglobin is carboxyhemoglobin; coma and death ensue when 60% is carboxyhemoglobin. The blood is cherry red, turning the lips cherry red as well. Carbon monoxide poisoning causes CNS hyperemia, edema, and focal hemorrhages with symmetric degeneration of the basal ganglia. There is loss of consciousness, coma, and death within minutes.
   b. **Chronic toxicity.** Slow poisoning causes systemic pathology with milder CNS changes. Fatty change occurs in the heart, liver, and kidney. The patient can usually recover completely.

C. **Acetaminophen.** Because of its widespread availability, acetaminophen has become a commonly ingested substance in accidental childhood poisonings and in suicide attempts.

1. **Pathogenesis.** Hepatotoxicity is mediated by a toxic reactive metabolite, which, after depleting glutathione stores, binds to hepatocyte macromolecules.
2. **Pathology.** Acetaminophen toxicity causes severe centrilobular hepatic necrosis. The severity correlates with the serum drug level.
3. **Clinical features.** Patients experience nausea, vomiting, abdominal pain, and shock. Hepatic failure is not evident until 2–6 days after ingestion.

D. **Salicylates** are another commonly ingested toxin. They may be ingested accidentally or in suicide attempts.

1. **Pathogenesis.** Initially, direct respiratory stimulation produces a respiratory alkalosis. In addition, the metabolic effects of salicylates cause a metabolic acidosis. Vomiting complicates fluid and electrolyte disturbances. Fatalities are most often due to dehydration and hypokalemia.
2. **Pathology.** Hemorrhagic gastritis, petechiae, systemic hemorrhages, and necrosis of lymphoid germinal centers occur.

E. **Mercury poisoning** is rare.

1. **Pathogenesis.** Mercury inactivates enzymes (particularly cytochrome oxidase) and damages cell membranes.
2. **Types**
   a. **Acute toxicity** causes necrosis of gastric and colonic epithelium, acute renal tubular necrosis, and possibly cerebral edema.
   b. **Chronic toxicity** causes excessive salivation, gingivitis, gastritis, renal tubular basement membrane thickening (which causes proteinuria and eosinophilic inclusions), and cerebral (particularly occipital) and cerebellar atrophy.

GENETIC DISORDERS

A. **Autosomal dominant disorders**

1. **Phacomatoses.** Tuberous sclerosis and von Hippel-Lindau disease are transmitted by autosomal dominant inheritance. Neurofibromatosis is transmitted in an autosomal dominant fashion in 50% of cases, and 50% of cases are sporadic mutations.

2. **Familial hypercholesterolemia**
   a. **Clinical features.** Homozygotes have more severe symptoms than heterozygotes, including xanthomas and extensive, early atherosclerosis often resulting in myocardial infarction in the second or third decade of life.
   b. **Pathogenesis.** There is a **loss of feedback inhibition of cholesterol synthesis** caused by decreased or defective low-density lipoprotein (LDL) receptors.

3. **Marfan's syndrome** is a **connective tissue abnormality**; approximately 85% of cases are autosomal dominant. The incidence of sporadic cases increases with increasing paternal age.
   a. **Pathogenesis** is unclear. There is probably a **defect in collagen structure** and possibly **defective elastin or mucopolysaccharide** ground substance due to mutations in the fibrillin glycoprotein gene.
   b. **Clinical features** are very variable. They include arachnodactyly (long, spider-like fingers), tall stature, ligamentous laxity, subluxed lens, dissecting aortic aneurysm, usually of the ascending aorta (secondary to cystic medial necrosis of the vessel wall), mitral valve prolapse, and a short life-span often as a result a ruptured aorta.

4. **Familial polyposis coli (FPC)**
   a. **Thousands of adenomatous polyps** appear, starting in the colorectum and spreading throughout the colon. Polyps first appear in the patient's twenties, become symptomatic in the thirties, and transform to adenocarcinoma by approximately age 40.
   b. **Gardner's syndrome** has colonic polyps with soft tissue and bone tumors.

5. **Adult polycystic kidney disease (APKD)**
   a. **Renal cysts** increasing with age, cause progressively enlarged kidneys. The rate of enlargement of kidneys proceeds at the same rate in affected families.
   b. Hypertension, renal failure, and anemia are the presenting signs, typically starting when patients are in their forties. The age of onset of symptoms also proceeds at the same rate in a given family.

Clinical Correlate

Nearly 100% of patients with FPC will get carcinoma of the colon by the fifth decade of life. The treatment of choice is to ***regionally remove the entire colon*** *usually in the second or third decade of life.*

c. Cysts are also found in the liver, pancreas, spleen, and gonads. There is an increased risk of berry aneurysms and abnormalities of the cardiac valves.

6. **Huntington's disease**
   a. This is a progressive neurologic disorder; the age of onset tends to be the same in affected families.
   b. The onset of symptoms is usually between the ages of 30 and 50 years with involuntary chorelc movements (Huntington's chorea), cognitive impairment, and changes in behavior. Death follows after 15–20 years.
   c. It is associated with degeneration of the caudate nucleus.

7. **Wilm's tumor**
   a. This is an embryonal tumor, one of the most common solid tumors in children under 4, involving one or both kidneys and characterized by primitive mesenchyme and immature tubules. Sporadic forms also occur.
   b. Wilm's tumor, aniridia, gonadoblastoma, and mental retardation (WAGR syndrome) are associated with a gene at chromosome 11p13.
   c. Tumors often reach enormous sizes and can be easily palpated on physical exam as large abdominal masses.

8. **Retinoblastoma**
   a. This disorder is an embryonal tumor affecting one or both eyes.
   b. Osteosarcoma is associated with familial forms.

B. **Glycogen storage diseases** are inherited via an autosomal recessive pattern.

1. **Type I (von Gierke's disease)** is caused by an enzyme defect in glucose-6-phosphatase.
2. **Type II (Pompe's disease)** is an enzyme defect in lysosomal α-1,4-glucosidase, which affects all organs, especially the heart and brain.
3. **Type III** is due to an enzyme defect in glycogen debranching enzymes, which affects all organs.
4. **Type IV** is due to an enzyme defect in branching enzymes, which affects all organs.
5. **Type V (McArdle's disease)** is due to a defect in striated muscle phosphorylase, which specifically affects striated muscle.
6. **Type VI** is due to a defect in liver phosphorylase, which affects only the liver.

C. **Lysosomal storage diseases**

1. **Mucopolysaccharidoses.** Various lysosomal enzymatic defects lead to the accumulation of glycosaminoglycans throughout the body and brain. All except Hunter's syndrome show autosomal recessive inheritance.

a. **Pathology.** Storage of glycosaminoglycans occurs mainly in the endothelium, reticuloendothelium, and fibroblasts of the liver, spleen, lymph nodes, vessels, and bone marrow. Balloon cells are formed. Patients also have cardiac valve lesions, hepatosplenomegaly, arterial lesions in coronary and cerebral vessels, and skeletal deformities.

b. **Types** of mucopolysaccharidoses (MPS) include
(1) **MPS I H (Hurler's syndrome)**
(2) **MPS I S (Scheie's syndrome)**
(3) **MPS I H/S (Hurler-Scheie syndrome)**
(4) **MPS II (Hunter's syndrome)**
(5) **MPS III (Sanfilippo's syndrome)**
(6) **MPS IV (Morquio's syndrome)**

2. **Sphingolipidoses**

a. **Tay-Sachs disease** (GM_2 gangliosidosis type 1) is due to a deficiency of hexosaminidase A, which leads to an accumulation of GM_2 ganglioside, affecting all organs but predominantly the brain, retina, and peripheral nervous system.
(1) **Clinical features.** The onset of symptoms begins at 6 months of age with an exaggerated startle response and progressive mental, motor, and visual deterioration, leading to death by age 3. It can be detected prenatally by amniocentesis. The highest incidence is in Ashkenazi Jews (carrier rate is 1/30).

b. **Gaucher's disease** is due to defects in β-glucocerebrosidase, leading to the accumulation of glucocerebroside, which affects reticuloendothelial cells and the central nervous system.

c. **Niemann-Pick disease** is due to a defect in sphingomyelinase, leading to an accumulation of sphingomyelin and cholesterol in a variety of organs.
(1) **Clinical features.** Eighty percent of cases are type A, which is characterized by extensive CNS and systemic accumulations. Patients suffer from hepatosplenomegaly, xanthomas, fever, vomiting, failure to thrive, neurologic dysfunction, and death by age 3.
(2) **Pathology.** Characteristic findings include enlarged "foamy" cells filled with distended lysosomes containing sphingomyelin.

D. **Other metabolic disorders**

1. **Phenylketonuria** is a disorder resulting from an absence of phenylalanine hydroxylase in homozygotes, which halts the conversion of phenylalanine to tyrosine, resulting in elevated levels of phenylalanine in the blood.

a. **Clinical features.** Infants are normal at birth, but within months develop an abnormal pattern on EEG with seizures and mental retardation. There is minimal melanin production, causing light

Note

Aspartame, an artificial sweetener, contains phenylalanine and should be avoided by phenylketonurics.

hair and skin and blue eyes. The urine has a musty odor as a result of the urinary excretion of phenylacetic acid. Pathology can be prevented with a special diet free of phenylalanine and supplemented with tyrosine during childhood.

b. **Diagnosis** is by the Guthrie bacterial inhibition assay (routine newborn screening) or by measurement of phenylalanine levels in the blood.

2. **Galactosemia** can result from two different enzyme deficiencies.
   a. **Galactokinase deficiency** is a benign disease. The main complication is cataract formation.
   b. **Galactose-1-phosphate uridyltransferase deficiency** is a severe form of galactosemia.

3. **Albinism** is caused by an enzymatic deficiency that prevents melanin synthesis from tyrosine.
   a. **Types**
      (1) Tyrosinase-negative type is due to a lack of tyrosinase in melanocytes.
      (2) Tyrosinase-positive type, in which tyrosinase is present, is due to a defect in tyrosine uptake.
   b. **Clinical features.** The lack of melanin may be limited to the eye (ocular albinism) or may involve total body pigmentation (oculocutaneous albinism). In the latter, the skin is particularly sensitive to the sun, resulting in premature wrinkling and a tendency to develop solar keratosis, as well as basal cell, squamous cell, and melanocyte carcinomas. Eyes are very photosensitive; visual acuity is decreased.

4. **Cystic fibrosis** is due to an abnormality in chloride channels.
   a. **Diagnosis** may be made by demonstrating elevated chloride and sodium in sweat.
   b. **Clinical features.** Hyperviscous secretions lead to meconium ileus (small bowel obstruction) in 5-10% of newborns. Patients suffer steatorrhea (from pancreatic insufficiency), pulmonary obstruction, and pneumonia, leading to infection. Secondary cardiac complications follow. Men may be sterile as a result of obstruction of the vas deferens. Cirrhosis of the liver is common.

5. **Alpha$_1$ antitrypsin deficiency**
   a. **Clinical features.** The patient experiences progressive emphysema of the lower lobes of the lungs. This is in contrast to smoking-related emphysema, in which the upper lobes are affected first. Cirrhosis of the liver is seen in some patients.

E. **Disorders of chromosome number or structure**

1. **Trisomic disorders** are usually secondary to a meiotic defect.
   a. **Down's syndrome (trisomy 21)**

(1) **Incidence.** This defect increases with maternal age. It affects 1 in 2,000 live births if maternal age is less than 30 and 1 in 50 live births if maternal age is greater than 45. The incidence of having a second affected child is 1 in 60.

(2) **Clinical features** include severe mental retardation, characteristic facies (flat nasal bridge, epicanthal folds, oblique palpebral fissures), dysplastic ears, hypotonia, a horizontal palmar crease, redundant neck skin, and a short trunk. There is also an increased incidence of ventricular septal defect (VSD), acute lymphoblastic leukemia (ALL), and neurologic changes similar to those of Alzheimer's disease.

b. **Edward's syndrome (trisomy 18)**

(1) **Incidence** is 1 in 5,000 births.

(2) **Clinical features** include severe mental retardation, VSD, micrognathia (a small lower jaw), rocker-bottom feet, low-set ears, prominent occiput, and hypertonia. The average lifespan is 2–3 months.

c. **Patau's syndrome (trisomy 13)**

(1) **Incidence** is 1 in 6,000 births.

(2) **Clinical features** include microcephaly, severe mental retardation, arhinencephalia, microphthalmia, cleft lip and palate, VSD, dextrocardia, and polydactly. Death is usually in the neonatal period.

2. **Chromosomal deletions**

a. **Cri du chat syndrome (5p–)**

(1) **Pathogenesis.** There is a deletion of the short arm of chromosome 5.

(2) **Clinical features.** The patient exhibits a cat-like cry up to 1 year of age, severe mental retardation, microcephaly, and epicanthal folds; one in four patients have a VSD. Patients may live to adulthood.

b. **DiGeorge's syndrome** is caused by absence of parathyroids and thymus, resulting in cardiovascular abnormalities and low-set ears. It results from a deletion of chromosome 22q11 during development.

3. **Disorders of sex chromosomes**

a. **Klinefelter's syndrome**

(1) **Karyotypes.** The most common karyotype is 47,XXY, but other patterns may also be seen.

(2) **Etiology.** Nondisjunction during meiosis in either the maternal or paternal gamete may result in an extra X chromosome.

(3) **Incidence** increases with maternal age or irradiation and affects 1 in 800 male births.

(4) **Clinical features** include testicular atrophy, sterility, a small penis, failure of development of male secondary sexual characteristics, gynecomastia, and mild mental retardation. Mental

deficiency is more marked with a greater number of X chromosomes.

(3) **Laboratory values** show positive X chromatin, azoospermia, low serum testosterone, and elevated urinary excretion of FSH.

b. **Turner's syndrome**

(1) **Karyotype** is typically 45,XO.

(2) **Incidence** is 1 in 3,000 female births.

(3) **Clinical features** may be subtle in mosaics. There is edema during infancy, a web neck, short stature, broad chest with wide-spaced nipples, low hairline, primary amenorrhea, infertility, coarctation of the aorta, streak ovaries, and usually abnormal intelligence.

There are many different organs included in the gastrointestinal system. Gastrointestinal pathology, therefore, includes a wide variety of disorders, from peptic ulcer disease to colorectal cancer to gallstones. Since many of these disorders initially present with similar symptoms (abdominal pain, diarrhea, constipation), it is important to be able to recognize the specific risk factors and signs associated with each disorder. This chapter will discuss the pathology of each organ in the gastrointestinal system, along with the associated risk factors and clinical presentations.

ORAL CAVITY

A. **Congenital malformations** include **cleft lip** and **cleft palate**. Both are generally treated surgically within the first six months of life.

B. **Teeth**

1. **Enamel hypoplasia** is due to a **defect in enamel formation**, resulting from **dysfunction of ameloblasts**, which form horizontal bands of discolored, pitted indentations. It may be caused by deficiencies of calcium, phosphorus, vitamins A, C, and D; excess fluoride; infections (e.g., syphilis); hypoparathyroidism; and hypothyroidism.
2. **Pigmentation of developing teeth** may be caused by **excess bile pigments in biliary disease**, bilirubin in hemolytic anemias, or tetracycline.
3. **Congenital syphilis** leads to malformation of teeth as a result of **inflammatory changes in ameloblasts and odontoblasts**.

C. **Oral mucosa**

1. **Common periodontal diseases**
   a. **Gingivitis** is a chronic inflammation of the gingivae.

NOTE

The pathologic effect of tetracycline on developing bones and teeth has long been a favorite NBME side effect. **Remember! No tetracycline for pregnant women and children under 9 years of age.**

b. **Periodontitis**, or **pyorrhea**, is gingivitis that has spread into tooth cementum and alveolar bone. Complications include suppurative infection, abscess, and bone resorption.

c. **Aphthous ulcers** are painful ulcers commonly known as "canker sores." They are not invasive and may be present as a single lesion or in crops, each of which is usually less than 0.5 cm. They often appear during febrile illness or other physical or emotionally stressful situations and are often found in patients with ulcerative colitis.

2. **Oral manifestations of systemic disease**

a. **Vitamin deficiencies**

(1) **Vitamin B deficiency** leads to **atrophic glossitis** as a result of reduced cell division in the squamous mucosa.

(2) **Vitamin C deficiency** causes **bleeding gums** as a result of weakened connective tissue.

b. **Pregnancy** may cause gingivitis and increased vascularity of the gingivae.

c. **Hematologic abnormalities**

(1) **Thrombocytopenia** may cause petechiae and excess bleeding.

(2) **Leukemia** may cause red, boggy gingivae infiltrated by leukemic cells.

(3) **Pernicious anemia** causes a smooth, beefy, red tongue due to squamous atrophy.

d. **Diabetes** may produce **dryness of the mouth** and a tendency to form abscesses as a result of impaired microcirculation.

e. **Addison's disease** leads to generalized excessive pigmentation; **Peutz-Jeghers syndrome** leads to **patchy pigmentation**.

f. **Systemic infectious diseases**

(1) **Scarlet fever**, **toxic shock syndrome**, and **Kawasaki's disease** cause a **strawberry tongue**.

(2) Measles produces **Koplik spots**, which are **tiny white specks on a red base**, found on the **buccal mucosa** in the prodromal stage of illness.

3. **Infections**

a. **Necrotizing gingivitis** ("trench mouth") ("ANUG") produces **crater-like** depressions at the gingival margin. It is painful and causes a **fetid odor**.

b. **Herpetic gingivostomatitis** is **due to herpes simplex** and is usually seen in children.

c. **Oral thrush** is caused by **Candida albicans**, which produces **white adherent patches**. Thrush is associated with impaired immunity or debilitation and is commonly seen in patients with AIDS or patients undergoing chemotherapy.

d. **Herpangina** is due to coxsackievirus A and causes vesicular lesions, typically in the pharynx.

e. **Syphilis** may produce a variety of lesions:
   (1) Primary syphilis produces chancres on the lips.
   (2) Secondary syphilis produces maculopapular eruptions.
   (3) Tertiary syphilis produces gummas of the palate and atrophic glossitis.

4. **Keratotic abnormalities**

a. **Lichen planus** appears as white reticulate lesions on the buccal mucosa and tongue.

b. **Leukoplakia** appears as white plaques on oral mucosa, produced by hyperkeratosis of the epithelium. Ten percent of cases of leukoplakia have epithelial dysplasia, a precancerous lesion. Smoking, smokeless tobacco, alcohol abuse, chronic friction, and irritants are predisposing factors.

c. **Erythroplakia** (dysplastic leukoplakia) appears flat, smooth, and red. Significant numbers of atypical epithelial cells are seen microscopically. There is a high risk of malignant transformation.

d. **Hairy leukoplakia** is so named because of its wrinkled surface. Patches occur on the side rather than the middle of the tongue. There are far fewer atypical cells than are seen in erythroplasia. Malignant transformation does not occur, despite its association with HIV and associated infections, including papilloma and Epstein-Barr viruses.

5. **Tumors**

a. **Benign tumors** include hemangiomas, hamartomas, fibromas, lipomas, adenomas, papillomas, neurofibromas, and nevi.

b. **Malignant tumors.** By far, the most common malignant tumor is squamous cell (epidermoid) carcinoma. The peak incidence ranges from age 40–70. Squamous carcinoma is associated with **tobacco and alcohol use,** particularly when used together. Pathologically, it may be papillary or ulcerative. The lower lip is the most common site, but cancer of the floor of the mouth, tongue, and buccal mucosa are frequently seen.

D. **Salivary glands**

1. **Inflammation**

a. **Sialolithiasis** produces a secondary inflammatory reaction to obstruction and the resultant enlargement of ducts by stones. It may be complicated by actual infection with mouth flora.

b. **Sialadenitis** is a primary inflammatory reaction, but it is not always infectious. It may be part of an autoimmune disease (e.g., Sjögren's syndrome) or the result of bacterial or viral (e.g., mumps) infection.

2. **Tumors.** The parotid gland accounts for more than three-quarters of these tumors, most of which are benign. Of the remainder, more occur in the submandibular gland than in the sublingual, and most of

these are malignant. Many are surgically cured, but local recurrence is common.

a. **Pleomorphic adenoma** is generally benign and accounts for approximately three-quarters of all salivary gland tumors. It is composed of multiple epithelial and mesenchymal cell types. Complications may arise due to involvement of cranial nerve VII.

b. **Warthin's tumor (adenolymphoma)** is also benign, occurring almost exclusively in the parotid gland. It is grossly cystic. Microscopic examination reveals cell types suggestive of branchial cleft origin embedded in a lymphoid matrix.

c. **Mucoepidermoid tumors** also occur primarily in the parotid and have a high rate of malignant transformation. The malignant component is usually squamous cell.

d. **Cylindroma (adenoid cystic carcinoma)** is more common in the minor salivary glands found in the oral mucosa, and metastases are more common than in other tumors of the salivary glands. Facial nerve complications are frequent.

(1) **Grossly**, the tumor forms multiple lobules surrounded by a capsule.

(2) **Microscopically**, small cells form glands containing mucoid material.

ESOPHAGUS

A. Congenital malformations

1. A **tracheoesophageal fistula** (the most prevalent esophageal anomaly) occurs most commonly as an upper esophageal blind pouch with a fistula between the lower segment of the esophagus and the trachea. It is associated with hydramnios, congenital heart disease, and other gastrointestinal malformations.

2. Esophageal atresia is associated with VATER syndrome (**v**ertebral defects, **a**nal atresia, **t**racheoesophageal fistula, and **r**enal dysplasia). It does not usually occur as an isolated anomaly.

3. **Stenosis** refers to a narrowed esophagus with a small lumen. It may be congenital or acquired, e.g., through trauma or inflammation.

B. Inflammatory disorders

1. **Esophagitis** most often involves the lower half of the esophagus.

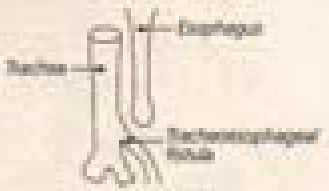
   a. **Clinical features.** Patients experience substernal burning associated with regurgitation, mild anemia, dysphagia, hematemesis, and melena. Esophagitis may predispose to esophageal cancer.

   b. **Etiology**

   (1) **Reflux esophagitis** is due to an incompetent lower esophageal sphincter (LES) that permits reflux of gastric juice into the lower esophagus.

Clinical Correlate

The most common type of tracheoesophageal fistula



Note

Reflux occurs when LES pressure decreases enough to allow reflux of stomach contents back into the esophagus.

(2) **Irritants** such as citric acid, hot liquids, alcohol, smoking, corrosive chemicals, and certain drugs, such as tetracycline, may provoke inflammation.

(3) **Infectious etiologies** include herpes, CMV, and *C. albicans*. The immunocompromised host is particularly susceptible to infectious esophagitis.

c. **Pathology**

(1) **Grossly**, there is hyperemia, edema, inflammation, and superficial necrosis.

d. **Complications** include ulceration, bleeding, stenosis, and squamous carcinoma.

2. In **Barrett's esophagus**, gastric or intestinal columnar epithelium replaces normal squamous epithelium in response to chronic reflux.

C. **Motor disorders.** Normal motor function requires effective peristalsis and relaxation of the lower esophageal sphincter.

1. **Achalasia** is a **lack of relaxation of the lower esophageal sphincter** (LES), which may be associated with aperistalsis of the esophagus and increased basal tone of the LES.

a. **Clinical features.** Achalasia occurs most commonly between the ages of **30 and 60**. Typical symptoms are **dysphagia**, regurgitation, aspiration, and chest pain. The lack of motility promotes stagnation and predisposes to carcinoma.

2. **Hiatal hernia** is the **herniation of the abdominal esophagus**, the stomach, or both, through the esophageal hiatus in the diaphragm.

3. **Scleroderma** is a **collagen vascular disease**, seen primarily in women, that **causes subendothelial fibrosis and widespread degenerative changes**. (A mild variant is known as CREST syndrome, which stands for calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia.) The esophagus is the most frequently involved region of the gastrointestinal tract.

a. **Clinical features** are mainly **dysphagia and heartburn** due to reflux esophagitis caused by aperistalsis and incompetent LES.

D. **Rings and webs**

1. **Webs** are **mucosal folds** in the upper esophagus above the aortic arch.

2. **Schatzki rings** are **mucosal rings** at the squamocolumnar junction below the aortic arch.

3. **Plummer-Vinson syndrome** consists of a triad of **dysphagia, atrophic glossitis,** and **anemia**. Webs are found in the upper esophagus. The syndrome is associated specifically with **iron deficiency anemia** and sometimes **hypochlorhydria**. Patients are at increased risk for carcinoma of the pharynx or esophagus.

C - calcinosis
R - Raynaud's phenomenon
E - esophageal dysfunction
S - sclerodactyly
T - telangiectasia

IN A NUTSHELL

Plummer-Vinson syndrome

- *Dysphagia*
- *Glossitis*
- *Iron deficiency anemia*
- *Esophageal webs*

In a Nutshell

Esophageal varices are often due to portal hypertension. They may bleed or ulcerate, which can be life-threatening.

In a Nutshell

Mallory-Weiss tears vs. esophageal varices:

While both are associated with alcohol abuse and can present with hematemesis, Mallory-Weiss tears typically occur acutely as a result of retching/vomiting. Esophageal varices result from portal hypertension and will usually present with a more significant bleeding episode.

Clinical Correlate

Pyloric stenosis: congenital hypertrophy of pyloric muscle, presenting with projectile vomiting and requiring surgical treatment.

E. **Mallory-Weiss tears** refers to small mucosal tears at the gastroesophageal junction secondary to recurrent forceful vomiting, usually seen in **alcoholics**. The tears occur along the long axis and result in **hematemesis** (sometimes massive).

F. **Esophageal varices** are dilated tortuous vessels of the esophageal venous plexus resulting from **portal hypertension**. When portal blood pressure increases, collateral circulation through the coronary veins to the esophageal veins and then to the azygous system develops, yielding vessel engorgement. Portal hypertension is most often caused by hepatic cirrhosis. Another common cause is obstructive thrombosis of the portal or splenic vein. Esophageal varices are prone to bleeding and ulceration, which may be life-threatening, especially in cirrhotics.

G. **Diverticula** are sac-like protrusions of one or more layers of the gingival or esophageal wall.

H. **Tumors**

1. **Benign** tumors are rare.
2. **Carcinoma of the esophagus** most commonly occurs after age 50 and has a male:female ratio of 4:1.
   a. **Incidence.** In the United States, the incidence is much higher in African Americans than in Caucasians.
   b. **Etiology.** It is associated with smoking, alcohol ingestion, nitrosamines in food, achalasia, webs, rings, diverticula, Barrett's esophagus, and deficiencies of vitamins A and C, riboflavin, and some trace minerals.
   c. **Clinical features** include dysphagia (first to solids), retrosternal pain, anorexia, weight loss, melena, and symptoms secondary to metastases.
   d. **Pathology.** 50% occur in the middle third of the esophagus, 30% in the lower third, and 20% in the upper third. Most esophageal cancers are squamous cell carcinomas. Adenocarcinomas arise mostly out of Barrett's esophagus.
   e. **Prognosis is poor.** Fewer than 10% of patients survive 5 years, usually because diagnosis is made at a late stage. The most common sites of metastasis are the liver and lung. The combination of cigarette **smoking** and **alcohol** is particularly causative for esophageal cancer (over 100× risk compared with nondrinkers/nonsmokers).

STOMACH

A. **Congenital malformations**

1. **Pyloric stenosis**
   a. **Clinical features.** Projectile vomiting 3–6 weeks after birth associated with a palpable "olive" mass in the epigastric region is observed.

b. **Pathology** shows hypertrophy of the muscularis of the pylorus and failure to relax.

2. **Diaphragmatic hernias** are due to weakness in an absence of parts of the diaphragm, allowing herniation of the abdominal contents into the thorax.

B. **Inflammation**

1. **Acute gastritis** (erosive)
   a. **Etiology.** Alcohol, aspirin and other NSAIDs, smoking, shock, steroids, and uremia may all cause disruption of the mucosal barrier, leading to inflammation.
   b. **Clinical features.** Patients experience heartburn, epigastric pain, nausea, vomiting, hematemesis, and even melena.

2. **Chronic gastritis** (nonerosive) may lead to atrophic mucosa with lymphocytic infiltration.
   a. **Types**
      (1) Parietal (Type A) gastritis is often autoimmune in origin. It is the type associated with pernicious anemia and, therefore, achlorhydria and intrinsic factor deficiency.
      (2) Antral (Type B) gastritis is most commonly caused by *Helicobacter pylori* and is the most common form of chronic gastritis in the U.S. *H. pylori* is also responsible for proximal duodenitis in regions of gastric metaplasia.
   b. **Clinical features.** The patient may be asymptomatic or suffer epigastric pain, nausea, vomiting, and bleeding. Gastritis may predispose to peptic ulcer disease, probably related to *H. pylori* infection.

3. **Peptic ulcers** are usually chronic, isolated ulcers observed in areas bathed by pepsin and HCl; they are the result of mucosal breakdown.
   a. **Common locations** are the proximal duodenum, the stomach, and the esophagus, often in areas of Barrett's esophagus.
   b. **Etiology.** There are several important etiologic factors. Duodenal ulcers occur predominantly in patients with excess acid secretion, while gastric ulcers usually occur in patients with lower than average acid secretion. Other predisposing conditions include smoking, cirrhosis, pancreatitis, hyperparathyroidism, and *H. pylori* infection. Aspirin, steroids, and NSAIDs are known to be associated with peptic ulcer disease. Next to *H. pylori* colonization, aspirin or NSAID ingestion is the most common cause of peptic ulcer.
   c. **Clinical features.** Patients experience episodic epigastric pain. Duodenal and most gastric ulcers are relieved by food or antacids. Approximately one-fifth of gastric ulcer patients get no relief from eating or experience pain again within 30 minutes.
   d. **Pathology.** Benign peptic ulcers are well-circumscribed lesions with a loss of the mucosa, underlying scarring, and sharp walls.

CLINICAL CORRELATE

Gastritis (due to acute (NSAIDs, alcohol, stress, etc.) or chronic (autoimmune or *H. pylori*)

CLINICAL CORRELATE

H. pylori has now been shown to be associated with gastritis, peptic ulcer disease, gastric adenocarcinoma, and some gastric lymphomas.

CLINICAL CORRELATE

Recent evidence raises the importance of H. pylori in the pathogenesis of peptic ulcer disease. Modification of acid secretion alone does not effect a lasting remission, but coupling this with antibiotic therapy that eradicates H. pylori is apparently curative in most patients.

In a Nutshell

Gastric ulcers may develop into, or develop from, a malignancy. Duodenal ulcers are never malignant.

Clinical Correlate

Virchow's node is a left supraclavicular lymph node. Its presence suggests metastatic stomach carcinoma.

Note

An adenocarcinoma with a diffuse desmoplastic response is called a linitis plastica (leather-bottle stomach).

a. **Complications** include hemorrhage, perforation, obstruction, and pain. Duodenal ulcers do not become malignant. Gastric ulcers do so only rarely; those found to be malignant likely originated as a cancer that ulcerated.

f. **Diagnosis** is made by upper gastrointestinal series, endoscopy, and biopsy to rule out malignancy or to demonstrate the presence of *H. pylori*.

4. **Stress ulcers** are superficial mucosal ulcers of the stomach or duodenum or both. Stress may be induced by burns, sepsis, shock, trauma, or increased intracranial pressure.

C. **Tumors**

1. **Benign**

a. **Leiomyoma**, often multiple, is the most common benign neoplasm of the stomach. Clinical features include bleeding, pain, and iron deficiency anemia.

b. **Gastric polyps** are due to proliferation of the mucosal epithelium.

2. **Malignant tumors**

a. **Carcinoma**

(1) **Etiology**: Primary factors include genetic predisposition and diet; other factors include hypochlorhydria, pernicious anemia, atrophic gastritis, adenomatous polyps, and exposure to nitrosamines. *H. pylori* is also implicated.

(2) **Clinical features.** Stomach cancer is usually asymptomatic until late, then presents with anorexia, weight loss, anemia, epigastric pain, and melena. **Virchow's node** is a common site of metastasis.

(3) **Pathology.** Symptomatic late gastric carcinoma may be expanding or infiltrative. In both cases the prognosis is poor (approximately 10% 5-year survival), and metastases are frequently present at the time of diagnosis. **Adenocarcinomas** are most common.

b. **Gastrointestinal lymphomas** may be primary in the gastrointestinal tract as solitary masses.

c. **Sarcoma** is a rare, large, ulcerating mass that extends into the lumen.

d. **Metastatic carcinoma. Krukenberg's tumor** is an ovarian metastasis from a gastric carcinoma.

e. **Kaposi's sarcoma.** The stomach is the most commonly involved GI organ in Kaposi's sarcoma. It primarily occurs in homosexual men, appearing as hemorrhagic polypoid or umbilicated nodular lesions, typically in a submucosal location. It rarely causes symptoms.

SMALL INTESTINE

A. **Congenital anomalies**

1. **Meckel's diverticulum** (a true diverticulum) is due to persistence of the **omphalomesenteric vitelline duct**.

2. **Atresia** is a congenital absence of a region of bowel, leaving a blind pouch or solid fibrous cord.
3. **Stenosis** refers to a narrowing of any region of the gastrointestinal tract, which may cause obstruction.
4. **Duodenal diverticula** are areas of congenital weakness permitting vascular enlargement. The duodenum is the most common region of the small bowel to contain diverticula.
5. **Diverticula of jejunum and ileum** are herniations of mucosa and submucosa at points where the mesenteric vessels and nerves enter.

B. **Infections**

1. **Bacterial enterocolitis** may be caused by the ingestion of preformed bacterial toxins, producing symptoms ranging from severe but transient nausea, vomiting, and diarrhea (*Staphylococcus aureus* toxin) to lethal paralysis (*Clostridium botulinum* toxin). **Ingestion of toxigenic bacteria** with colonization of the gut (e.g., *Vibrio cholera*, toxigenic *E. coli*, various species of *Campylobacter jejuni*, *Shigella*, *Salmonella*, *Yersinia*, and many others) is another potential cause.
2. Nonbacterial gastroenterocolitis
   a. Viral
      (1) Rotavirus (children)
      (2) Parvovirus (adults)
   b. Fungal—*Candida*
   c. Parasitic
      (1) *Entamoeba histolytica*
      (2) *Giardia lamblia*
3. **In HIV patients.** Causes of infectious diarrhea in HIV patients include *Cryptosporidium*, *Microsporidia*, *Isospora belli*, CMV, and *M. avium-intracellulare*.

C. **Malabsorption** is defined as impaired intestinal absorption of dietary constituents. Clinical features include diarrhea, steatorrhea, weakness, lassitude, and weight loss. Steatorrhea results in deficiency of fat-soluble vitamins (A, D, E, K) and calcium.

1. **Celiac sprue**
   a. **Etiology.** Celiac sprue (nontropical sprue or gluten enteropathy) is caused by an allergic, immunologic, or toxic reaction to the gliadin component of gluten. There is a genetic predisposition.
2. **Tropical sprue**
   a. **Etiology.** Tropical sprue is of unknown etiology but may be caused by enterotoxigenic *E. coli*.
3. **Disaccharidase deficiency** is due to a deficiency of brush border enzymes. **Lactase deficiency** is most common.

CLINICAL CORRELATE

Lactase deficiency leads to malabsorption with symptoms of bloating, diarrhea, and cramping after ingestion of dairy products.

D. **Vascular abnormalities** often lead to ischemic bowel disease.

1. **Transmural infarction** is more common in the small intestine, which does not have the rich collaterals of the colon.
   a. **Etiology**
      (1) **Thrombosis or embolism of the superior mesenteric artery** accounts for approximately 50% of cases. The thrombosis is most often secondary to atherosclerosis, but emboli may arise from cardiac sources or atherosclerotic plaques higher in the aorta. The inferior mesenteric artery accounts for approximately 25% of cases.
      (2) **Venous thrombosis** accounts for 25% of cases. It typically occurs post-CHF, in polycythemia, in hypercoagulable states, or in inflammations of the abdomen.
      (3) **Internal hernias** can strangulate entrapped loops of bowel. They can occur congenitally in children and young adults, or as a result of abdominal surgery (peritoneal adhesions) in adults.
   b. **Clinical features.** There is a 50–75% mortality rate. Infarction of the bowel usually occurs after age 60 and presents as an **acute abdomen** with abdominal pain, nausea, and vomiting.

E. **Obstructive lesions**

1. **Hernias** cause 15% of small intestinal obstruction. They are due to a protrusion of a serosa-lined sac through a weakness in the wall of the peritoneal cavity. They occur most commonly at the inguinal and femoral canals, at the umbilicus, and with scars. They may lead to entrapment, incarceration, and strangulation of the bowel.

F. **Tumors** of the small bowel account for only 5% of gastrointestinal tumors.

1. **Benign tumors** in descending order of frequency include: leiomyomas, lipomas, adenomas (polyps), angiomas, and fibromas. Adenomatous polyps are most common in the stomach and duodenum and may be single or multiple, sessile, or pedunculated. The larger the polyp, the greater the incidence of malignant transformation.
2. **Malignant tumors,** in descending order of frequency, include: endocrine cell tumors, lymphomas, adenocarcinomas, and leiomyosarcomas.

LARGE INTESTINE (COLON)

A. **Congenital anomalies**

1. **Hirschsprung's disease** produces a **markedly distended colon,** usually proximal to the rectum.

Clinical Correlate

Small bowel infarcts are often due to thromboembolic events and present as an acute abdomen.

3. **Imperforate anus** is due to a failure of perforation of the membrane that separates the endodermal hindgut from the ectodermal anal dimple.

B. **Benign conditions**

1. **Diverticular disease** refers to multiple outpouchings of the colon.
   a. **Incidence.** Diverticular disease is present in 30–50% of adult autopsies in the United States. There is a higher incidence with increasing age.
   b. **Pathogenesis.** Herniation of mucosa and submucosa through weak areas of the gut wall where arterial vasa recta perforate the muscularis is a characteristic pathologic finding of the disease.
   c. **Clinical features**
      (1) **Diverticulosis** is often asymptomatic, but may present with pain and/or **rectal bleeding.**
      (2) In contrast, **diverticulitis** presents with pain and fever. It is distinguished from diverticulosis by the presence of **inflammation,** which may or may not cause symptoms. When symptomatic, the patient experiences colicky left lower abdominal pain, change in bowel habits, and melena, so-called "left-sided appendicitis."
   d. **Pathology**
      (1) **Grossly,** diverticula are seen most frequently in the sigmoid colon.

C. **Inflammatory diseases**

1. **Crohn's disease,** or **regional enteritis,** causes a segmental, recurrent, **granulomatous inflammatory disease** of the bowel. It most commonly involves the terminal ileum and colon but may involve any part of the gastrointestinal tract. There is a familial disposition.
   a. **Etiology.** There is probably a similar etiology for both Crohn's disease and ulcerative colitis, which together are called **inflammatory bowel disease.** The following possible etiologies have been considered: infectious; immunologic (both antibody-mediated and cell-mediated); deficiencies of suppressor cells; and nutritional, hormonal, vascular, and traumatic factors.
   b. **Clinical features.** Crohn's disease usually begins in early adulthood and is common in Ashkenazic Jews. Patients present with colicky pain, diarrhea, weight loss, malaise, malabsorption, low-grade fever, and melena. There is typically a remitting and relapsing course. If the involved bowel is resected, lesions frequently develop in previously uninvolved regions of the bowel.
   c. **Pathology: Crohn's disease** has a very characteristic pathology.
      (1) **Grossly,** there are **segmental areas (skip lesions)** of involvement, most commonly in the terminal ileum.

Note

Since only two layers of the gut wall are involved, the outpouchings are technically **pseudodiverticula.**

Clinical Correlate

Crohn's disease presents with pain, diarrhea, weight loss, malabsorption, and melena.

In a Nutshell

Ulcerative colitis is a chronic disease characterized by colonic mucosal and submucosal streaming. Bloody diarrhea is the hallmark clinical presentation.

In a Nutshell

Crohn's disease

- Anywhere along GI tract (usually terminal ileum and cecum)
- Skip lesions (not continuous)
- Transmural
- Cobblestone mucosa

Ulcerative colitis

- Continuous involvement from rectum proximally
- Limited to mucosa and submucosa (not transmural; no fissures or fistulas)
- Pseudopolyps
- Greater risk of developing colon adenocarcinoma than in Crohn's

2. **Ulcerative colitis** is a chronic relapsing disease characterized by ulcerations, predominantly of the rectum and left colon, but which may affect the entire colon and occasionally the terminal ileum.
   a. **Incidence** is higher in Caucasians than in Blacks, and is also more frequent in women than in men. The typical age of onset ranges from 15–35 years of age. There is a definite familial predisposition.
   b. **Etiology:** Etiologic theories are similar to those for Crohn's disease. Some inflammatory bowel disease has microscopic features of both ulcerative colitis and Crohn's disease.
   c. **Clinical course** is characterized by relapsing bloody mucoid diarrhea, which may lead to dehydration and electrolyte imbalances, lower abdominal pain, and cramps. There is an increased incidence of carcinoma of the colon, up to 30% after 25 years with the disease.
   d. **Pathology**
      (1) **Grossly**, the disease almost always involves the rectum. It may extend proximally to involve part of the colon or its entirety. There are superficial mucosal ulcers, shortening of the bowel, narrowing of the lumen, **pseudo-polyps**, and **backwash ileitis**.
      (2) In contrast to Crohn's disease, the inflammation is usually confined to the mucosa and submucosa.
3. **Pseudomembranous colitis** is an inflammatory process characterized by a pseudomembranous exudate coating the colonic mucosa.
   a. **Pathogenesis.** The syndrome is associated with antibiotic use (especially **clindamycin**), allowing proliferation of *Clostridium difficile*, which produces an exotoxin.
   b. **Clinical features** include diarrhea that is often bloody, fever, and leukocytosis.
   c. **Diagnosis** is made by identification of *C. difficile* and toxin in stool.
   d. **Treatment** includes stopping the original antibiotic and starting oral **vancomycin** or **metronidazole**. This disease is often a terminal complication in immunosuppressed patients.

D. **Vascular lesions**

Hemorrhoids are vertical dilatations of the anal and perianal venous plexus. They are caused by elevated intra-abdominal venous pressure, often from constipation and pregnancy and are occasionally due to portal hypertension, where they are associated with esophageal varices. Hemorrhoids may undergo thrombosis, inflammation, and recanalization. **External hemorrhoids** are due to dilatation of the inferior hemorrhoidal plexus, whereas **internal hemorrhoids** are due to dilatation of the superior hemorrhoidal plexus.

E. **Polyps** are mucosal protrusions.

1. **Hyperplastic polyps** comprise 90% of all polyps. They are non-neoplastic and occur mostly in the rectosigmoid colon.
   a. **Grossly**, they form smooth, discrete, round elevations.

2. **Adenomatous polyps** are **true neoplasms**. There is a higher incidence of cancer in larger polyps and in those containing a greater proportion of villous growth.
   a. **Tubular adenomas (pedunculated polyps)** make up 75% of adenomatous polyps. They may be sporadic or familial. For sporadic polyps, the ratio of **men** to women is 2:1. The average age of **onset is 60**.
      (1) **Grossly**, **most occur in the left colon**. Cancerous transformation (i.e., invasion of the lamina propria or the stalk) occurs in approximately 4% of patients.
   b. **Villous adenomas** are the **largest, least common polyps**, and are usually sessile. About one-third are cancerous. Most are within view of the colonoscope.
      (1) **Grossly**, they form "**cauliflower-like**" **sessile growth 1–10 cm** in diameter, which are **broad-based and have no stalks**.
3. **Familial polyposis** is due to deletion of a gene located on chromosome 5q.
   a. **Familial multiple polyposis (adenomatous polyposis coli)** shows **autosomal dominant inheritance** and the appearance of polyps during adolescence; polyps start in the rectosigmoid area and spread to cover the entire colon. The polyps are indistinguishable from sporadic adenomatous polyps. Virtually all patients develop cancers. When diagnosed, total colectomy is recommended.
   b. **Gardner's syndrome** refers to colonic polyps associated with other neoplasms (e.g., in skin, subcutaneous tissue, bone) and desmoid tumors. The risk of colon cancer is nearly 100%.
   c. **Peutz-Jeghers syndrome** presents with polyps on the entire gastrointestinal tract (especially the small intestine) associated with **melanin pigmentation** of the buccal mucosa, lips, palms, and soles. The polyps are hamartomas and are not premalignant. Peutz-Jeghers syndrome shows autosomal dominant inheritance.
   d. **Turcot's syndrome** is characterized by colonic polyps associated with brain tumors (i.e., gliomas, medulloblastomas).

I. **Malignant tumors**

1. **Adenocarcinoma** is the histologic type of 98% of all colonic cancers. Both environmental and genetic factors have been identified.
   a. **Incidence** is very **high in urban**, Western societies. It is the **third-most common tumor in both women and men**. The peak incidence is in the **seventh decade of life**.
   b. **Pathogenesis** is associated with villous adenomas, ulcerative colitis, Crohn's disease, familial polyposis, and Gardner's syndrome. Incidence is possibly related to high-meat intake, low-fiber diet, and deficient vitamin intake. A number of chromosomal abnormalities have been associated with the development of colon cancer.

c. **Clinical features** include rectal bleeding, change in bowel habits, weakness, malaise, and weight loss in high-stage disease. The tumor spreads by direct extension and metastasis to nodes, liver, lung, and bones. **Carcinoembryonic antigen** (CEA) is a tumor marker that helps to monitor tumor recurrence after surgery or tumor progression in some patients.

d. **Pathology**
(1) **Grossly,** 75% of tumors occur in the rectum and sigmoid colon.
(2) **Microscopically,** these tumors are typical mucin-producing adenocarcinomas.

2. **Squamous cell carcinoma** forms in the anal region. It is often associated with papilloma viruses and its incidence is rising in homosexual males with AIDS.

APPENDIX

A. **Inflammation**

1. **Appendicitis** is almost always acute in onset.
   a. **Pathogenesis.** Obstruction leads to mucus retention and distention, compromise of blood supply, and subsequent bacterial infection.
   b. **Clinical features** typically include initial periumbilical pain that then localizes to the right lower quadrant, accompanied by anorexia, nausea, vomiting, fever, and moderate leukocytosis.

B. **Mucocele of the appendix** is dilatation of the appendix caused by mucin accumulation.

C. **Tumors.** Carcinoids are most common; carcinomas are rare. Primary lymphoma is occasionally seen.

PERITONEUM

A. **Peritonitis** is inflammation of the peritoneum.

1. **Sterile peritonitis** may be caused by bile, pancreatic enzymes, and foreign materials.

2. **Bacterial peritonitis.** In this condition, the membrane becomes dull with an accumulation of turbid fluid. The exudate becomes frankly purulent and may cause abscesses and adhesions after healing.

B. **Mesenteric cysts** are cysts within the mesenteries or attached to the peritoneum. They are usually single and of variable size. Most are benign.

C. **Sclerosing retroperitonitis** is a dense fibrotic proliferation of the retroperitoneum. The etiology is unknown.

D. **Tumors** of the peritoneum are usually malignant.

In a Nutshell

Adenocarcinoma is the most common type of colon cancer. It can present with rectal bleeding, changed bowel habits, weight loss, and other systemic symptoms.

Clinical Correlate

Appendicitis pain begins periumbilically and then localizes to the actual anatomic site of the appendix.

1. **Primary mesotheliomas** are rare. Eighty percent are associated with **asbestos exposure.**
2. **Secondary (metastatic)** tumors are common; most are ovarian or pancreatic. Implants from metastatic teratomas sometimes mature and lose their capacity to invade or metastasize further.

EXOCRINE PANCREAS

A. **Congenital anomalies**

1. **Ectopic pancreatic tissue** most commonly occurs in the stomach, duodenum, jejunum, Meckel's diverticulum, and ileum. It may be either asymptomatic or cause obstruction, bleeding, or intussusception.
2. **Annular pancreas** is a ring of pancreatic tissue that encircles the duodenum and may cause duodenal obstruction.

B. **Cystic fibrosis** is a systemic disorder of exocrine gland secretion, presenting during infancy or childhood.

1. **Incidence** is 1:2500 in Caucasians; it is less common in Blacks, and extremely rare in Asians.
2. **Pathogenesis.** Cystic fibrosis shows autosomal recessive transmission; heterozygotes are unaffected. It results in a **defective chloride channel** which leads to **secretion of very thick mucus.**
3. **Characteristics**
   a. Tissues other than exocrine glands are normal, and glands are structurally normal until damaged by cystic fibrosis.
   b. The only characteristic biochemical abnormalities are an **elevation of sodium and chloride levels in sweat** and a **decrease in mucin and bicarbonate secretion from pancreatic cells**, resulting in a viscous secretion.
4. **Clinical features**
   a. Fifteen percent of cases present with **meconium ileus.**
   b. Most cases present during the first year with **steatorrhea** (with resultant deficiencies of vitamins A, D, E, and K), abdominal distention, and **failure to thrive.**
   c. Complications are also related to pulmonary infections and obstructive pulmonary disease as a result of viscous bronchial secretions.
5. **Pathology**
   a. There is **mucus plugging of the pancreatic ducts** with cystic dilation, fibrous proliferation, and atrophy. Similar pathology develops in salivary glands.
   b. **Lungs.** Mucus impaction leads to bronchiolar dilatation and secondary infection.

CLINICAL CORRELATE

CF presents with steatorrhea and frequent respiratory infections in young children (often Staphylococcal). An abnormal sweat chloride test will confirm the diagnosis.

   i. **The gastrointestinal tract** shows obstruction caused by mucus impaction in the intestines with areas of biliary cirrhosis, resulting from intrahepatic bile duct obstruction.

6. **Diagnosis** depends on demonstrating a "**sweat test**" abnormality associated with at least one clinical feature. In the sweat test, high levels of chloride are demonstrated.

7. **Prognosis.** Mean survival is age 20; mortality is most often due to pulmonary infections.

C. **Degenerative changes**

1. **Iron pigmentation** (e.g., from hemochromatosis) may be deposited within acinar and islet cells and may cause insulin deficiency.

2. **Atrophy**

   a. **Ischemic atrophy** is due to atherosclerosis of pancreatic arteries and is usually asymptomatic.

   b. **Obstruction of pancreatic** ducts affects only the exocrine pancreas, which becomes small, fibrous, and nodular.

D. **Acute hemorrhagic pancreatitis** presents as a **diffuse necrosis of the pancreas caused by the release of activated pancreatic enzymes.** Associated findings include fat necrosis and hemorrhage into the pancreas.

1. **Incidence.** This disorder is most often associated with alcoholism and biliary tract disease. It affects **middle-aged individuals** and often occurs after a large meal or excessive alcohol ingestion; approximately 50% of patients have gallstones.

2. **Pathogenesis.** There are four theories.

   a. **Obstruction of the pancreatic duct** causes an **elevated intraductal pressure**, which results in leakage of enzymes from small ducts. Obstruction may be caused by a **gallstone at the ampulla of Vater**; chronic alcohol ingestion may cause duct obstruction by edema.

   b. **Hypercalcemia** may cause **activation of trypsinogen**. Its mechanism is unclear. Pancreatitis occurs in 20% of patients with hyperparathyroidism.

   c. **Direct damage to acinar cells** may occur by **trauma, ischemia, viruses, and drugs**.

   d. **Hyperlipidemia** may occur as a **result of exogenous estrogen intake and alcohol ingestion.**

3. **Clinical features** are typically the sudden onset of acute, continuous, and intense **abdominal pain, often radiating to the back** and accompanied by nausea, vomiting, and fever. This syndrome frequently results in **shock. Laboratory tests** reveal **elevated amylase (lipase elevated after 3–4 days) and leukocytosis**. Hypocalcemia is a poor prognostic sign.

E. **Chronic pancreatitis** refers to **recurring and relapsing episodes of acute pancreatitis, causing progressive pancreatic damage.**

1. **Incidence** is similar to acute pancreatitis. It is also seen in patients with ductal anomalies. Almost half the cases occur without known risk factors.
2. **Pathogenesis** is unclear; possibly, there is excess protein secretion by the pancreas, causing ductal obstruction.
3. **Clinical features** include flareups precipitated by alcohol, overeating, and drugs. Attacks are characterized by upper abdominal pain, tenderness, fever, and jaundice. **Laboratory values** reveal **elevated amylase and alkaline phosphatase**. **X-rays** reveal **calcifications in the pancreas**. Chronic pancreatitis may result in pseudocyst formation, diabetes, and steatorrhea.

F. **Carcinoma of the pancreas**

1. **Incidence**

   Carcinoma of the pancreas accounts for approximately 5% of all cancer deaths. Increased risk is associated with smoking, high-fat diet, and chemical exposure. There is a higher incidence in the elderly, Blacks, males, and diabetics.

2. **Clinical features**
   a. The disease is usually **asymptomatic** until late in its course.
   b. Manifestations include weight loss, abdominal pain frequently radiating to the back, weakness, malaise, anorexia, depression, and ascites.
   c. There is **jaundice** in half of the patients who have carcinoma of the head of the pancreas.
   d. **Courvoisier's law** holds that **painless jaundice with a palpable gallbladder** is suggestive of pancreatic cancer.
3. **Pathology.** Carcinomas arise in ductal epithelium. Most are adenocarcinomas.
   a. **Carcinoma of the head of the pancreas** accounts for 60% of all pancreatic cancers.
   b. Carcinoma of the body (20%) and tail (5%) produce large, indurated masses that spread widely to the liver and lymph nodes.
   c. In 15% of patients, carcinoma involves the pancreas diffusely.
4. **Complications** include **Trousseau's syndrome**, a **migratory thrombophlebitis** that occurs in 10% of patients.
5. **Prognosis** is **very poor**. If resectable, the **5-year survival rate** is less than 5%. The usual course is rapid decline; on average, death occurs 6 months after the onset of symptoms.

G. **Cysts**

1. **Congenital cysts** frequently occur with **cystic disease of the liver and kidney**. They are usually **multiple**.

IN A NUTSHELL

Chronic pancreatitis presents with **chronic serious alcoholics and abdominal mass (pseudocyst)**

2. **Pseudocysts** occur as sequelae of pancreatitis or trauma. They are caused by loculation of fluid (suppurative, hemorrhagic, or necrotic debris).
3. **Cystadenomas** and **cystadenocarcinomas** are neoplastic cysts. These are true cysts, lined by epithelium with papillary projections.

LIVER

A. **Congenital malformations**
   1. **Accessory lobes** are most often inferior. They are not associated with any specific disease process.
   2. **Congenital cystic disease** is associated with congenital polycystic disease of the kidneys and is asymptomatic.
   3. **Congenital hepatic fibrosis** is a disorder demonstrating autosomal recessive inheritance. It is characterized by periportal fibrosis, resulting in hepatosplenomegaly and esophageal varices.
   4. **Extrahepatic biliary atresia** causes cholestasis, which results in cirrhosis and portal hypertension.
   5. **Intrahepatic biliary atresia** results in a diminished number of bile ducts.

B. **Jaundice, or icterus,** is caused by excess bilirubin accumulation in the skin and sclerae, producing a yellow discoloration of these tissues. Icterus is visible when the serum bilirubin exceeds 2 mg/dl. In unconjugated hyperbilirubinemia, bilirubin is not excreted into the urine because of tight protein binding in serum. In conjugated hyperbilirubinemia, small amounts of bilirubin are excreted in the urine because it is less tightly protein bound.

C. **Hepatic failure**
   1. **Etiology. Chronic hepatic disease** (e.g., chronic active hepatitis or alcoholic cirrhosis) is the most common cause of hepatic failure, although acute liver disease may also be responsible.
      a. **Widespread liver necrosis** may be seen with carbon tetrachloride and acetaminophen toxicity. Widespread steatosis is seen in Reye's syndrome, a cause of acute liver failure most often seen in children with a recent history of aspirin ingestion for an unrelated viral illness.
      b. **Massive necrosis** may also be seen in acute viral hepatitis, after certain anesthetic agents, and in shock from any cause.
   2. **Clinical features.** Hepatic failure causes jaundice, musty odor of breath and urine, encephalopathy, renal failure (either by simultaneous toxicity to the liver and kidneys or the hepatorenal syndrome), palmar erythema, spider angiomas, gynecomastia, testicular atrophy (secondary to impaired estrogen degradation), prolonged prothrom-

bin time (impaired hepatic synthesis of coagulation factors), weight loss, muscle wasting, pruritus, malabsorption, hypoalbuminemia, hypercholesterolemia, and anemia.

D. **Hemodynamic and vascular abnormalities**

1. **Chronic passive congestion** is associated with right-heart failure and is a common postmortem finding.
2. **Central hemorrhagic necrosis** may be seen in severe heart failure.
3. **Cardiac sclerosis** is a sequela of chronic passive congestion and central hemorrhagic necrosis.
4. **Infarctions** are rare because of the dual blood supply (hepatic artery and portal vein).
5. **Hepatic vein thrombosis (Budd-Chiari syndrome)** is a rare syndrome that may be acute or insidious.
   a. **Etiology.** The Budd-Chiari syndrome may be seen in many unrelated conditions, including **neoplasms invading hepatic veins**, polycythemia vera, intrahepatic infection, paroxysmal nocturnal hemoglobinuria, myeloproliferative syndromes, and intravascular webs or membranes. All of these syndromes can **promote clotting** either through platelet activation, abnormal platelet function, or activation of the extrinsic clotting system.

E. **Portal vein obstruction and thrombosis**

   a. **Etiology**
      (1) **Extrahepatic causes** include abdominal neoplasms (notably renal cell carcinoma), pancreatitis, sepsis, and postsurgical conditions.
      (2) **Intrahepatic causes** include cirrhosis and primary or secondary neoplastic invasion.
   b. **Clinical features** include portal hypertension and splenomegaly.

F. **Hereditary disorders of bilirubin metabolism**

1. **Gilbert's syndrome** is a benign autosomal dominant disease characterized by **unconjugated hyperbilirubinemia**.
2. **Crigler-Najjar syndrome**
   a. **Type-1** shows autosomal recessive inheritance and complete **absence of glucuronyl transferase**, causing **marked unconjugated hyperbilirubinemia**, severe kernicterus, and death.
   b. **Type-2** shows a mild deficiency of glucuronyl transferase. Kernicterus does not develop.

G. **Viral hepatitis**

1. **Hepatitis A (HAV)** is a self-limited hepatitis caused by an RNA virus with an incubation period of approximately 2–6 weeks. Infection is identified by HAV-specific antibodies (IgM in acute, IgG in past disease). The usual route of infection is fecal-oral transmission by conta-

IN A NUTSHELL

Budd-Chiari syndrome is a hepatic vein obstruction leading to clinical and pathologic features of chronic congestive liver

Basics to Microbiology

- *Hepatitis A is a picornavirus. It has a naked icosahedral nucleocapsid and single-stranded RNA.*
- *Hepatitis B is a double-stranded DNA virus classified as a hepadnavirus. It has an enveloped icosahedral nucleocapsid.*
- *Hepatitis C is classified as a flavivirus. It is a positive-strand RNA virus with an enveloped icosahedral nucleocapsid.*
- *Hepatitis D is caused by the delta agent—a protein capsule surrounding low-molecular weight RNA.*
- *Hepatitis E is classified as a calicivirus. It is a single-stranded RNA virus with a naked icosahedral nucleocapsid.*

In a Nutshell

- *HBsAg indicates current infection.*
- *HBcAg indicates infectivity.*

minated food, particularly molluscs. There is **no carrier state** and **no chronic disease**.

2. **Hepatitis B (HBV)** may cause **acute hepatitis**, a carrier state, chronic active disease, chronic persistent disease, fulminant hepatitis, or hepatocellular carcinoma. It is caused by a **DNA virus**; the virions are called **Dane particles**. The incubation period is from **1-6 months**. Transmission is through **contact with infected blood or other body fluids**. It can be transmitted by sexual intercourse and is frequently transmitted to newborns of infected mothers by exposure to maternal blood during the birth process.
   a. **Associated antigens** include **core antigen (HBcAg) and surface antigen (HBsAg)**. The latter is usually identified in the blood for diagnosis. HBsAg is the earliest marker of acute infection. **HBeAg** is also associated with the core. Its presence indicates active acute infection; when anti-HBeAg appears, the patient is no longer infective.
   b. HBV is associated with hepatocellular carcinoma; HBsAg+ patients have a 200-fold greater risk of hepatocellular carcinoma than subjects who have not been exposed.
   c. **Antibodies**
      (1) **Antibodies to surface antigen (anti-HBs)** are considered protective and usually appear after the disappearance of the virus.
      (2) **Antibodies to HBcAg** are not protective. They are detected just after the appearance of HBsAg and are used to confirm infection when both HBsAg and anti-HBs are absent (window).
      (3) **Antibodies to HBeAg** are associated with a low risk of infectivity.
3. **Hepatitis C (HCV)** is most often **anicteric** but occasionally severe with fulminant hepatic failure. It is caused by an **RNA virus**, which may be **transmitted parenterally** (a cause of post-transfusion hepatitis); the route of transmission is undetermined in 40-50% of cases.
   a. Antibody is detected by enzyme-linked immunosorbent assay (**ELISA**). The incubation period is between **2 and 26 weeks** with peak onset of illness **6-8 weeks** after infection.
   b. Most patients progress to chronic liver disease, specifically chronic persistent hepatitis or chronic active hepatitis. Cirrhosis is common in patients with chronic active hepatitis and occurs in 20-25% of infected patients. HCV is also associated with hepatocellular carcinoma.
4. **Delta hepatitis (HDV)** is associated with a **defective RNA virus** composed of a **delta antigen-bearing core surrounded by HBV's Ag coat**. **HDV requires HBV for replication.** Delta hepatitis can cause quiescent HBV states to suddenly worsen. Its transmission is the same as that of HBV.
5. **Hepatitis E (HEV)** is caused by a **single-stranded RNA virus**. The disease is typically **self-limited** and does not evolve into chronic hepati-

Table 2-1. Types of Hepatitis

Hepatitis	Mode of Transmission	Incubation	Carrier State?	Causes Chronic Disease?	Genome
Hepatitis A	Fecal-oral	2-6 weeks	No	No	ssRNA
Hepatitis B	Parenteral, sexual	1-6 months	Yes	Yes (5–10% of cases)	DNA
Hepatitis C	Blood transfusion, blood products	2-26 weeks	Yes	Yes (50% of cases)	RNA
Delta hepatitis	Parenteral, sexual	1-several months	In association w/hepatitis B	Yes	RNA
Hepatitis E (NANB)	Water-borne, fecal-oral	6 weeks	Not known	No	ssRNA

tis; it may, however, be cholestatic. **Pregnant women** may develop fulminant disease. Transmission is by the fecal-oral route. HEV occurs mainly in India, Nepal, Pakistan, and Southeast Asia.

6. **Acute viral hepatitis**
   a. **Clinical features.** Acute viral hepatitis may be icteric or anicteric. Symptoms include malaise, anorexia, fever, nausea, upper abdominal pain, and hepatomegaly, followed by jaundice, putty-colored stools, and dark urine. In HBV, patients may have **urticaria**, arthralgias, arthritis, vasculitis, and glomerulonephritis (because of circulating immune complexes). Blood tests show elevated serum bilirubin (if icteric), elevated transaminases, and alkaline phosphatase. The acute illness usually lasts 4–8 weeks.
   b. **Pathology**
      (1) **Grossly**, there is an enlarged liver with a tense capsule.
      (2) **Microscopically**, there is ballooning degeneration of hepatocytes and liver cell necrosis.
7. **Chronic hepatitis** occurs in 5–10% of HBV infections and in well over 50% of HCV; it does not occur in HAV. Most chronic disease is due to chronic persistent hepatitis. The chronic form is more likely to occur in the very old or very young, in males, in immunocompromised hosts, in Down's syndrome, and in dialysis patients.
   a. **Chronic persistent hepatitis** is a benign, self-limited disease with a prolonged recovery. Patients are **asymptomatic except for elevated transaminases.**
   b. **Chronic active hepatitis** features chronic inflammation with hepatocyte destruction, resulting in cirrhosis and liver failure.
      (1) **Etiology**: HBV, HCV, HDV, drug toxicity, Wilson's disease, alcohol, α_1-antitrypsin deficiency, and autoimmune hepatitis are common etiologies.

IN A NUTSHELL

- HAV, HEV: fecal-oral infections
- HBV, HCV, HDV: parenteral infections

IN A NUTSHELL

Pathology of hepatitis:

Grossly, enlarged liver; microscopically coagulative necrosis with increased eosinophilia

NOTE

HBV and HCV can lead to chronic hepatitis, and may predispose to hepatocellular carcinoma

(2) **Clinical features** may include fatigue, fever, malaise, anorexia, and elevated liver function tests.

(3) **Diagnosis** is made by liver biopsy.

B. **Carrier state** for HBV and HCV may be either asymptomatic or with liver disease; in the latter case, the patient has elevated transaminases.

a. **Incidence** is most common in immunodeficient, drug-addicted, Down's syndrome, and dialysis patients.

b. **Pathology** of asymptomatic carriers shows **"ground-glass" hepatocytes** with finely granular eosinophilic cytoplasm.

3. **Fulminant hepatitis** leads to submassive and massive hepatic necrosis.

a. **Etiology**: HAV, HBV, HCV, delta virus (HDV) superinfection, HEV, chloroform, carbon tetrachloride, isoniazid, halothane, and other drugs (acetaminophen overdose) all may cause fulminant hepatitis.

b. **Clinical features** include progressive hepatic dysfunction with a mortality of 25–90%.

c. **Pathology**

(1) **Grossly**, one sees progressive shrinkage of the liver as the parenchyma is destroyed.

G. **Cholangitis is inflammation of the bile ducts.**

1. It is usually associated with biliary duct obstruction by gallstones or carcinoma, which leads to infection with enteric organisms. This results in purulent exudation within the bile ducts and bile stasis.

2. Clinically, cholangitis presents with jaundice, fever, chills, leukocytosis, and right upper quadrant pain.

H. **Pericholangitis** is inflammation around the bile ducts without intraductal involvement.

I. **Pyogenic liver abscesses** may be caused by *E. coli*, Klebsiella, Streptococcus, Staphylococcus, Bacteroides, Pseudomonas, and fungi.

J. **Parasitic infections**

1. **Schistosomiasis** is caused by different organisms in different parts of the world.

a. **Clinical features** include splenomegaly, portal hypertension, and ascites. Lesions are caused by the immune response to ova.

2. **Amebiasis** is caused by Entamoeba histolytica.

a. **Clinical features** include bloody diarrhea, pain, fever, jaundice, and hepatomegaly.

K. **Drug-induced liver damage** may be caused by agents that are direct hepatotoxins, such as carbon tetrachloride, acetaminophen, methotrexate, anabolic steroids, and oral contraceptive pills.

L. **Cirrhosis** is the diffuse involvement of the whole liver by fibrosis due to hepatocellular injury. Fibrosis in the form of dense scars or delicate

Clinical Correlate

Infants with HBV infected postnatally or during birth rarely develop active hepatitis but they often become chronic carriers. They also have an increased rate for hepatocellular carcinoma and hepatic cirrhosis.

Clinical Correlate

Cholangitis = Charcot's triad = jaundice, fever, and right upper quadrant pain

Note

Schistosomiasis, Schistosomiasis, and Schistosomiasis are three parasitic infections of the liver.

bands, and nodules caused by fibrous bands and regenerating hepatocytes. These so called **regenerative nodules**, which lack the usual architectural landmarks, such as ordered sinusoids and a central vein, are hallmarks of cirrhosis.

1. **Epidemiology.** Cirrhosis is the third leading cause of death in the 25-65-year-old age group. Leading types include alcoholic cirrhosis, postnecrotic cirrhosis, biliary cirrhosis, and hemochromatosis-related cirrhosis.
2. **Clinical features**
   a. **Portal hypertension** is most commonly caused by cirrhosis of the liver.
      (1) **Other causes** include posthepatic (e.g., right-sided heart failure, Budd-Chiari syndrome), prehepatic (e.g., portal vein obstruction), or intrahepatic (e.g., schistosomiasis, sarcoid).
      (2) **Signs and symptoms** include **ascites** (an accumulation of fluid in the peritoneal cavity); portosystemic shunts that form **hemorrhoids, esophageal varices** (which may cause massive hematemesis), **periumbilical (caput medusae)** and retroperitoneal dilatations, and portosystemic encephalopathy; and **splenomegaly** with hypersplenism.
   b. **Impaired estrogen metabolism** and male hypogonadism may cause female hair distribution and **gynecomastia** in males, gonadal atrophy, amenorrhea in females, **spider angiomata,** and **palmar erythema.**
   c. Other associated disorders include **Dupuytren's contractures,** hypoalbuminemia, peripheral edema, low levels of vitamin K-dependent clotting factors (causing **bleeding diathesis**), rare hepatorenal syndromes, and hepatic encephalopathy.
3. **Etiologies.** Already mentioned are the **chronic hepatitides** (HBV, HCV, but never HAV, HEV) and chronic drug reactions.
   a. **Postnecrotic cirrhosis** produces a macronodular pattern.
      (1) **Etiology:** Most cases are secondary to chronic active hepatitis.
   b. **Biliary cirrhosis**
      (1) **Primary biliary cirrhosis** has an **autoimmune etiology** and causes sclerosing cholangitis and cholangiolitis. It is associated with other autoimmune diseases and primarily affects **middle-aged women.**
      (2) **Secondary biliary cirrhosis** is caused by long-standing large bile duct obstruction, producing stasis of bile, leading to inflammation, secondary infection, and scarring. It usually presents with jaundice.
      (3) **Sclerosing cholangitis** is a chronic fibrosing inflammatory disease of the extrahepatic and larger intrahepatic bile ducts.
   c. **Hemochromatosis** is a disease with autosomal recessive inheritance. Deposits of iron occur in the liver, pancreas, heart, adrenal,

IN A NUTSHELL

Cirrhosis is the diffuse fibrosis and regeneration of the liver due to hepatocellular injury by toxins, drugs, viruses, or deposition of metabolites or minerals (e.g., glycogen storage diseases, Wilson's disease).

CLINICAL CORRELATE

Cirrhosis and portal hypertension can cause numerous physical exam findings:

- *Ascites (↓ albumin synthesis)*
- *Varices, hemorrhoids, and caput medusae (due to portosystemic shunts)*
- *Splenomegaly*
- *Gynecomastia, spider angioma, and palmar erythema (due to impaired estrogen metabolism)*
- *Dupuytren's contractures and clubbing*
- *Bleeding diathesis*

CLINICAL CORRELATE

The prothrombin time (PT), not the PTT, is used to assess coagulopathy due to liver disease.

CLINICAL CORRELATE

Hemosiderin deposits are seen in the liver and pancreas of hemochromatosis patients.

thyroid, parathyroid, and anterior pituitary with resultant organ dysfunction. It should be distinguished from **hemosiderosis**, which is a term used to describe iron overload from any cause.

d. **Wilson's disease (hepatolenticular degeneration)** is an autosomal recessive disease characterized by **inadequate hepatic excretion of copper**. Wilson's disease causes hepatitis or macronodular cirrhosis, degenerative changes in the lenticular nuclei of the brain, and pathognomonic **Kayser-Fleischer rings**, a deposition of copper in the corneal limbus.

e. **Alpha$_1$-antitrypsin deficiency** is an autosomal recessive disease characterized by **deficiency of a protease inhibitor**, resulting in **pulmonary emphysema** and **hepatic damage**.

f. **Syphilitic cirrhosis** causes scarring due to gummas.

M. **Alcoholic liver disease** causes fatty liver, alcoholic hepatitis, and alcoholic cirrhosis, which are separated although possibly interrelated entities.

1. **Epidemiology.** Alcoholic liver disease accounts for 60–70% of cirrhosis in the Western Hemisphere. The male:female ratio is 2:1. There is a possible genetic predisposition.

2. **Clinical features.** **Fatty change** is generally asymptomatic. Alcoholic hepatitis presents with fever, hepatomegaly, jaundice, elevated aspartate transaminase (AST), alkaline phosphatase, and alanine aminotransferase (ALT), and possible portal hypertension. Cirrhosis often presents with portal hypertension. Patients die due to liver failure, infection, upper gastrointestinal bleeds, hepatocellular carcinoma, encephalopathy, and renal failure (secondary to hepatorenal syndrome).

3. **Pathology**

a. **Fatty liver (steatosis)** is reversible.

(1) **Grossly, fatty changes appear as a yellow, greasy, enlarged liver.**

b. **Alcoholic hepatitis** is usually associated with fatty change and is occasionally seen with cirrhosis. It results from prolonged alcoholic abuse. Pathologic findings include swelling of hepatocytes, followed by necrosis and polymorphonuclear inflammation, formation of **alcoholic hyaline (Mallory bodies)** in swollen hepatocytes, cholestasis, and beginning fibrosis. The appearance of fibrosis may be linked to the onset of cirrhosis.

c. **Alcoholic cirrhosis.** Early stages of disease show a large liver with micronodular formation. The end stage resembles postnecrotic cirrhosis. The amount of fat decreases as the amount of fibrous tissue increases.

N. **Benign tumors**

1. **Liver cell adenoma** incidence is increased with anabolic steroid and oral contraceptive use. It forms a mass, which may be mistaken for carcinoma or may rupture (especially during pregnancy).

Clinical Correlate

Both ***hemochromatosis and Wilson's disease*** *are associated with an increased risk of hepatocellular carcinoma.*

In a Nutshell

Alcoholic liver disease:

- *Fatty liver*
- *Alcoholic hepatitis*
- *Alcoholic cirrhosis*

Note

Steatosis *is usually asymptomatic and reversible. Fatty vacuoles displace hepatocellular nuclei peripherally.*

Note

Mallory bodies *may also be seen in Wilson's disease, hepatocellular carcinoma, and primary biliary cirrhosis. Besides history, the other helpful feature in distinguishing alcoholic hepatitis from these other entities is the extreme fatty change.*

2. **Nodular hyperplasia**
   a. **Focal nodular hyperplasia** refers to a solitary nodule that often has a fibrous capsule and bile ductules.
   b. **Nodular regenerative hyperplasia** describes multiple nodules composed of normal hepatocytes with a loss of normal radial architecture.
3. **Cavernous hemangiomas** are large, vascular, endothelial-lined spaces filled with red cells. Radiologically, they must be considered in the differential diagnosis of metastases to the liver.
4. **Bile duct adenomas** form small nodules that are not bile stained.
5. **Cysts** may be **single** (with serous fluid) or **multiple** (with brown, bile-stained fluid). Multiple cysts may be associated with adult polycystic kidney disease.

C. **Malignant tumors**

1. **Hepatocellular carcinoma (hepatoma)**
   a. **Epidemiology.** Hepatocellular carcinoma comprises 90% of primary liver neoplasms. It is strongly associated with cirrhosis and HBV infection, as well as with oral contraceptives, androgens, and aflatoxin B.
   b. **Clinical features** include tender hepatomegaly, ascites, weight loss, fever, polycythemia, and hypoglycemia. A friction rub may also be heard. **Alpha-fetoprotein (AFP)** is present in 50–80% of patients' serum. (AFP is also found with other forms of liver disease, pregnancy, fetal neural tube defects, and germ cell carcinomas of the ovaries and testes.) Death is due to gastrointestinal bleed and liver failure. Generally, metastases first occur in the lungs.
2. **Cholangiocarcinomas** are cancers of the intrahepatic bile duct and comprise 10% of primary liver neoplasms. In developing countries, this tumor is associated with infection with ***Clonorchis sinensis* (liver fluke)** and with primary sclerosing cholangitis.
3. **Hepatoblastoma** is a rare, malignant neoplasm of children.
4. **Angiosarcoma** is associated with **exposure to vinyl chloride** and **arsenic**.
5. **Metastatic tumors** are much more common than primary neoplasms, most commonly coming from the breast, lung, and colon. Multiple, well-circumscribed nodules in a markedly enlarged liver are seen.

II. **Reye's syndrome** is characterized by **fatty change in the liver and edema (non-encephalopathy)**. It usually affects children between 6 months and 15 years of age.

1. **Etiology** is unclear. It is frequently preceded by a mild upper respiratory infection, varicella, or influenza A or B infection. It is also associated with **aspirin administration** at levels that are not ordinarily toxic.

CLINICAL CORRELATE

In addition to liver disease, alcoholics suffer from a variety of other disorders. If a question presents an **alcoholic patient, keep in mind increased incidence of the following disorders:**

Esophagus:
- *Cancer*
- *Mallory-Weiss tears (after vomiting)*
- *Varices (with portal hypertension)*

Stomach:
- *Gastritis, reflux*
- *Peptic ulcer disease*

Pancreas:
- *Pancreatitis (#1 cause of chronic pancreatitis)*
- *Cancer*

Cardiac:
- *Cardiomyopathy (dilated)*

Respiratory:
- *Aspiration pneumonia*
- *Klebsiella pneumonia*
- *Tuberculosis*

Heme:
- *Megaloblastic anemia (folate deficiency)*
- *Coagulation defects (liver dysfunction)*
- *Thrombocytopenia due to congestive splenomegaly*
- *Acquired sideroblastic anemia*

Neuromuscular:
- *Wernicke's encephalopathy*
- *Korsakoff's amnestic syndrome*
- *Vestibulopathy*
- *Peripheral neuropathies*
- *Acute cerebellar degeneration*
- *Myopathy (in chronic alcoholism)*
- *Alcohol withdrawal syndrome, delirium tremens*

Acid/Base:
- *Ketoacidosis (increased anion gap)*

IN A NUTSHELL

Hepatocellular carcinoma is predisposed by cirrhosis, HBV, oral contraceptives, and aflatoxin B (fungal toxin).

IN A NUTSHELL

Reye's syndrome:
- *Fatty liver changes*
- *Vomiting*
- *Encephalopathy*
- *Preceded by URI or chickenpox with aspirin administration*

BILIARY DISEASE

A. [redacted]

1. **Incidence.** Cholelithiasis occurs in [redacted] and 8% of men in the United States. It is rare before age 20 but is seen in 25% of persons greater than [redacted].

2. **Etiology**
   a. [redacted]
      (1) **Pure cholesterol stones** are radiolucent, solitary, 1–5 cm in diameter, yellow, and smooth, with a glistening radial pattern on cut section.
      (2) The typical patient is [redacted] (multiparous), and [redacted] years of age [redacted]
      (3) Exogenous estrogens, clofibrate, high-calorie diet, obesity, diabetes mellitus, pregnancy, celiac disease, and increasing age all predispose to cholesterol stones.
   b. [redacted] are [redacted]. Pigment stones are clumps of pigment derived from [redacted].
   c. [redacted] comprise 80% of all stones and are associated with chronic cholecystitis. They are composed of [redacted].

3. **Pathogenesis.** Supersaturation of bile pigment or cholesterol and/or a decreased amount of phospholipid or bile salts predisposes to stone formation.

4. **Clinical features**
   a. Most stones remain in the gallbladder and are [redacted].
   b. Obstruction of the gallbladder or cystic duct may cause biliary colic, acute cholecystitis, or [redacted].
   c. Obstruction of the common bile duct may lead to obstructive jaundice and ascending cholangitis. Pancreatitis and gallstone ileus may also result from [redacted].

B. **Acute cholecystitis.** Most cases are caused by [redacted].

1. **Incidence** and risk factors are the same as those for cholelithiasis.

2. **Pathogenesis.** Calculus obstruction is followed by secondary bacterial infection in 75% of cases and by chemical irritation.

3. **Clinical features**
   a. Acute cholecystitis presents with [redacted].
   b. Most cases resolve with medical management. The remainder progress to empyema, gangrenous necrosis, or rupture. Patients exhibit symptoms of acute abdomen and require cholecystectomy.

Clinical Correlate

[redacted]

More

[redacted]

Figure 2-1. Chronic cholecystitis and cholelithiasis (gross).

C. **Chronic cholecystitis** is usually not preceded by acute cholecystitis but is always accompanied by cholelithiasis.

1. **Pathogenesis** is unclear. Inflammation is probably due to chemical injury from supersaturated bile not to irritation by stones.

D. **Cholesterolosis** refers to lipid-foci deposited in the gallbladder wall ("strawberry" gallbladder). It is asymptomatic and unrelated to cholelithiasis.

E. **Benign tumors**

1. **Papillomas** are small, pedunculated, branching lesions.
2. **Adenomas** form small, flat, elevated plaques.
3. **Adenomyomas** are a proliferation of smooth muscle and glands.

F. **Malignant tumors**

1. **Carcinoma of gallbladder**
   a. **Incidence.** The disease occurs predominantly in the elderly.
   b. **Risk factors** include cholelithiasis and cholecystitis (in up to 90% of patients).
   c. **Clinical features.** The disease is asymptomatic until late. It may present with dull abdominal pain, mass, weight loss, and anorexia.
   d. **Pathology**
      (1) Grossly, the tumor typically involves the fundus and neck.
      (2) Microscopically, 90% are differentiated or undifferentiated adenocarcinomas.
   e. **Prognosis** is poor with a 3% five-year survival rate.
2. **Carcinoma of bile ducts (cholangiocarcinoma)**
   a. **Incidence.** Men are affected more frequently than women, and patients are usually elderly.

IN A NUTSHELL

Gallbladder cancer is rare, often asymptomatic, and is usually adenocarcinoma.

CLINICAL CORRELATE

Cholangiocarcinoma or tumor of the bile ducts often presents with obstructive jaundice, right upper quadrant pain, and sometimes symptoms of pancreatitis due to obstruction of the pancreatic duct.

b. **Risk factors** include chronic inflammation, infections (e.g., liver flukes), and ulcerative colitis.
c. **Clinical features.** The disease presents with obstructive jaundice and its associated symptomatology.
d. **Prognosis** is usually poor because of ductal, lymphatic, and, to a lesser extent, hematogenous spread.

NUTRITIONAL DISORDERS

A. Marasmus

1. **Definition.** Marasmus is a condition of severe malnutrition or emaciation resulting from inadequate calorie intake.
2. **Clinical features** include "failure to thrive," loss of subcutaneous fat, muscle wasting, and a lower percentile in weight than in height.
3. **Pathology.** There is generalized hypoplasia and atrophy of tissues, and there may be mild anemia.

B. Kwashiorkor

1. **Definition.** Kwashiorkor refers specifically to inadequate protein intake. It may develop despite adequate caloric intake.
2. **Clinical features** include edema, anemia, dermatoses (e.g., pigmentary changes, desquamation, dusky erythema), hepatomegaly, hair changes, growth retardation, irritability, apathy, and low energy.
3. **Laboratory values.** Serum chemistry shows decreased serum total protein and albumin.

C. Iron deficiency

1. **Etiology.** Although iron deficiency is caused by dietary insufficiency, malabsorption may also play a causative role. In the United States, the most common cause of iron deficiency is blood loss from the GI tract.
2. **Clinical features** of iron deficiency, all of which are due to the varied metabolic functions of iron, include:
   a. **Hypochromic microcytic anemia**
   b. Functional folate deficiency
   c. Depressed cell-mediated immunity
   d. Gastric erosions

D. Zinc deficiency

1. **Etiology** is usually dietary insufficiency.
2. **Clinical features** include delayed wound healing, short stature, and diminished axillary, facial, and pubic hair. Zinc deficiency may predispose to alcoholic cirrhosis.

In a Nutshell

Marasmus:
- Calorie deficiency
- No edema

Kwashiorkor:
- Protein deficiency
- Edema

Cardiovascular disease affects a large segment of the population. In fact, atherosclerosis is the leading cause of death in the United States. Because the effects of cardiovascular disease are widespread and potentially lethal, it is important to be able to identify the major risk factors for each type of disease. This chapter will focus on the structural and functional changes that occur with diseases of the heart and vessels, as well as the major risk factors associated with each disease entity.

CONGENITAL ABNORMALITIES OF THE HEART

A. Overview

1. Etiology

a. During cardiac development, insults must occur before the end of week 16 (completion of heart development) for a congenital defect to occur.

b. Chromosomal abnormalities (e.g., trisomy 13, 18, 21) may lead to specific cardiac anomalies.

c. Mendelian hereditary syndromes (e.g., Marfan's, Ehlers-Danlos) may also be associated with specific cardiac defects, as well as with other developmental anomalies.

d. Environmental causes (e.g., maternal rubella, alcohol, smoking) may have variable effects, depending on when and how severe the insult is to the mother and fetus.

e. Up to 90% of congenital heart disease is of unknown etiology.

f. Cardiomegaly, heart murmurs, and congestive heart failure

g. Chronic cyanosis, which will cause polycythemia, clubbing of fingers and toes, and hypertrophic osteoarthropathy

Clinical Correlate

Some of the resultant mismatch are VSDs.

5. **Acyanotic congenital heart disease** (left-to-right shunts). In this disease, blood is abnormally shunted from the **left to the right** side of the heart. This causes chronic right heart failure and secondary pulmonary hypertension as a result of increased pressure and flow. Right heart pressure may eventually increase to become greater than left heart pressure, and the shunt will reverse, becoming a right-to-left shunt that results in late onset cyanosis.
   1. **Ventricular septal defect (VSD)** is an abnormal communication between ventricles, usually at the membranous interventricular septum. The clinical significance depends on the volume of the shunt. It is often associated with other defects.

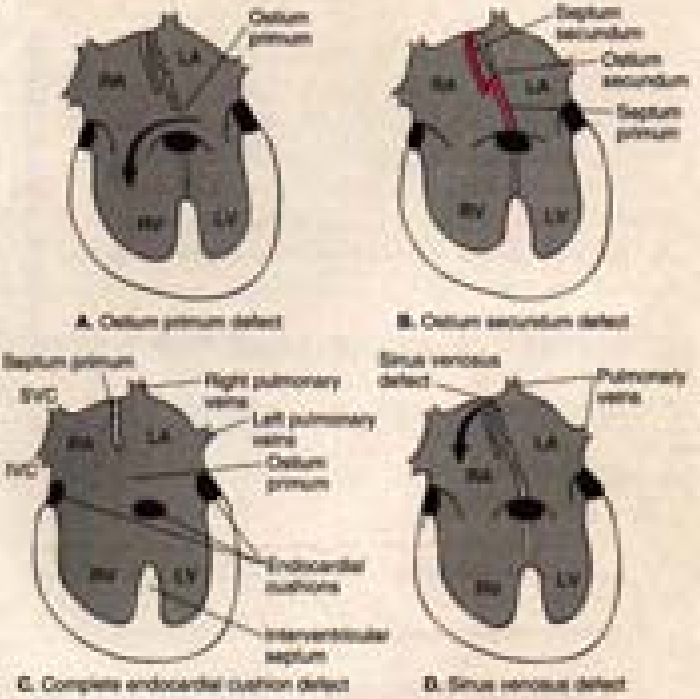


Figure 3-1. Common configurations of atrial septal defects.

Note

In approximately 25% of adult hearts, the atrial septum actually remains open, but is kept functionally closed by the normal pressure differential between the right and left atria.

   2. **Atrial septal defect (ASD)** is an abnormal communication between the atria (Figure 3-1). The clinical significance depends on the volume of the shunt.
      a. **Ostium primum defects** account for approximately 5% of all ASDs. The defect is in the lower atrial septum above the atrioventricular (AV) valves. It may be associated with maldeveloped AV valves.
      b. **Ostium secundum** defects account for approximately 80% of all ASDs. The defect is in the center of the atrial septum at the fora-

ostia ovalis, resulting from abnormalities of the septum primum, septum secundum, or both. It is not associated with maldeveloped AV valves.

c. **Complete endocardial cushion defect** results in an ASD, a VSD, and a common AV canal.

d. **Sinus venosus** accounts for approximately 5% of all ASDs. It occurs a defect in the upper part of the atrial septum and may cause anomalous venous return from the pulmonary veins into the superior vena cava or right atrium.

e. **Patent foramen ovale** is a slit-like remnant of the foramen ovale and is usually not of clinical significance.

3. **Patent ductus arteriosus (PDA)** is a defect in which oxygenated blood flows from the aorta to the pulmonary artery. This deprives the systemic circulation of oxygenated blood and eventually leads to pulmonary hypertension. Indomethacin can be used to close a PDA, whereas the prostaglandin PGE1 can be utilized to keep it open if necessary.

C. **Cyanotic congenital heart disease** (right-to-left shunts): in these diseases, blood is shunted from the right to the left side of the heart, causing poorly oxygenated blood to be pumped out to the systemic circulation. This causes immediate cyanosis and paradoxic paradoxical embolism, in which venous emboli bypass the pulmonary circulation and directly enter the systemic circulation (Figure 3-2).

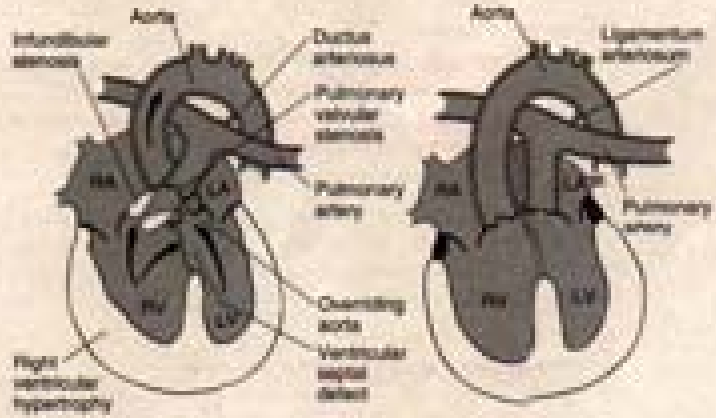


Figure 3-2. Common forms of cyanotic congenital heart disease

1. **Tetralogy of Fallot** has four specific anomalies and is the most common cyanotic congenital heart disease in older children and adults.

Kaplan

RVH/cor pulmonale: pulmonary hypertension due to excess blood to pulmonary artery (leads to ↑ pressure)

a. The four lesions are:
   (1) **VSD**
   (2) **An overriding aorta** that receives blood from both ventricles
   (3) **Right ventricular hypertrophy**
   (4) **Pulmonic stenosis** (right ventricular outflow obstruction)
b. The clinical significance depends on the degree of right ventricular outflow obstruction.
c. Deoxygenated blood is shunted to the left side of the heart through the VSD, and blood flows from both ventricles into the enlarged aorta with little reaching the lungs.
d. A PDA permits survival if the pulmonary artery is completely obstructed.

2. **Transposition of the great vessels** results from a failure of the truncoconal septum to spiral during development. The aorta arises from the right ventricle, and the pulmonary artery arises from the left ventricle. This is often associated with other anomalies. Either PDA, a VSD, an ASD, or a patent foramen ovale mixes venous and systemic blood and therefore permits survival.
3. **Persistent truncus arteriosus** is the failure of the aorta and pulmonary arteries to separate. There is also a VSD, usually at the membranous interventricular septum. The truncus arteriosus receives blood from both ventricles, so cyanosis results.

D. **Obstructive congenital heart disease.** This form of developmental defect typically does not cause cyanosis.

1. **Coarctation of the aorta**
   a. In the **preductal (infantile) type**, there is narrowing of the aorta proximal to the opening of the ductus arteriosus.
   b. In the **postductal (adult) type**, there is narrowing of the aorta distal to the opening of the ductus arteriosus. This is the most common type and generally allows survival into adulthood.
2. **Pulmonary valve stenosis or atresia.** This lesion may be due to an unequal division of the truncus arteriosus so that the pulmonary trunk has no lumen or opening at the level of the pulmonary valve. It may cause cyanosis if severe.
3. **Aortic valve stenosis or atresia**
   a. Complete atresia will not support neonatal life.
   b. Bicuspid aortic valves may be asymptomatic but can lead to infective endocarditis, left ventricular overload, and sudden death. This lesion is the second most common cause of aortic stenosis, after rheumatic fever.

E. **Abnormalities associated with genetic syndromes**

1. **Marfan's syndrome.** One-third of patients have congenital cardiovascular disease characterized by aortic dilatation and incompetence, aortic dissection, and ASD.

2. **Down's syndrome** (trisomy 21). Twenty percent of patients may have congenital cardiovascular disease, characterized by an [redacted]
3. **Turner's syndrome** patients frequently have [redacted]

f. **Abnormalities associated with perinatal insults**

1. **Maternal infection with rubella** in the fifth to tenth weeks can lead to [redacted]
2. **Fetal alcohol syndrome** can lead to [redacted], including VSD.
3. **Maternal ingestion of drugs** such as [redacted] (anticonvulsant medication) and [redacted] (retin-A) can cause [redacted]

ISCHEMIC HEART DISEASE (IHD)

A. **Overview**

1. IHD occurs when the [redacted]. It is the leading cause of death (along with hypertensive and valvular diseases) in the United States.
2. Ischemia is caused (alone or in combination) by the following conditions:
   a. **[redacted]**, often precipitated by vasospasm or overlying thrombus, is the most frequent cause of cardiac ischemia. Most infarctions occur when multiple vessels are narrowed.
      (1) Ninety percent of cases are due to atherosclerosis.
      (2) The underlying lesion is usually a complicated plaque, with calcification, ulceration, or overlying thrombus.
      (3) Less common causes include dissecting aortic aneurysm, arteritis, coronary embolism, and cocaine-induced vasospasm.
      (4) Perfusion is impaired when the cross-sectional area of the lumen is reduced by more than 75%.
   b. **[redacted]** of the blood from anemia, carbon monoxide poisoning, pulmonary disease, or smoking may lead to cardiac ischemia, particularly in combination with atherosclerosis.
   c. **[redacted]** from tachycardia or hypertrophy may also increase the risk of ischemia.
3. IHD is categorized into four syndromes.
   a. **[redacted]** is [redacted] due to ischemia.
   b. **[redacted]** is [redacted] due to insufficient blood supply.
   c. **[redacted]** may or may not cause angina or myocardial infarction. Some patients merely experience heart failure.

d. **Sudden cardiac death** is the presenting symptom in 25% of patients with IHD.

B. **Angina pectoris.** This syndrome is **paroxysmal substernal or precordial chest pain,** caused by transient myocardial ischemia without myocardial infarction. Prolonged and repeated angina pectoris may cause focal fibrosis and subendocardial myocardial vacuolization, indicating gradual loss of myocytes. Angina and its resultant fibrosis are associated with impaired diastolic relaxation, increased diastolic filling pressure, and subsequent pulmonary congestion with resultant dyspnea.

1. **Stable angina pectoris**
   a. Paroxysms are associated with a fixed amount of exertion.
   b. Typical attacks last less than 10 minutes and are relieved with rest or sublingual nitroglycerin.
   c. EKG may show ST segment depressions (ischemia limited to subendocardium).
   d. Most angina pectoris is caused by severe atherosclerotic narrowing of coronary arteries.
2. **Prinzmetal's angina pectoris** (paroxysmal vasospasm)
   a. Vasospasm causes decreased blood flow through atherosclerotic vessels.
   b. This form of attack frequently occurs at rest with ST-segment elevations on EKG.
3. **Unstable angina pectoris** often leads to myocardial infarction.
   a. It can present with prolonged chest pain, abnormally severe pain, or pain at rest in a person with stable angina.
   b. It is often unresponsive to nitroglycerin.

C. **Myocardial infarction**

1. **Overview**
   a. Myocardial infarction is **ischemic necrosis of the myocardium,** resulting from an abrupt decrease in coronary blood flow or a sudden demand for increased myocardial delivery, which cannot be met because of coronary artery narrowing. It is more commonly transmural but can be subendocardial.
   b. Myocardial infarction is more common in men than women; the highest incidence of fatal myocardial infarction is from 55–64 years old.
   c. **Risk factors** include hypertension, hypercholesterolemia, cigarette smoking, family history, diabetes mellitus, oral contraceptive use, and sedentary life style.
   d. **Type A personalities** (aggressive, compulsive) may have an increased risk.
   e. **Regular exercise and moderate alcohol use** (one glass of wine per day) may decrease the risk by raising the level of high-density lipoprotein (HDL).

2. **Types of infarcts**
   a. **Transmural infarcts** are infarctions of the full thickness of the ventricular wall. They are usually due to occlusion of vessels from severe coronary atherosclerosis, formation of complicated atheromatous plaques with ulceration or fissure, and thrombosis. Occlusions occur most often in the proximal left anterior descending (50%), right coronary (25%), and left circumflex (15%) arteries.
   b. **Subendocardial infarcts** are infarctions limited to the inner half of the ventricular wall. The subendocardium is more vulnerable to generalized myocardial hypoperfusion than are other areas, usually because of diffuse atherosclerosis without thrombosis and resultant borderline ischemia. Infarction occurs when flow is further compromised (e.g., CHF, shock, arrhythmia, vasospasm, severe hypertension) or when oxygen demand is increased (e.g., exertion, tachycardia).

3. **Clinical features**
   a. There is acute, severe, crushing chest pain, often radiating to the jaw or left arm.
   b. The pain is associated with diaphoresis, a sense of impending doom, nausea, anxiety, and shortness of breath.
   c. ECG abnormalities consist of ST elevation and T-wave inversion (with Q-wave development) and ST depression (without Q-wave development). Q waves may develop with transmural infarcts.
   d. Elevated cardiac enzymes (Figure 3-3) include:
      (1) **MB isoenzyme of creatine kinase (CK-MB)**, which is the most sensitive in common use
      (2) **Lactate dehydrogenase** (specifically the LDH 1 isoenzyme), which is elevated rather specifically in myocardial infarction
      (3) **Serum glutamic-oxaloacetic transaminase** (SGOT) or **aspartate transaminase** (AST) also rises and falls predictably in myocardial infarction but may indicate liver damage instead.

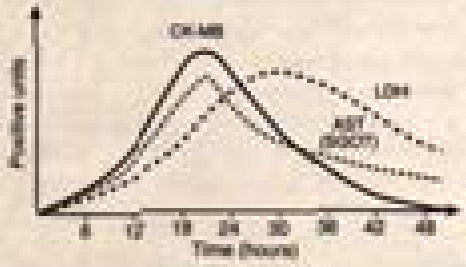


Figure 3-3. Enzymology of myocardial infarction. CK = creatine kinase, LDH = lactate dehydrogenase, AST = aspartate transaminase, and SGOT = serum glutamic-oxaloacetic transaminase

Note

Atypical presentations of MI with little or no chest pain can be seen most frequently in women, the elderly, diabetic patients, and surgical patients.

4. **Prognosis**
   a. Sudden cardiac death, secondary to a fatal arrhythmia, occurs in 25% of patients with an acute myocardial infarction.
   b. Mortality after myocardial infarction is 25% in the first year, 45% in the second year, and 55% in the third year.
   c. 85–90% of survivors develop complications.
5. **Complications** are listed below in order of frequency.
   a. **Arrhythmias** (ventricular fibrillation is the most serious). Ischemia and necrosis of the AV node and three fascicles of the conduction system can lead to heart block with compromise of cardiac function.
   b. **CHF** may be seen with a loss of 20% or more of the ventricular muscle.
   c. **Cardiogenic shock** results when there is a loss of 40% or more of the left ventricular muscle, resulting in the inability of the heart to maintain an adequate output to vital organs. Mortality is greater than 80%.
   d. **Thrombus formation**, resulting from lack of contractility of the infarcted area and abnormal endothelium, may follow myocardial infarction. This may be a source of systemic or cerebral emboli in large anterior wall infarctions.
   e. **Aneurysm formation** (outpouching of noncontractile scar) results in depression of cardiac output; rupture is uncommon. It may be the site of ectopic ventricular electrical activity, leading to fibrillation.
   f. **Myocardial (ventricular) rupture**
      (1) Patients are most susceptible 1–7 days after infarct when the myocardium is necrotic but granulation tissue formation has not really begun.
      (2) Rupture is most common with anteroapical infarction and is almost uniformly fatal; it results from sudden bleeding into the pericardial sac and tamponade.
   g. **Postinfarction pericarditis** (Dressler's syndrome) occurs 2–10 weeks postinfarction.
   h. **Acute mitral insufficiency** may be caused by papillary muscle infarction with or without rupture.
6. **Treatment and management**
   a. **Coronary artery bypass** with saphenous vein or internal mammary artery grafts restores circulation and eliminates angina. Grafts last approximately 10 years before restenosis typically occurs.
   b. **Angioplasty** (balloon dilatation) also restores circulation; half restenose in one year.

RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

A. **Acute rheumatic fever (ARF)** is a recurrent inflammatory disease that typically follows pharyngitis caused by **group A β-hemolytic streptococci**.

1. **Incidence.** ARF is found mainly in children 5–15 years old. There has been a declining incidence and mortality in the last 40 years, mostly due to penicillin, though the incidence began to drop even before penicillin was widely used.
2. **Pathogenesis.** Antistreptococcal antibodies made by the infected host cross-react with host connective tissue (i.e., cardiac, pulmonary, synovial, peritoneal) antigens and lead to end-organ damage by an immunologic mechanism.
3. **Clinical features**
   a. Onset is typically 1–3 weeks after streptococcal pharyngitis, otitis media, or tonsillitis.
   b. **Major Jones criteria.** In context of prior streptococcal infection, the presence of two of five clinical features (**major Jones criteria**) is sufficient to diagnose ARF. Alternatively, the presence of one major Jones criterion plus two minor Jones criteria (see "c" below) is also highly suggestive of the disease.
      (1) **Migratory polyarthritis** involves the larger joints of the extremities, producing red, swollen, and painful manifestations. This feature is more common in adults than children.
      (2) **Erythema marginatum** is a macular skin rash, often in a "bathing suit" distribution.
      (3) **Sydenham's chorea** is involuntary, choreiform movements of the extremities that are seen more frequently in women.
      (4) **Subcutaneous nodules** containing Aschoff bodies.
      (5) **Carditis** may affect the endocardium, myocardium, or pericardium. Myocarditis causes most deaths during the acute stage. Chronic scarring of the endocardium and heart valves may lead to chronic rheumatic heart disease (RHD).
   c. **Minor Jones criteria** include previous rheumatic fever, fever, arthralgias, prolonged P-R interval on ECG, elevated erythrocyte sedimentation rate, leukocytosis, and elevated C-reactive protein.
4. **Complications.** Initial episodes of ARF last weeks to months and often recur into young adulthood. Mortality is low, but the disease often leads to chronic valvulitis of the mitral and aortic valves.

B. **Rheumatic heart disease (RHD)** causes dysfunctional, deformed heart valves through chronic inflammatory insult, deposition of fibrin and platelet thrombi, and then fibrosis.

1. **Clinical features.** The patient is usually asymptomatic from puberty until young adulthood.
   a. Valve leaflets become red and swollen and develop fibrinous, friable vegetations (verrucae) along lines of closure.
   b. The mitral valve is most commonly (75–80%) affected. Next in frequency is the aortic and mitral valve combination (20–25%). The aortic valve alone is involved in 50% of patients. The tricuspid and pulmonic valves are rarely affected.

BRIDGE TO MICROBIOLOGY

Key features of group A streptococci:
- *β hemolytic*
- *Have M protein that confers virulence*
- *Catalase negative*
- *Sensitive to bacitracin*
- *Produce streptolysins S and O*

CLINICAL NOTE

Rheumatic heart disease is an indication for premedication before a dental appointment.

c. Valve dysfunction usually presents as a combination of stenosis and insufficiency with one predominating.
d. Fibrosis and deformity lead to "fish mouth" or "buttonhole" stenosis of the mitral valve, which may cause the patient to present with cardiac murmurs, left atrial dilatation, mural thrombi, and right ventricular hypertrophy.
e. Chronic valvulitis predisposes to infective endocarditis. CHF is the ultimate result, although it takes years to develop.

2. **Pathology**
   a. **Aschoff bodies.** Aschoff bodies are pathognomonic lesions, usually located in interstitial myocardial connective tissue, especially near vessels but may be found elsewhere (e.g., subcutaneous nodules, pericardium).
3. **Treatment** involves prophylaxis of infective endocarditis, balloon valvuloplasty, or valve replacement.

In a Nutshell

Aschoff bodies = rheumatic heart disease

CONGESTIVE HEART FAILURE (CHF)

A. **Overview**
   1. CHF is often the final outcome of many cardiac diseases, resulting from the inability of the heart to provide adequate cardiac output to meet the body's metabolic demands.
   2. It is most often due to decreased myocardial contractility (e.g., myocardial infarction or fibrosis) or pressure/volume overload (e.g., hypertension).
   3. Compensatory changes that increase the workload of the heart and ultimately result in CHF:
      a. Hypertrophy and dilatation of the heart caused by compensation for increased workload or volume.
      b. Tachycardia in response to decreased stroke volume.
      c. Salt and water retention, which causes an expansion of blood volume.

B. **Left-sided heart failure** (decreased systolic ejection of blood)
   1. **Etiology.** Left-sided heart failure is most often caused by ischemic heart disease and valvular disease (particularly aortic stenosis or insufficiency), hypertension, or cardiomyopathy.
   2. **Clinical features**
      a. **Pulmonary congestion and edema,** resulting from pooling of blood in the pulmonary circulation, cause increased pulmonary venous pressure. Clinically, patients present with shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, and cough.
      b. **Renal hypoperfusion** stimulates the renin-angiotensin-aldosterone axis, causing retention of salt and water. Fluid retention exacer-

lates the pulmonary edema. Hypoperfusion may also cause prerenal azotemia and acute tubular necrosis.

c. **Cerebral hypoxia**, secondary to decreased perfusion, may lead to encephalopathy, stupor, or coma.

C. **Right-sided heart failure**

1. **Etiology.** Right-sided heart failure is most often caused by:
   a. Left-sided heart failure, causing back pressure through the lungs
   b. Cor pulmonale, valvular disease (particularly pulmonary stenosis or insufficiency), and cardiomyopathy. Mitral stenosis and insufficiency lead to back pressure on the right ventricle.
2. **Clinical features.** Right-sided failure is characterized by systemic venous congestion, leading to:
   a. Chronic passive congestion of the liver (nutmeg liver) with eventual centrilobular necrosis, followed by central hemorrhagic necrosis, and finally, (with fibrosis) cardiac sclerosis
   b. Renal hypoperfusion with salt and water retention (more severe than in left-sided heart failure)
   c. Splenomegaly
   d. Ascites, edema, pleural effusions, and cerebral hypoxia

D. **Cor pulmonale** is right ventricular failure, resulting specifically from pulmonary hypertension.

1. **Etiology**
   a. Pulmonary parenchymal disease, causing increased pulmonary vascular resistance (e.g., COPD, TB, pneumoconiosis, or carcinoid)
   b. Pulmonary vascular disease (e.g., vasculitis, shunts, or multiple emboli)
   c. Restrictive chest wall abnormalities (a rare cause)
2. **Types**
   a. **Acute cor pulmonale** is a dilatation of the right ventricles caused by massive pulmonary embolization that may cause tricuspid regurgitation.
   b. **Chronic cor pulmonale** is a gradual hypertrophy of the right ventricle, usually due to pressure overload.

SHOCK

A. **Pathogenesis.** Shock occurs when decreased blood volume or decreased circulation leads to inadequate perfusion of body tissues and cells.

B. **Etiology**

1. **Decreased cardiac function** leads to inadequate cardiac output. Myocardial infarction, arrhythmia, tamponade, or aortic stenosis all may lead to reduced output.
2. **Reduction of blood volume,** resulting from hemorrhage, adrenal insufficiency (Addison's disease), or fluid loss (vomiting and diarrhea), may lead to poor perfusion even with adequate cardiac function.

CLINICAL CORRELATE

The clinical hallmarks of right-sided failure:

- *Jugular venous distension (JVD)*
- *Hepatomegaly*
- *Splenomegaly*
- *Generalized edema*

3. **Pooling of blood in peripheral vessels** may occur as a result of the loss of vascular tone caused by bacterial toxins and vasoactive substances (free radicals, anaphylatoxins). This results in loss of vascular volume into the extracellular space.

C. **Complications. Cellular hypoxia** leads to increased anaerobic metabolism and resultant lactic acidosis, causing:

1. Encephalopathy
2. Myocardial necrosis and infarcts
3. Pulmonary edema and "shock lung" (adult respiratory distress syndrome)
4. Acute tubular necrosis in the renal cortex
5. Various hypoxic injuries to other organs

D. **Stages of compensation in shock**

1. **Compensated stage.** In this stage, early hypotension leads to reflex tachycardia and to peripheral vasoconstriction, stimulated by the CNS, causing cold, clammy, and pale extremities.
2. **Decompensated stage**
   a. Initial compensatory changes become insufficient to maintain adequate cardiac output.
   b. Decreased blood pressure, increased tachycardia, metabolic acidosis, respiratory distress, and decreased renal output may all eventually occur.
3. **Irreversible stage.** The above changes lead to irreversible cellular damage, coma, and death.

E. **Treatment.** Correction of the initial metabolic and physiologic derangements (prior to the irreversible stage) permit reversal of organ damage and prevent coma and death.

Flashback to Physiology

Reflex tachycardia and peripheral vasoconstriction occur via baroreceptor mechanisms.

Table 3-1. Prophylactic regimens for dental, oral respiratory tract, or esophageal procedures.

Situation	Agent	Regimen*
Standard general prophylaxis	Amoxicillin	Adults: 2.0 g; children: 50 mg/kg orally 1 h before procedure
Unable to take oral medications	Ampicillin	Adults: 2.0 g intramuscularly (IM) or intravenously (IV); children: 50 mg/kg IM or IV within 30 min before procedure
Allergic to penicillin	Clindamycin	Adults: 600 mg; children: 20 mg/kg orally 1 h before procedure
	Cephalexin† or cefadroxil†	Adults: 2.0 g; children: 50 mg/kg orally 1 h before procedure
	Azithromycin or clarithromycin	Adults: 500 mg; children: 15 mg/kg orally 1 h before procedure
Allergic to penicillin and unable to take oral medications	Clindamycin	Adults: 600 mg; children: 20 mg/kg IV within 30 min before procedure
	Cefazolin†	Adults: 1.0 g; children: 25 mg/kg IM or IV within 30 min before procedure

* Total children's dose should not exceed adult dose.
† Cephalosporins should not be used in individuals with immediate-type hypersensitivity reaction (urticaria, angioedema, or anaphylaxis) to penicillins.

ENDOCARDITIS

A. **Infective endocarditis** is the colonization of heart valves with bacteria.

1. **Pathology**
   a. **Grossly**, the colonies form large, friable, vegetative masses, overhanging the free margins of the valve leaflet, prosthetic valve, or other cardiac defect.
   b. **Microscopically**, a mass of clot, fibrin, and bacteria is seen. In the healing phase, there is fibrosis and calcification.
   c. Infective endocarditis usually involves the **mitral valve**.
   d. It can involve right-sided valves in intravenous drug users, but left-sided valves may be involved as a result of paradoxic embolization or when bacteria flow through the pulmonary capillaries.

2. **Etiology**
   a. There may be implantation of colonies from transient (i.e., dental procedures, minor skin infections) or persistent bacteremia (i.e., infected intravenous catheter).
   b. **Streptococci** cause 65% of infective endocarditis, usually producing a subacute bacterial endocarditis.
   c. **Staphylococci** cause 25–30% of infective endocarditis, usually producing acute bacterial endocarditis. Intravenous drug abuse often causes staphylococcal infection from the skin, but the spectrum of organisms is wide.
   d. **Candida** is a cause of endocarditis in intravenous drug users.
   e. **Risk factors**
      (1) Congenital cardiac anomalies with high pressure jet streams (e.g., VSD or stenoses) that produce endothelial injury.
      (2) Valvular abnormalities (e.g., mitral valve prolapse, prosthetic valves, bicuspid aortic valve, and RHD).
      (3) Immunosuppression, neutropenia, and intravenous drug abuse may contribute to infective endocarditis.
   f. **Bacterial byproducts** are swept off infected valves, resulting in the absence of an inflammatory reaction. This explains how a typically nonvirulent organism (e.g., Streptococcus viridans) can cause progressive disease.

3. **Types**
   a. **Acute bacterial endocarditis (ABE)**
      (1) Infection is usually caused by highly virulent organisms such as Staphylococcus aureus (50%) and Streptococci (35%), and it is typically seen in previously normal valves.
      (2) It often involves the tricuspid valve in intravenous drug abusers.
      (3) **Vegetations** may become large, leading to myocardial abscess formation or systemic septic emboli. Vegetations may eat

NOTE

- *Acute bacterial endocarditis → most likely Staphylococcus aureus*
- *Subacute → more likely Streptococcus viridans*

CLINICAL CORRELATE

Endocarditis involving the right side of the heart suggests intravenous drug abuse.

through valve leaflets, producing the sudden onset of valvular incompetence and a new heart murmur.

b. **Subacute bacterial endocarditis (SBE)**

(1) **Etiology.** Infection is caused by organisms of low virulence, such as *Streptococcus viridans*, *Staphylococcus epidermidis*, Enterococci, or Gram-negative bacilli. Candida infections are rare and are usually associated with indwelling vascular catheters.

(2) **Pathology.** It is typically seen on previously abnormal valves. Regions of turbulent blood flow produced by abnormal valves permit formation of sterile platelet-fibrin aggregates on valve leaflets that become seeded during transient bacteremia. Vegetations are less bulky and less invasive than in ABE.

(3) **Clinical features.** There is an insidious onset, clinically presenting with positive blood cultures, fatigue, low-grade fever without chills, anemia, splenomegaly, and hematuria.

4. **Complications of infective endocarditis**

a. Cardiac valve perforation with acute heart failure in acute infective endocarditis

b. Myocardial abscess formation with perforation of the septum or involvement of the conduction system, leading to heart block

c. Mitral annulus and papillary muscle abscesses, leading to mitral valve prolapse

d. Right-sided septic emboli, causing pneumonia or lung abscess

e. Left-sided septic emboli, causing strokes and abscesses in the brain, spleen, and kidney

f. Nephritis may occur by:

(1) Immune complex deposition of IgM, complement component C3, and bacterial antigen in glomerular basement membranes

(2) Septic emboli, leading to renal abscess formation with rupture of the abscess into renal tubules, causing hematuria

VALVULAR HEART DISEASE

A. **Mitral valve prolapse**

1. **Etiology**

a. Prolapse of the mitral valve will lead to mitral insufficiency. The mitral leaflets (usually the posterior leaflets) billow into the left atrium during systole, leading to insufficiency.

b. Some cases may be due to a defect in connective tissue metabolism.

2. **Pathology**

a. **Grossly,** it presents as large ballooning leaflets with elongated, drawn out, and possibly ruptured chordae tendineae.

b. **Microscopically,** degeneration of the outer zona fibrosa and thickening of the inner zona spongiosa are seen.

3. **Incidence.** Mitral valve prolapse (MVP) is found in 7% of the United States population, most commonly in young women; it is seen in most patients with Marfan's syndrome.
4. **Clinical features**
   a. Mitral prolapse presents with a characteristic **midsystolic click** and **high-pitched murmur.** Patients are usually asymptomatic but may have dyspnea, tachycardia, chest pain, syncope, eventual CHF, or rarely, sudden death.
   b. Prolapse may coincide with tricuspid or pulmonary valve disease. It may also be associated with psychiatric conditions (e.g., anxiety, depression) through an unknown mechanism.
5. **Complications** include atrial thrombosis, calcification, infective endocarditis, embolization (to brain), rupture of chordae, arrhythmias, and sudden death. MVP can also lead to mitral regurgitation/insufficiency and premature ventricular contractions (PVCs).

B. **Mitral stenosis**

1. **Pathogenesis.** Mitral stenosis is due to scarring, calcification, and fusion of the mitral valve, interfering with its opening. It is most commonly caused by rheumatic heart disease.
2. **Clinical features**
   a. Mitral stenosis presents with increased left atrial pressure and an enlarged left atrium. Stenosis may be combined with mitral valve prolapse.
   b. An **early diastolic opening snap** is characteristic of mitral stenosis. Severe mitral stenosis can lead to backward failure (e.g., CHF) if the valve fails to open sufficiently.
3. **Complications.** Prolonged stenosis, producing left atrial enlargement, may eventually produce chronic atrial fibrillation, which predisposes to atrial thrombosis.

C. **Aortic valve insufficiency**

1. **Acute**
   a. It may lead to left ventricular failure due to increased left ventricular filling pressure, inadequate stroke volume, decreased diastolic filling time (due to reflex tachycardia), and myocardial ischemia.
   b. Acute insufficiency may result from perforations or tears from infective endocarditis.
2. **Chronic**
   a. The left ventricle will dilate and hypertrophy to accommodate the gradual increase in regurgitating diastolic volume and to maintain adequate net cardiac output.
   b. A wide pulse pressure (clinically seen as bounding pulses) causes reflex tachycardia.

NOTE

Insufficiency = regurgitation

Backflow through the aortic valve leads to ↑ LV volume, therefore ↑ filling pressure leading to LV failure.

c. It may be due to a congenitally bicuspid aortic valve, RHD, or syphilis.

D. **Aortic valve stenosis**

1. **Etiology**
   a. Calcific (degenerative) heart disease causes 90% of stenotic valves.
   b. The aortic valve is affected somewhat less than the mitral valve in RHD.
   c. Congenital heart disease causes a higher percentage of stenosis since the advent of penicillin.
2. **Incidence** increases with age.
3. **Pathology**
   a. It is often associated with a congenitally abnormal (e.g., bicuspid) aortic valve.
   b. **Grossly**, it presents as large calcified masses with thickening and fibrosis of valve cusps without fusion of valve commissures; rheumatic aortic valve stenosis involves fusion of the valve leaflets.
4. **Clinical Features**
   a. It presents with angina, syncope, and CHF; it is often asymptomatic until late in the course of the disease.
   b. Signs of increasing stenosis include decreasing peripheral pulse pressure, slowing of the carotid upstroke, and increasing left ventricular hypertrophy as a result of chronic pressure overload.
   c. A systolic ejection click is characteristic of aortic valve stenosis.
5. **Complications.** It may lead to sudden death, secondary to an arrhythmia or CHF.
6. **Treatment.** Definitive treatment is surgical replacement of the aortic valve.

E. **Mitral annulus calcification** is a deposition of calcium within the ring of tissue surrounding the base of the mitral valve. It is a degenerative, non-inflammatory disorder.

1. It may lead to mitral regurgitation because of the inability of the mitral valve ring to close during contraction of the left ventricle.
2. It usually occurs in the elderly and is associated with IHD.

F. **Valve replacement**

1. Both mechanical and bioprosthetic (usually porcine) valves may be indicated in:
   a. Mitral and aortic valve stenosis
   b. Mixed mitral valve stenosis and insufficiency
   c. Mitral and aortic valve insufficiency (regurgitation)
2. **Complications** that occur in 10% of patients a year, include:

a. Thromboembolism
b. Infective endocarditis
c. Paravalvular leak through the suture line (a problem exacerbated by calcification of the mitral annulus)
d. Microangiopathic hemolysis (mechanical trauma to passing RBCs as a result of the presence of an artificial valve). This is diagnosed by observing fragmented RBCs (schistocytes) on the blood smear.

MYOCARDITIS

A. **Overview.** Myocarditis is an inflammation of the myocardium that may lead to necrosis. **Noninfectious myocarditis** may be due to a hypersensitivity reaction seen in collagen vascular diseases, rheumatic fever, SLE, and drug allergies. It may also contribute to pathology in viral myocarditis. Trauma, which produces inflammation or necrosis, may also produce myocarditis.

B. **Pathology**

1. **Grossly**, it presents with dilatation and hypertrophy of all four chambers. A diffuse but patchy hemorrhage in the myocardium with eventual small, pale foci of fibrosis can be seen.
2. **Microscopically**, myocarditis is characterized by focal inflammatory lesions with:
   a. A neutrophilic infiltrate, abscess, or granuloma in bacterial myocarditis
   b. A mononuclear infiltrate and necrosis in viral myocarditis
   c. An eosinophilic infiltrate with giant cell and granuloma formation in Fiedler's myocarditis

C. **Etiology**

1. **Viral myocarditis** is the most common form of myocarditis (especially **coxsackie B virus**).
   a. Polio, rubella, and influenza viruses have also been described as etiologic agents.
   b. It is usually self-limited, but it may be recurrent and lead to cardiomyopathy and death.
   c. Approximately one-third of AIDS patients show focal myocarditis on autopsy.
2. **Bacterial myocarditis** may be due to diphtheria, meningococci, or other bacteria. These bacteria may damage the heart directly or via secreted toxins, such as diphtheria toxin.
3. **Protozoal etiology**
   a. *Trypanosoma cruzi* causes **Chagas' disease**, which is characterized by trypanosome-containing myocardial pseudocysts, causing myocardial necrosis. Fifty percent of the population is infected in

BRIDGE TO MICROBIOLOGY

Coxsackie B viruses are positive-sense RNA viruses belonging to the Picornavirus family.

CLINICAL CORRELATE

Romaña's sign—unilateral swelling of the eyelid—is a sign of Chagas' disease.

endemic areas of South America, and it is an important cause of congestive heart failure in that area of the world.

b. Toxoplasmosis also causes myocardial pseudocysts.

D. **Clinical features**

1. Myocardial involvement appears days to weeks after the primary infection. There is a variable severity, depending on the etiology.
2. Myocarditis may be asymptomatic with EKG abnormalities only, or it may present with the acute onset of dyspnea, tachycardia, weakness, or severe CHF. Edema is common to all forms of myocarditis.
3. It may have a protracted or a fulminant course; most patients recover fully without long-term adverse effects.

PERICARDIAL EFFUSION

Pericardial effusion is leakage of fluid (transudate or exudate) into the pericardial space. It may result in cardiac tamponade, in which the collection of fluid compresses the heart, limiting filling during diastole, and decreasing cardiac filling.

A. **Serous effusion** results from hypoproteinemia or CHF. It usually develops slowly, rarely causing cardiac compromise.

B. **Serosanguineous effusion** is usually due to trauma (e.g., cardiopulmonary resuscitation), tumor, or TB. It rarely causes cardiac compromise.

C. **Hemopericardium** occurs when blood flows into the pericardial sac as a result of trauma, ventricular rupture (after myocardial infarction), or aortic rupture. There is no inflammatory infiltrate. This condition can quickly cause cardiac tamponade and death.

Clinical Correlate

Hemopericardium can be a complication of algunas CHF.

CONGENITAL ABNORMALITIES OF VESSELS

A. **Berry aneurysms** are focal weakenings in **cerebral vessel walls**, resulting in an outpouching. They are most common at branch points in the anterior circle of Willis and at the bifurcation of the middle cerebral artery. Symptoms are rare before age 20, after which time they may burst and cause a subarachnoid hemorrhage.

B. **Arteriovenous (AV) fistula** is a rare abnormal communication between a vein and an artery.

1. By diverting blood from the arterial to the venous circulation, it increases venous return, increases the workload to the right heart, and may therefore cause right heart failure.
2. AV fistulas may also form as a result of trauma.

ARTERIAL HYPERTENSION

A. **Clinical features**

1. Arterial hypertension is defined as a consistent diastolic pressure over 100 mm Hg (if the patient is over 60 years of age) or over 90 mm Hg (if the patient is under 60 years of age with a systolic pressure over 160 mm Hg.)
2. Hypertension causes hypertensive heart disease with progressive thickening of the left ventricle, myocyte dropout, fibrosis, and eventual heart failure.

B. **Morbidity and mortality**

1. Hypertension is the second leading cause of cardiac mortality after ischemic heart disease.
2. Hypertension is strongly associated with both stroke and myocardial infarction. It may also lead to CHF, renal failure, coronary and peripheral artery disease, and aortic dissection.
3. Mortality has been declining as a result of early recognition, antihypertensive therapy, and control of obesity.

C. **Essential (primary) hypertension** is idiopathic and accounts for approximately 90% of cases. The pathophysiology is unknown, but it may be due to genetic or environmental factors, most likely resulting in increased systemic vascular resistance or increased cardiac output. Type A personality, obesity, stress, high-salt diet, and oral contraceptives increase the risk; it is most common in African American males around 40 years of age.

D. **Secondary hypertension** is hypertension resulting from other diseases, most commonly renal disease.

ATHEROSCLEROSIS

Atherosclerosis involves the progressive formation of elevated **fatty plaques (atheromata)** in the intima of large- and medium-sized muscular and elastic arteries. The atheromata cause narrowing of the vessel lumen, weakening of the media, and possibly progression to ulceration, calcification, thrombosis, intralesional hemorrhage, or aneurysm formation. This disorder affects primarily the coronary, cerebral, and iliac arteries and the aorta. It accounts for 50% of all deaths in the United States. Death occurs mainly from myocardial or cerebral infarcts.

A. **Pathology**

1. **Grossly**, atherosclerosis presents with:
   a. White or pale yellow plaques 0.5–1.5 cm in diameter bulging into the lumen with a soft "gruel-like" center

NOTE

Foam cells = macrophages after lipid ingestion.

   b. Lesions occur (in order of frequency) in the abdominal aorta, coronary arteries, popliteal arteries, descending thoracic aorta, internal carotid arteries, and circle of Willis.

2. **Microscopically**, atherosclerosis presents (from inside the lumen to the outer vessel wall) as:
   a. A fibrous cap composed of smooth muscle cells, collagen, connective tissue matrix, and scattered leukocytes
   b. A cellular zone composed of smooth muscle cells, macrophages, and lymphocytes
   c. A central core composed of necrotic cells, cholesterol clefts, lipid-filled foam cells, and plasma proteins
   d. Proliferating capillaries when lesions are well advanced

3. **Complicated plaques** are seen in advanced disease. They arise when calcification and thickening cause ischemia of the intima. Fissure, ulceration, and rupture of atheromas into the lumen may cause:
   a. Thrombus formation with occlusion of the vessel, leading to infarction of the tissue it supplies
   b. Cholesterol emboli
   c. Hemorrhage into the lesion
   d. Aneurysmal dilatation

4. **Fatty streaks** have the following characteristics:
   a. They are elevated, poorly demarcated, yellow intimal lesions less than 2 mm wide and 1 cm long.
   b. They may be present in children as young as 1 year old and may or may not evolve into atheromas.
   c. They are composed of lipid-containing cells (macrophages and smooth muscle cells), collagen, elastic fibers, proteoglycans, and extracellular lipid.
   d. They are most common in the thoracic aorta (< 1 year) and coronary arteries.

B. **Etiology of atheromatous plaques**

1. **Response to injury**
   a. Endothelial injury may be due to hypertension, hyperlipidemia, chemicals in tobacco smoke, diabetic angiopathy, and gross physical or chemical injury.
   b. Injury may lead to increased permeability of plasma proteins, platelet and inflammatory cell adherence, and thrombus formation at the site.
   c. Chemical mediators from the above cells may induce migration and proliferation of smooth muscle cells from the media into the intima.
   d. Production of abundant connective tissue matrix (collagen, elastin fibers, proteoglycans) by smooth muscle cells follows with ingrowth of intimal capillaries from the vasa vasorum for nourish-

ment. This may lead to subsequent leakage of more plasma proteins, finally resulting in the deposition and accumulation of lipid in the plaque.

2. **The loss of growth control hypothesis** suggests that smooth muscle proliferation in the media may be the initial event.

C. **Risk factors**

1. **Hypertension.** The risk of atherosclerosis correlates more closely with diastolic than with systolic pressure.
2. **Cigarette smoking.** The death rate from ischemic heart disease is 70–200% higher in men who smoke at least one pack per day than in nonsmoking men.
3. **Hyperlipidemia**
   a. Elevated serum cholesterol levels, especially low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL)
   b. Hyperlipidemia may be due to genetic (e.g., familial hypercholesterolemias), dietary (e.g., high cholesterol and saturated fat intake), other clinical conditions (e.g., nephrotic syndrome, hypothyroidism), or a sedentary lifestyle.
   c. Elevated high-density lipoproteins (HDLs) may decrease risk because HDL transports cholesterol out of tissues back to the liver, whereas LDL transports cholesterol from the liver to the tissues.
4. **Diabetes** causes damage to arterioles by depositing hyaline material in their walls and reducing blood flow.
5. **Increasing age.** Significant atherosclerosis is rarely seen in patients younger than 30 years of age; it becomes symptomatic in patients in their fifties and sixties.
6. Incidence is higher in men, postmenopausal women, and individuals with a positive family history.
7. Sedentary lifestyle, obesity, oral contraceptives, stress, and a compulsive, workaholic behavior pattern (type A personality) all increase the risk.

D. **Clinical features**

1. Atherosclerosis may be asymptomatic for decades.
2. Ischemia due to gradual vessel occlusion (e.g., gangrene of the lower extremities, intermittent claudication) may eventually develop.
3. Infarction due to sudden occlusion by thrombosis or embolization (e.g., myocardial infarction, renal artery occlusion) is the most dramatic sign. Twenty-five percent of cases of coronary atherosclerosis present with sudden death.
4. Aneurysm formation with subsequent rupture (e.g., abdominal aortic aneurysm) may also be a presenting sign.

ARTERIOLOSCLEROSIS

Arteriolosclerosis is a diffuse thickening of arterioles and small arteries, resulting in narrowing of the lumen and ischemia of involved tissue.

Note

The kidney is particularly vulnerable to arteriolosclerosis.

A. **Hyperplastic arteriolosclerosis** is associated with malignant hypertension or necrotizing vasculitis and is characterized by "onion-skin hyperplasia," i.e., concentric thickening of the intima, deposition of basophilic ground substance, smooth muscle proliferation, and hypertrophy of the adventitia.

B. **Hyaline arteriolosclerosis** is associated with diabetes, hypertension, and old age. It is characterized by hyaline thickening of arterioles that narrows the vessel lumen. This form of arteriolosclerosis is further characterized by eosinophilic material (thickened basement membrane of endothelial and smooth muscle cells) in the intima and media and is a degenerative process. It is best recognized in the arterioles of adipose tissue, where the vessel walls appear as thick as the diameter of the lumen.

EMBOLISMS

Emboliums may arise from solid, liquid, or gaseous masses transported within the vessels and originating from thrombi (98%), fat (bone fractures), atheromas, gases (deep sea divers), or amniotic fluid (pregnancy).

A. **Emboli arising from the venous circulation** involve the pulmonary circulation (pulmonary emboli). These may paradoxically involve the systemic circulation via a right-to-left cardiac shunt (e.g., atrial septal defect), which was not previously known to exist.

B. **Emboli arising from the arterial circulation** involve nonpulmonary structures.

1. Seventy-five percent arise from cardiac mural thrombi due to myocardial infarction. Grossly, mural thrombi appear grey-red with alternating light and dark lines (lines of Zahn), which represent clotted plasma and red blood cells (RBCs), respectively.
2. Arterial emboli most commonly involve the legs, then the brain, other viscera, and the arms.

ANEURYSMS

Aneurysms are focal, abnormal, dilatations of arterial vessels as a result of wall weakness. They may lead to rupture, which is a recognized cause of sudden death, compression of nearby structures, and thrombus formation and embolism, which may cause infarction of distal organs or structures.

A. **Atherosclerotic aneurysms** are secondary to atheroma formation. They usually occur in the abdominal aorta below the renal arteries, are associated with hypertension, and are found in men over 50 years of age. Fifty

percent of atherosclerotic aneurysms over 6 cm in diameter will rupture within 10 years.

B. **Syphilitic aneurysms** are due to chronic damage to the vasa vasorum of the aortic media by syphilitic aortitis. This damage results in obliterative endarteritis, ischemia, and smooth muscle cell atrophy. It usually occurs in the ascending aorta and may impinge on the aortic valve, causing aortic insufficiency due to dilatation of the valve ring.

C. **Microaneurysms** may appear in cerebral vessels as a result of hypertension and in retinal vessels as a result of diabetic vasculitis.

D. **Dissecting aneurysms** are due to degeneration of the tunica media, which allows blood from the lumen to enter an intimal tear and dissect through the layers of the media. They most frequently occur in the **aorta**.

   1. They may progressively spread into aortic branches (e.g., renal or coronary arteries), leading to compression and obstruction of the lumen of the branch.
   2. Etiology is unknown, but hypertension and Marfan's disease are predisposing factors.

E. **Berry aneurysms** were previously discussed.

VASCULITIS

Vasculitis is an inflammation of the vessels that may be localized (due to trauma, infections, toxins) or systemic. Multifocal vasculitis may lead to widespread, patchy necrosis and thrombi formation and is usually due to an immune reaction.

A. **Polyarteritis nodosa (PAN)** is a systemic necrotizing vasculitis of small and medium-sized muscular arteries (often at bifurcations).

   1. **Etiology**
      a. Hepatitis B antigenemia can be demonstrated in 30% of cases.
      b. Essentially, all cases of PAN are thought to be due to **antigen-antibody complexes**.
      c. Autoantibodies may also play a role when they form complexes with self-antigens. P-ANCA (perinuclear antineutrophil cytoplasmic autoantibodies) are frequently observed in PAN and may correlate with disease activity.
   2. **Pathology**
      a. **Grossly**, PAN presents as up to 1-cm segmental aneurysmal dilatations in vessels. It is seen predominantly in the kidneys, heart, and gastrointestinal tract; the pulmonary circulation is spared.
   3. **Clinical features**
      a. Symptoms depend on the system involved. Patients most commonly have low-grade fever, weakness, and weight loss. They may

BRIDGE TO BIOCHEMISTRY

In Marfan's disease, there is a defect in the gene for fibrillin on chromosome 15q. Fibrillin is a 350-kD molecule, a glycoprotein present in connective tissue, particularly the suspensory ligament of the lens, the walls of blood vessels, and the skin.

BRIDGE TO IMMUNOLOGY

Antigen-antibody (Ag-Ab) complexes precipitate onto vessel walls, where they fix complement and attract neutrophils by means of gradients of C5a fragments. Neutrophils phagocytose the complexes and discharge lysosomal granules that destroy smooth muscle and elastic fibers.

also have abdominal pain, hematuria, renal failure, hypertension, and leukocytosis.

b. PAN is most common in young adults.

In a Nutshell

headache + tenderness at temples + elevated ESR = temporal arteritis.

B. **Temporal (giant-cell) arteritis** is a granulomatous inflammation of small- and medium-sized arteries, **particularly extracranial arteries** (especially the temporal artery). This is perhaps the most common form of vasculitis. **Etiology** is unknown.

1. **Clinical features**

a. Giant cell arteritis occurs in both males and females, usually greater than 50 years old and mainly affects the cranial and most commonly, the temporal arteries.

b. It clinically presents with:

(1) **Headache and facial pain** (the most common symptoms)

(2) Fever, malaise, weight loss, muscle aches, anemia, claudication of the jaw, visual disturbances in 40% of cases, and tender, firm temporal arteries

(3) **Elevated ESR,** as in all inflammatory diseases

(4) Blindness, if not treated early (due to occlusion of ophthalmic artery)

C. **Hypersensitivity (leukocytoclastic) angiitis** affects small vessels (i.e., arterioles, venules, capillaries) predominantly in the skin. It may also affect vessels, lungs, kidneys, and other organs simultaneously and may cause crescentic glomerulonephritis. Hypersensitivity angiitis may be distinguished from PAN by the involvement of smaller vessels. Lesions are usually all in the same stage at the same time.

1. **Etiology.** Immune complexes are thought to be involved because it is often precipitated by a specific antigen, such as bacteria (e.g., Streptococcus), drugs (penicillin), tumor antigens, or serum sickness. The disease remits if the offending agent is removed.

In a Nutshell

If you see gangrene in a young smoker, think Buerger's disease.

D. **Thromboangiitis obliterans (Buerger's disease)** is a recurrent acute and chronic inflammatory disorder of small and medium-sized arteries and veins, causing **segmental thrombosis** that occurs in the extremities and may also affect adjacent nerves. It occurs **almost exclusively in cigarette smokers** less than 35 years of age.

1. **Etiology.** Possible causes include a genetic predisposition, an immunologic reaction, and a direct toxic response (tobacco).

E. **Wegener's granulomatosis** consists of a triad of necrotizing vasculitis of lungs and airways, necrotizing granulomas of the upper respiratory tract, and necrotizing glomerulitis. It occurs in men more often than women. Patients are usually older than 50 years of age. **Etiology** is unknown.

F. **Takayasu's arteritis (pulseless disease)** is a granulomatous inflammation of medium-to-large arteries, often branches of the aortic arch.

1. **Etiology**. The cause is unknown.

G. **Kawasaki's disease (mucocutaneous lymph node syndrome)** was first described in Japan and is still more common there.

1. **Epidemiology**. The disease is usually seen in young children, but adult patients have been described (rare).
2. **Etiology**. The cause is unknown. An RNA-dependent DNA polymerase has been found in some lesions, suggesting a viral etiology.
3. **Pathology**. Microscopically, it presents with inflammation and necrosis of the entire vessel wall and possible aneurysm formation.
4. **Clinical features.** Kawasaki's disease is an acute syndrome consisting of:
   a. Fever, conjunctivitis, erythema and erosions of the oral mucosa, a generalized maculopapular skin rash, and adenopathy
   b. A mortality rate of 1–2% as a result of coronary vasculitis or coronary aneurysm, thrombosis, or rupture
   c. Self-limited course

VENOUS DISEASE

A. **Thrombophlebitis** is inflammation and thrombus formation of the veins. Ninety percent of cases occur in the **deep veins of the leg** (i.e., deep venous thrombosis).

1. **Pathology**. Factors involved in thrombus formation (Virchow's triad) are endothelial injury, alterations in blood flow, and hypercoagulability of blood. Thrombi grossly appear blue-red.
2. **Clinical features**
   a. Thrombophlebitis may be associated with or may be secondary to:
      (1) Clotting disorders (deficiency of antithrombin III, protein C or protein S). In these deficiencies, normal clot dissolution (fibrinolysis) is abnormally slow.
      (2) Heart disease (CHF, myocardial infarction, valvular disease), leading to sluggish flow
      (3) Immobilization (including bed rest), slowing venous flow
      (4) Neoplasia, sometimes producing enzymes that promote clotting
      (5) Advanced age with sclerotic veins and slow flow
      (6) Pregnancy with obstruction of pelvic veins
      (7) Oral contraceptives, which activate some clotting factors
      (8) Tissue injury (postoperative course, trauma), which also activates clotting, sometimes systemically
   b. Thrombi may cause:
      (1) Embolization, particularly to the lungs
      (2) Bacterial superinfection, producing a septic nidus
      (3) Postphlebitic syndrome (predisposition of recurrent thrombosis due to loss of venous valves)
      (4) Recanalization of the thrombus, restoring more normal flow

c. Clinically, thrombophlebitis presents insidiously with few symptoms (localized pain, erythema, and edema). It often presents initially as a **pulmonary embolism** or as multiple emboli; a large embolus may cause sudden death.

B. **Venous occlusion** may occur as a result of thrombophlebitis, deep venous thrombosis, or obstruction of outflow (pregnancy).

C. **Varicose veins** are dilated, tortuous veins, most likely resulting from increased intraluminal pressure and inadequate external support. They occur most frequently in the superficial veins of the lower extremities. They are more common in women.

1. **Pathogenesis.** Varicose veins are associated with the venous stasis of pregnancy, obesity, compression by tumors, prolonged immobility of legs, and congenital defects in venous walls (including valves). They may result in venous thrombosis and valve damage.

2. **Clinical features.** Varicosities present with edema, thrombosis, stasis dermatitis, and ulcerations. Unlike venous abnormalities of the deep veins of the lower extremities, varicose veins are rarely a source of emboli.

Note

Some of the vasculitides affect the veins and venules—see the previous section on "Vasculitis."

VASCULAR NEOPLASMS

Vascular neoplasms include all of the neoplastic growths of the vascular endothelial cells, forming well-defined endothelial-lined vascular channels in benign tumors or ill-defined masses of anaplastic endothelial cells in malignant tumors.

A. **Benign tumors**

1. **Hemangiomas**

a. **Capillary hemangiomas** form unencapsulated well-defined masses of capillaries with a small amount of connective tissue that usually occur in the skin and mucous membranes.

b. **Cavernous hemangiomas** form sharply defined, sponge-like tumors composed of large, dilated, cavernous vascular spaces. They usually occur on the skin, mucous membranes, and viscera and are rarely clinically significant except for their cosmetic effects.

c. **von Hippel-Lindau disease** is a syndrome of multiple cavernous hemangiomas involving the cerebellum, brain stem, liver, pancreas, and eyes. It is associated with renal cysts and renal cell carcinoma. This disease is transmitted via an autosomal dominant pattern with the gene localized to chromosome 3p.

2. **Vascular ectasias** (telangiectasias) are actually a developmental abnormality but can closely mimic benign vascular neoplasms. They may be composed of abnormal aggregations of arterioles, capillaries, or venules.

a. **Nevus flammeus** is a flat birthmark on the head or neck that usually spontaneously regresses.

b. **Port-wine stain** may grow proportionately with the child and may be associated with **Sturge-Weber syndrome**, a nevus formation in the skin supplied by the trigeminal nerve, and associated with glaucoma, meningeal angiomas, and mental retardation.

c. **Spider telangiectasias** are a radial array of tiny arterioles, commonly occurring in **pregnant women** and patients with **hepatic cirrhosis**. In men, they may be related to elevated estrogen levels occurring as a result of liver disease (e.g., alcoholism).

E. **Malignant tumors**

1. **Hemangiosarcomas** are growths of atypical, anaplastic endothelial cells that usually metastasize and are associated with a high mortality.

a. **Gross pathology.** Hemangiosarcomas most commonly occur in skin, breast, liver, and soft tissues. They are usually sharply defined red nodules, which become large, pale, soft masses.

b. **Microscopic pathology.** Hemangiosarcomas show varying degrees of anaplasia and vessels of different sizes and shapes. Vessels are often merely slit-like spaces.

2. **Hepatic angiosarcomas** are tumors caused by toxic exposures.

3. **Kaposi's sarcoma** was once a rare, slowly progressive disease seen in older men of Mediterranean or African descent or immunosuppressed transplant patients. It is now seen in one-third of **AIDS patients**, most frequently in homosexual males. This form of the disease may be more aggressive and frequently disseminates.

a. **Pathology**

(1) **Grossly**, it presents as multiple **violaceous nodules** that may remain confined to the skin or may disseminate.

(2) **Microscopically**, it presents as a proliferation of endothelial cells, spindle cells, and inflammatory cells with RBCs scattered throughout slit-like vascular spaces.

b. **Prognosis.** Kaposi's sarcoma rarely causes death. It is responsive to chemotherapy and interferon-α (IFN-α), but it usually spreads relentlessly in AIDS patients.

Endocrine pathology is primarily concerned with the hypothalamic-pituitary-end organ axis. Knowledge of the complex homeostatic feedback mechanisms affecting the hypothalamus and pituitary is critical in making an accurate diagnosis of hyper- or hypofunctioning of the endocrine glands or organs. In general, hyperplasia of glands implies an excess of stimulating hormone, whereas adenomas and carcinomas may arise completely independently of normal regulatory hormone secretion. Hyperplasias are almost always functional. In contrast, adenomas vary in the amount of functional product they secrete; moreover, their responses to regulatory hormone vary considerably. Carcinomas are usually the least functional and are usually independent of regulatory hormonal influence.

HYPOTHALAMUS AND PITUITARY GLAND

A. Lesions of the hypothalamus

1. **Destructive lesions** include tumors such as craniopharyngiomas, gliomas, hamartomas, and inflammatory conditions (e.g., sarcoidosis).
2. **Craniopharyngiomas** arise from [redacted], forming the most common pituitary tumor in children. Pathology shows stratified squamous epithelium with areas of keratinization and cysts. Lamellar bone deposits and calcium may be seen. Malignant transformation is rare. The tumor may be detected on x-ray by its opaque calcifications.

B. Anterior pituitary hyperfunction

1. **Etiology.** Most cases of anterior pituitary hyperfunction are caused by **adenomas**, which usually secrete prolactin, growth hormone, or adrenocorticotropic hormone (ACTH).
2. **Clinical syndromes** correspond to the hormone secreted.

Flashback to Physiology

The [redacted] produces growth hormone-releasing hormone (GnRH), somatostatin, dopamine, gonadotropin-releasing hormone (GnRH), corticotropin-releasing hormone (CRH), antidiuretic hormone (ADH), thyrotropin-releasing hormone (TRH), and oxytocin.

Clinical Correlate

A pituitary tumor may impinge on the optic chiasm, producing a bitemporal hemianopsia (loss of peripheral visual fields).

a. **Hyperprolactinemia** (amenorrhea-galactorrhea syndrome) results from elevated serum prolactin associated with pituitary adenomas (prolactinoma). It is the **most common pituitary tumor**. In women, it results in **amenorrhea and galactorrhea**; in men, this tumor may result in galactorrhea and infertility.

b. **Excess growth hormone**

(1) **Gigantism** occurs if there is excessive GH secretion **before the growth plates are fused** (i.e., before the end of puberty). Excessive skeletal growth may result in heights up to 9 feet tall.

(2) **Acromegaly** occurs if there is excessive secretion **after closure of the epiphyseal plates**. There is a gradual coarsening of facial features (i.e., thick lips, protruding jaw, large tongue) and enlargement of the hands and feet. It may be associated with diabetes mellitus, hypertension, osteoporosis, and other symptoms associated with space-occupying lesions in the pituitary region, such as visual field defects.

c. **Cushing's disease** is caused by ACTH-secreting tumors. Lesions are usually small and rarely cause mass effect. Cushing's disease is discussed later this section.

C. **Anterior pituitary hypofunction** is usually manifested as panhypopituitarism, resulting from the destruction of at least 75% of the adenohypophysis.

1. **Clinical features** include symptoms of hypothyroidism, hypoadrenalism, and hypogonadism. Growth hormone deficiency in children results in **primary dwarfism** with normal limb and skull proportions.

D. **Posterior pituitary hypo- and hyperfunction**

1. **Diabetes insipidus (DI)** is due to insufficient or absent antidiuretic hormone (ADH).

a. **Etiology**. Disorders involving the hypothalamus or neurohypophysis (e.g., malignancy, meningitis, TB, sarcoid, postsurgical trauma to base of skull) may all cause central diabetes insipidus. **Nephrogenic diabetes insipidus** is caused by a lack of renal response to ADH.

b. **Clinical features** include **polydipsia** and **polyuria** with excretion of **large volumes of dilute urine**, even during states of dehydration.

In a Nutshell

Diabetes insipidus (DI)

- *Polydipsia*
- *Polyuria*
- *Large volumes of dilute (hypotonic) urine*
- *High serum osmolality*
- *Hypernatremia*

Central DI responds to exogenous ADH therapy; nephrogenic DI does not because renal receptors do not respond to ADH.

ADRENAL GLANDS

A. **Adrenal cortical hyperfunction**

1. **Cushing's syndrome** is caused by cortisol excess.

a. **Etiology**. Cushing's syndrome may take one of four distinct forms, depending on its cause.

(1) **Pituitary Cushing's syndrome** (approximately two-thirds of the cases of Cushing's). Pituitary or hypothalamic dysfunction is the most common noniatrogenic cause. It is caused by basophilic adenomas, referred to as **Cushing's disease**, or more commonly, by multiple corticotroph microadenomas. Pituitary Cushing's syndrome is characterized by **bilateral adrenal hyperplasia** and **elevated serum ACTH**.

(2) **Adrenal Cushing's syndrome** is usually caused by an **adrenal adenoma**. It is characterized by **low serum ACTH**.

(3) **Ectopic Cushing's syndrome** is caused by ectopic secretion of ACTH, most commonly by **bronchogenic cancer**.

(4) **Iatrogenic Cushing's syndrome** is rather common and is caused by exogenous administration of glucocorticoids or ACTH.

b. **Clinical features** usually result from excess cortisol but may also be due to excess aldosterone, corticosterone, or adrenal androgens. The syndrome is most common in women in the 20–40-year-old age group. Patients exhibit **hypertension, abnormal glucose tolerance** (frank diabetes 20%), **truncal obesity, muscle wasting** in the extremities, **moon facies, buffalo hump**, cutaneous **striae, osteoporosis**, hirsutism and amenorrhea in women, weight gain, edema, weakness, fatigue, susceptibility to infection, and personality disturbances. Children show growth retardation, delayed skeletal maturation, and precocious puberty if associated with adrenal androgens.

2. **Primary hyperaldosteronism (Conn's syndrome)** is due to increased aldosterone secretion, producing **sodium retention, increased total plasma volume,** increased renal artery pressure, and **inhibition of renin secretion**.

a. **Etiology**. An adrenal adenoma secreting aldosterone is the most common cause.

b. **Clinical features** include sodium retention, extracellular fluid expansion, and potassium depletion with diastolic hypertension, weakness, fatigue, polyuria, polydipsia, and headache.

c. **Laboratory values reveal hypokalemia, low renin levels, metabolic alkalosis, hypernatremia**, and (for adenomas) failure to suppress aldosterone with salt loading.

3. **Secondary hyperaldosteronism**

a. **Etiology**. The causes are decreased renal blood flow or perfusion pressure, edematous states with sodium retention, renin-producing neoplasms, and **Bartter's syndrome,** which is characterized by juxtaglomerular cell hyperplasia, hyperreninemia, hyperaldosteronism, and failure to thrive; it is often associated with low blood pressure.

b. **Laboratory values** include **high renin levels**, hypernatremia, and hypokalemia. Secretion of aldosterone is triggered by elevated renin-angiotensin levels.

B. **Adrenal cortical hypofunction**

1. **Acute adrenocortical insufficiency** can be caused by:
   a. **Rapid withdrawal of exogenous steroids** in patients with chronic adrenal suppression
   b. **Stress** (e.g., trauma, surgery, infection), Addison's disease, or chronic adrenal suppression caused by administration of exogenous corticosteroids
   c. **Adrenal apoplexy**, such as in the **Waterhouse-Friderichsen syndrome**: a massive, sudden adrenal hemorrhage usually associated with meningococcal septicemia

2. **Chronic or primary adrenocortical insufficiency (Addison's disease)**
   a. **Etiology.** Tuberculosis was once the most common cause. The most common etiology today is idiopathic (probably autoimmune).
   b. **Pathogenesis.** To produce clinical insufficiency, 90% of the adrenal gland must be nonfunctional.
   c. **Clinical features** are due to insufficient cortisol and aldosterone secretion, leading to weakness, weight loss, anorexia, nausea, vomiting, hypotension, skin pigmentation, hypoglycemia with prolonged fasting, inability to tolerate stress, and abdominal pain.
   d. **Laboratory values** show decreased serum sodium and chloride with metabolic acidosis and increased serum potassium. **ACTH levels are high.**

3. **Secondary adrenocortical insufficiency**
   a. **Etiology.** Causes include metastases, irradiation, infection, and infarction, affecting the hypophysial-pituitary axis and resulting in **decreased ACTH**.
   b. **Clinical features.** Secondary insufficiency usually produces less mineralocorticoid malfunction and less pigmentation.

C. **Adrenal neoplasms**

1. **Adrenal adenomas**
   a. **Clinical features.** Adrenal adenomas are mostly asymptomatic and nonsteroid-producing.

2. **Adrenal carcinomas**
   a. **Clinical features.** Adrenal carcinoma is relatively rare and usually very malignant. Greater than 90% are steroid-producing (often more than one steroid).

3. **Pheochromocytoma**
   a. **Etiology.** Pheochromocytoma is a neoplasm of neural crest–derived chromaffin cells that **secrete catecholamines**, resulting in **hypertension**.
   b. **Clinical features** are related to catecholamine release. Paroxysmal or constant **hypertension** is the most classic symptom. Also, sweat-

NOTE

Pigmentation of the skin in Addison's is due to ACTH also having a weak stimulatory effect on melanocytes. ACTH and melanocyte-stimulating hormone (MSH) share amino acid sequences.

ing, headache, arrhythmias, palpitations, and nervousness may be seen in any combination.

c. **Laboratory values** show **elevated urinary catecholamines and catecholamine metabolites.**

4. **Neuroblastoma is the most common malignant extracranial solid tumor of childhood.**

a. **Clinical features.** Tumors grow rapidly, metastasize widely (especially to bone), and produce elevated urinary catecholamines.

b. **Pathology.** Neuroblastoma occurs most frequently in the adrenal medulla but may also arise in the cervical, abdominal, and thoracic sympathetic chain.

THYROID GLAND

A. **Overview of hyperthyroidism**

1. **Etiology.** Hyperthyroidism may be seen most often in Graves' disease, toxic multinodular goiter, and toxic adenoma. Thyroiditis, thyroid carcinoma, and iodine ingestion are less frequent causes.

2. **Pathogenesis** is due to increased circulating levels of the thyroid hormones triiodothyronine (T_3) and thyroxine (T_4), causing a **hypermetabolic state.**

3. **Clinical features**

a. Cardiac symptoms include tachycardia, cardiac palpitations, cardiomegaly, occasional cardiac arrhythmias (usually atrial fibrillation), and cardiomyopathy.

b. The skin is warm, flushed, and moist due to vasodilatation.

c. The eyes show a wide stare with upper lid retraction and lid lag. **Exophthalmos** is characteristic of Graves' disease, due to swelling of extraocular muscles and periorbital tissues.

d. Patients also show increased sweating, heat intolerance, hyperactivity, nervousness, tremor, weight loss, diarrhea, oligomenorrhea, and myopathy.

4. **Diagnosis** is based on increased T_4 and suppressed TSH measurements.

B. **Overview of hypothyroidism**

1. **Etiologies**

a. Congenital thyroid dysplasia or hypoplasia

b. Hypothalamic or pituitary disease

c. Thyroid conditions causing goiter including iodine deficiency and Hashimoto's (autoimmune) thyroiditis

d. Surgical or radiation destruction of gland

e. Peripheral resistance to thyroid hormone

2. **Clinical features** depend on the age group.

CLINICAL CORRELATION

Clinical diagnosis of hyperthyroidism may be difficult in pregnancy, which is an intrinsically hypermetabolic state and is often associated with mild degrees of thyromegaly. In addition, the increase in TBG that results from the high estrogen levels elevates the total serum T_4 but not the free serum T_4.

a. **Infants** lacking sufficient thyroid hormone develop **cretinism.** The major effects are on skeletal and CNS development (i.e., short stature, retarded bone age, epiphyseal dysgenesis, and mental retardation). Once apparent, the syndrome is irreversible. The initial presentation includes failure to thrive, feeding difficulties, constipation, and somnolence. Children develop protuberant abdomens, wide-set eyes, dry rough skin, broad nose, and delayed epiphyseal closure. Neonatal screening for elevated TSH is essential for early detection.

b. **Older children** show short stature, retarded linear growth, and delayed onset of puberty.

c. **In adults,** hypothyroidism causes lethargy, weakness, fatigue, decreased appetite, weight gain, cold intolerance, hair loss, dry skin, constipation, apathy, myopathy, psychosis, metrorrhagia (irregular uterine bleeding), and accelerated atherosclerosis with elevated serum cholesterol. **Myxedema,** a syndrome associated with severe hypothyroidism, shows periorbital puffiness, pale doughy skin due to accumulation of hydrophilic mucopolysaccharides, sparse hair, cardiac enlargement, cardiomyopathy, pleural effusions, anemia, and thickened facial features.

3. **Diagnosis** of primary hypothyroidism is based on an elevated TSH and low T_4.

C. **Graves' disease**

1. **Incidence.** Graves' disease peaks in the third and fourth decades and is five times more common in women. There is a familial predisposition, and it is associated with other autoimmune diseases such as pernicious anemia and Hashimoto's thyroiditis.

2. **Pathogenesis** is **autoimmune,** resulting from production of **thyroid-stimulating immunoglobulin** (TSI) and **thyroid growth immunoglobulin,** two autoantibodies that cause glandular hyperplasia and hormone production by binding to TSH receptors.

3. **Clinical features** are present in varying combinations.
   a. **Thyrotoxicosis** has symmetric glandular enlargement.
   b. **Ophthalmopathy** is characterized by lid lag, retraction of the upper lid, proptosis, periorbital edema, and stare.
   c. **Dermopathy** is characterized by thickened edematous nodules or plaques on the lower extremities.

D. **Hashimoto's thyroiditis** is a chronic lymphocytic thyroiditis featuring **goitrous** enlargement of the thyroid gland produced by **lymphocytic** and **plasma cell infiltrates,** with the eventual development of hypothyroidism.

1. **Etiology** is **autoimmune.** There may be autoantibodies to the TSH receptor, T_3, T_4, microsomes, and thyroglobulin.

Note

In contrast to primary hypothyroidism, secondary (pituitary gland failure) and tertiary (hypothalamic failure) hypothyroidism have low (or normal) TSH levels.

2. **Incidence.** Hashimoto's thyroiditis is the most common type of thyroiditis and is the **leading cause of goitrous hypothyroidism** in the U.S. The highest incidence is in **middle-aged women**, and there is a higher incidence in patients with a family history of Hashimoto's or other autoimmune diseases (e.g., Graves' disease, Sjögren's syndrome, systemic lupus erythematosus).
3. **Clinical features** include painless goiter. Hypothyroidism develops, along with malaise, fever, a decreased T_4, and elevated TSH.

E. **Diffuse nontoxic goiter** is used to describe diffuse enlargement of the gland in **euthyroid patients.**

1. **Incidence**
   a. **Endemic goiters** have a high incidence in certain geographic regions (e.g., mountainous regions or regions far from the ocean). They are caused by **iodine-deficient diets** or increased intake of **goitrogens** (e.g., calcium, fluorides).
   b. **Sporadic simple goiter** is less common. The incidence in women is much greater than in men.

F. **Multinodular goiter** develops from chronic diffuse goiters; it may be toxic or nontoxic and may become very large (Figure 4-1).

1. **Clinical features.** Glandular enlargement may cause stridor, dysphagia, and even superior vena cava syndrome (mass effect). Fifty percent produce thyrotoxicosis. These tumors must be differentiated from thyroid cancer, particularly asymmetric tumors in euthyroid patients.

G. **Congenital thyroid conditions**

1. **Agenesis or dysgenesis** are frequent causes of cretinism.
2. **Thyroglossal duct or cyst** may communicate with the skin or base of the tongue. It is formed from nests of incompletely descended midline thyroid tissue.
3. **Ectopic thyroid nests** are usually at the base of the tongue. Prior to removal, it must be documented that the patient has other functioning thyroid tissue.

H. **Tumors.** Thyroid nodules are very common (4–7% adults in the U.S.), but thyroid cancer is uncommon (less than 2 cases per 1,000 nodules). There is a higher incidence of neoplasia in solitary nodules and in younger patients.

1. **Adenomas. Follicular adenoma** is the most common.
   a. **Clinical features.** Adenomas may cause pressure symptoms, pain, and rarely, thyrotoxicosis.
2. **Cysts** make up 10–25% of solitary nodules and usually represent cystic degeneration of follicular adenomas.

In a Nutshell

Hyperthyroidism ($\downarrow$ TSH, $\uparrow T_3$, $\uparrow T_4$)	***Hypothyroidism*** ($\uparrow$ TSH, $\downarrow T_3$, $\downarrow T_4$)
• *T HR*	• *Cretinism in children*
• *Skin moist and flushed*	• *Lethargy in adults*
• *Lid lag*	• *Fatigue*
• *Sweating*	• *Weight gain*
• *Heat intolerance*	• *Cold intolerance*
• *Weight loss*	

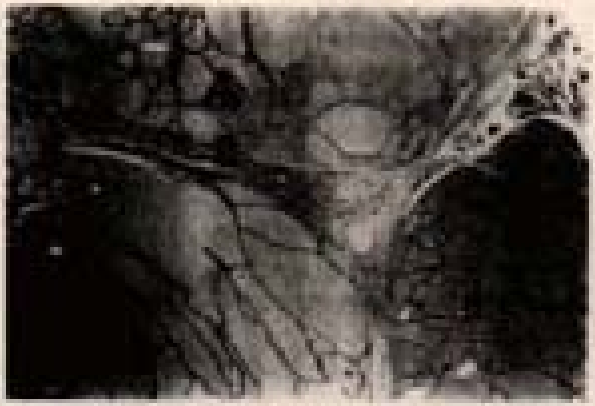


Figure 4-1. Thyroid: multinodular goiter (microscopic)

3. **Carcinomas** represent neoplasia of **follicular cells** (i.e., papillary, follicular, or anaplastic cancer), **parafollicular cells** (i.e., medullary cancer), or **connective tissue.** Risk factors include radiation and a genetic predisposition.
   a. **Papillary carcinoma** is the most common type. The incidence is higher in women.
   b. **Follicular carcinoma** makes up 20% of thyroid cancers and is more malignant than papillary cancer.

PARATHYROID GLANDS

A. **Primary hyperparathyroidism**
   1. **Etiology**
      a. **Parathyroid adenoma** is the most common cause, usually involving a single gland.
      b. **Parathyroid hyperplasia** shows diffuse enlargement of four glands, usually composed of chief cells.
   2. **Clinical features.** Patients with **elevated serum calcium** are often asymptomatic. They may present with bone abnormalities secondary to elevated parathyroid hormone (e.g., osteomalacia, osteitis fibrosa cystica, subperiosteal resorption). Hypercalcemia may cause metastatic calcification (e.g. kidney stones).

B. **Secondary hyperparathyroidism**
   1. **Etiology.** Secondary hyperparathyroidism is usually caused by **chronic renal failure,** leading to decreased Ca^{2+} absorption, which in turn results in a feedback loop and increased PTH. Vitamin D deficiency and malabsorption are less common causes.

Clinical Correlate

Osteitis fibrosa cystica, also known as von Recklinghausen's disease of bone, occurs as a result of chronic primary hyperparathyroidism. Cystic changes in bone occur due to osteoclastic resorption. Fibrous replacement of resorbed bone may lead to a "brown tumor," a non-neoplastic tumor mass.

2. **Clinical features** show soft tissue calcification and osteosclerosis. Mild-to-moderate hypocalcemia is characteristic.

C. **Hypoparathyroidism**

1. **Etiology.** Common causes are removal of glands during thyroidectomy, idiopathic, radioactive iodine therapy for Graves' disease, metastatic cancer, and DiGeorge's syndrome. The idiopathic form may be familial and autoimmune.

2. **Clinical features** include hypocalcemia, hyperphosphatemia, irritability, anxiety, neuromuscular excitability, tetany, intracranial calcifications, lens calcification, dental abnormalities, and cardiac conduction defects.

D. **Pseudohypoparathyroidism**

1. **Etiology.** Pseudohypoparathyroidism is an autosomal recessive disorder resulting in a kidney unresponsive to circulating PTH.

2. **Clinical features** include skeletal abnormalities such as short stature and shortened fourth and fifth carpals and metacarpals.

E. **Hypercalcemia** is defined as a persistent serum calcium over 10.4 mg/dl.

1. **Etiology.** Hypercalcemia may be caused by metastatic disease to bone, such as myeloma or epithelial neoplasm, vitamin D intoxication, sarcoidosis, primary or secondary hyperparathyroidism, the milk alkali syndrome, or Paget's disease of bone.

2. **Clinical features. Renal stones** are often seen; hyperparathyroidism is also usually associated with **hypercalciuria** and with **hypophosphatemia.** Alkaline phosphatase activity is usually elevated. Patients may experience an altered sensorium, often first noticed as drowsiness.

3. **Pathologic features** in bone range from obvious metastases to osteoclast tunneling through bony trabeculae in hyperparathyroidism.

ENDOCRINE PANCREAS (Islets of Langerhans)

A. **Diabetes mellitus** is caused by inadequate or abnormal insulin secretion, causing impaired glucose usage and resulting in hyperglycemia, glycosuria, and characteristic systemic pathology.

1. **Types**

a. **Insulin-dependent (type I) diabetes mellitus (IDDM).** There is an abrupt onset with patients prone to **ketoacidosis,** insulin dependence, and severe metabolic derangements.

b. **Noninsulin-dependent (type II) diabetes mellitus (NIDDM).** This disease constitutes most cases of idiopathic diabetics. It is characterized by an abnormality of insulin secretion or peripheral insulin resistance. Most patients have central obesity with an onset of dis-

CLINICAL CORRELATE

DiGeorge's syndrome is also associated with absence of the thymus due to a common embryologic defect. Tetany occurs shortly after birth due to congenital absence of the parathyroid glands. Cardiac structural defects and immunodeficiency are also noted.

CLINICAL NOTE

Hypoparathyroidism can affect periodontal bone.

MNEMONIC

Hypercalcemia:
Malignancy
*I*ntoxication
Sarcoidosis
*H*yperparathyroidism
*A*lkali syndrome
*P*aget's disease

ease usually after age 40. These patients are not prone to ketoacidosis.

c. **Secondary diabetes** may be caused by destruction of pancreatic islet cells from inflammation, hemochromatosis, tumor, surgery, or hormonal disease.

2. **Pathogenesis**

a. **IDDM** shows a marked, absolute insulin deficiency resulting from **diminished β-cell mass**. It is therefore characterized by **low serum insulin levels**. There are three etiologic theories; in many cases of IDDM, all three mechanisms may be operative.

(1) A **viral infection** (e.g., mumps, coxsackievirus B, rubella, CMV, mononucleosis) may lead to destruction of β cells.

(2) There is clearly a **genetic predisposition**.

(3) **Autoimmune response.** Eighty percent of patients with IDDM have **anti-islet cell antibodies**.

b. **NIDDM** is characterized by mild-to-moderate insulin deficiency and is not associated with a specific HLA haplotype. There are two theories:

(1) Delayed or inadequate insulin secretion may develop for unknown reasons.

(2) Insulin resistance, the impaired ability of tissues to react to circulating insulin, results from a decrease in the number of cell-surface insulin receptors, again for unknown reasons.

3. **Clinical features**

a. **Predisposing factors** are obesity, pregnancy, trauma, infections, and stress.

b. **Presentation.** Both IDDM and NIDDM may present with **polydipsia, polyuria, polyphagia, weight loss**, and muscle weakness. Laboratory values may show **hyperglycemia, glycosuria**, and **hyperlipidemia**.

c. **Acute metabolic complications**

(1) **Diabetic ketoacidosis (DKA)** may occur in insulin-dependent diabetics. It leads to an oversupply of glucose, fueled by high rates of protein catabolism, lipolysis in adipose tissue, and fatty acid oxidation in liver. The accelerated rate of fatty acid oxidation produces acetyl-CoA faster than it can be burned by the TCA cycle, and the liver conserves the excess acetyl-CoA by synthesizing ketones. Metabolic acidosis results from the accumulation of the ketones. The high level of blood glucose leads to dehydration via an osmotic diuresis. Treatment with insulin normalizes the metabolism of carbohydrate, protein, and fat. Fluids are given to correct the dehydration.

(2) **Hyperosmolar nonketotic coma** occurs in patients with mild adult-onset diabetes when blood glucose levels exceed approximately 600 mg/dl.

d. **Late complications of diabetes.** Patients with long-standing diabetes of either type may develop a series of long-term complications.
   (1) **Atherosclerosis** causes strokes, myocardial infarcts, and gangrene, frequently of the toes.
   (2) **Nephropathy** causes proteinuria, hypertension, and edema, and it may lead to renal failure.
   (3) In the **Kimmelstiel-Wilson syndrome**, intercapillary glomerulosclerosis with hypertension and edema lead to proteinuria, beginning approximately 20 years after the onset of disease.
   (4) There is a predisposition to **infections** (tuberculosis, pyelonephritis, pneumonia, skin infections).
   (5) **Neuropathy** is usually a distal, symmetric polyneuropathy ("stocking-glove" distribution) but may be a mononeuropathy. In addition to this **peripheral neuropathy**, diabetics can also have **autonomic neuropathy**.
   (6) **Retinopathy** may lead to blindness.

4. **Prognosis**
   a. **NIDDM** decreases life span by approximately 8 years. There is a much higher mortality from IDDM.
   b. **Causes of death** in decreasing frequency are:
      (1) Myocardial infarction
      (2) Renal failure
      (3) Stroke
      (4) Ischemic heart disease
      (5) Infections

B. **Islet-cell tumors**

1. **β-cell tumors. Insulinomas** most commonly occur between the ages of 30 and 60.
   a. **Pathogenesis.** β-cell tumors produce hyperinsulinemia, causing **hypoglycemia**.
   b. **Clinical features.** Patients experience episodes of altered sensorium (i.e., disorientation, dizziness, diaphoresis, nausea, tremulousness, coma) that are relieved by glucose intake.
   c. **Pathology.** Most tumors are solitary, well encapsulated, and well differentiated adenomas of various sizes. Ten percent are malignant carcinomas.

2. **Zollinger-Ellison syndrome** is due to a gastrinoma and is often associated with MEN type I.
   a. **Pathogenesis.** Tumors of pancreatic islet cells secrete gastrin, causing gastric hypersecretion of acid.
   b. **Clinical features** include **intractable peptic ulcer disease** and severe diarrhea.
   c. **Pathology.** Sixty percent are malignant. Most tumors are located in the pancreas, with 10% in the duodenum.

CLINICAL CORRELATE

Diabetics are also a high-risk group for the following infections:

- *Klebsiella pneumonia*
- *Sinus mucormycosis*
- *Malignant otitis externa (Pseudomonas aeruginosa)*
- *Chronic osteomyelitis*

The lung is a major destination for anything that can float in the air, including pollutants, spores, bacteria, viruses, and smoke. As a result, it is a primary site for inflammation, infection, and neoplasia.

Lung cancer is now the leading cause of cancer death in both men and women; approximately 90% of cases are due to cigarette smoking. In addition, common allergic and destructive inflammatory conditions, such as asthma, bronchitis, and emphysemas, are seriously exacerbated by smoking. This chapter will discuss the different pulmonary pathologies associated with infectious and neoplastic diseases, as well as the common environmental agents known to cause and/or exacerbate pulmonary disorders.

CONGENITAL ANOMALIES

A. **Pulmonary cysts.** There are two types of pulmonary cysts caused by premature separation of the embryonic foregut.

   1. **Bronchogenic cysts** are centrally located, adjacent to bronchi or bronchioles, and occur with or without connections to airways. They are lined by ciliated, mucus-secreting bronchial columnar epithelium and may be single or multiple. Their size varies from microscopic to greater than 5 cm in diameter, and they may be associated with other cysts of the liver, kidney, or pancreas.
   2. **Pulmonary cysts** are multiple and peripherally located, lacking communication with main bronchi. Infection is frequent (e.g., abscess); rupture can cause pneumothorax and compression of adjacent lung tissue. Dilatation may rupture vessels, leading to hemoptysis.

B. **Pulmonary atresia.** Bilateral pulmonary atresia is not compatible with life; unilateral atresia is usually accompanied by other serious malformations.

Bridge to Gastrointestinal

Neonates with either esophageal atresia or tracheoesophageal fistula are vulnerable to aspiration pneumonia.

C. **Pulmonary hypoplasia** refers to incomplete development of the entire lung or a single lobe of the lung.

D. **Congenital lobar overinflammation** results from bronchial obstruction due to absence or hypoplasia of the bronchial cartilage with compensatory overinflation of the remaining lung.

E. **Pulmonary sequestrations.** Extrapulmonary lung tissue is usually supplied by systemic blood vessels rather than by pulmonary arteries. It is usually located behind the lung or below the diaphragm.

INFECTIONS

Infections in the lung are more common than infections in any other organ; viral infections are more frequent than other forms of pulmonary infection.

A. **Bacterial pneumonia** occurs when pulmonary defense mechanisms are weakened (e.g., decreased cough, gag, or nasal clearance; mucociliary damage; macrophage phagocytic defects; pulmonary edema; pooling of secretions; bronchial injury) or when the host is otherwise immunocompromised (e.g., chronic disease, immunologic deficiency, immunosuppressive therapy, leukopenia). It can be classified in several ways:

1. **By etiologic agent** (e.g., staphylococcal, streptococcal)
2. **By host response** (e.g., suppurative, fibrinous)
3. **By anatomic distribution** (e.g., bronchopneumonia, lobar pneumonia, interstitial pneumonia)

B. **Bronchopneumonia** causes a patchy consolidation of the lung and usually arises as an extension of pre-existing bronchitis or bronchiolitis.

1. **Incidence.** It occurs most commonly in infancy and old age. The most common agents include *Streptococcus pneumoniae*, *Staphylococcus*, *Haemophilus influenzae*, *Pseudomonas*, and coliforms. Fungi may be pathogenic in immunosuppressed hosts.
2. **Clinical features** include fever, a cough productive of purulent sputum, rales over involved areas, and pleuritic chest pain if peripheral regions are involved. Chest x-ray shows focal opacities.
3. **Pathology**
   a. **Grossly**, up to 3–4 cm foci of lung consolidation with purulent inflammation are seen. Consolidation is frequently multilobar, bilateral, and basal because of gravitational pooling of the infection.
   b. **Microscopic findings** are usually a purulent exudate, dominated by neutrophils filling airways and alveoli, unless the patient is immunosuppressed.
4. **Complications** include lung abscess, spread to the pleural space (empyema), spread to the pericardial cavity (suppurative pericarditis), bacteremia with metastatic infection, and respiratory failure.

NOTE

The spectrum of infectious agents causing pneumonia continues to change as antibiotics evolve, and the number of immunocompromised patients rises.

IN A NUTSHELL

Bronchopneumonia:

- *Patchy consolidation involving one or more lobes*
- *Acute inflammation (neutrophils) extending into alveoli from bronchioles*

C. **Lobar pneumonia** is usually due to a bacterial infection, most commonly caused by *S. pneumoniae*, leading to widespread consolidation in large portions of a lobe.

1. **Incidence.** Lobar pneumonia occurs most often in mid-life. Men are involved 3–4 times more frequently than women. *Klebsiella* and type II pneumococcus occur in the elderly, alcoholics, and diabetics.
2. **Clinical Features.** There is an acute onset of fever, chills, malaise, and cough with watery sputum initially, followed by frankly purulent, **rusty sputum.** Shortness of breath, orthopnea, and cyanosis can occur if pneumonia is sufficiently severe. Pleuritic chest pain and pleural friction rub occur with peripheral involvement. Limited breath sounds and rales occur early, proceeding to dullness and percussion with egophony, increased tactile and vocal fremitus occur with more severe consolidation. Chest x-ray shows lobar involvement.
3. **Complications** include lung abscess, empyema, and exudate organization rather than resorption. This causes respiratory difficulty and bacteremia, with metastases to heart valves (endocarditis), spleen, brain (meningitis), kidney, joints, and pericardium (pericarditis).

D. **Viral and mycoplasmal pneumonia (atypical pneumonia).** These reactions are called atypical because of lack of alveolar exudate. Instead, inflammation is found in the lung interstitium and alveolar septae **(interstitial pneumonia).** Pneumonia is frequently caused by *Mycoplasma pneumoniae* in crowded conditions and by viruses, including influenza A and B, respiratory syncytial virus (RSV), and rhinovirus.

1. **Clinical Features** include fever, malaise, and a **dry hacking cough;** these symptoms resemble those of a severe upper respiratory infection. Constitutional symptoms are common: headache, muscle aches, and leg pains. **Elevated cold agglutinins** are found in 50% of patients with mycoplasmal pneumonia and 25% of patients with adenovirus. There is less than 1% mortality. Symptoms are out of proportion to physical findings.
2. **Pathology**
   a. **Grossly,** there is patchy-to-diffuse involvement, bilaterally or unilaterally. Affected areas are red-blue with a congested interstitium but without consolidation or pleural involvement. There is no pus.

E. **Pneumocystis carinii pneumonia (PCP).** *Pneumocystis carinii* is now believed to be a fungal organism. It infects immunocompromised patients. It is commonly seen in **acquired immunodeficiency syndrome (AIDS),** in oncology patients, as well as in undernourished children.

1. **Clinical Features.** Patients present with fever, dyspnea (shortness of breath), hypoxia (low oxygen saturation), and bilateral interstitial infiltrate on x-ray. Less often, patients complain of cough.

BRIDGE TO MICROBIOLOGY

Pneumonia in diabetics or alcoholics → think Klebsiella. Another classic clue for Klebsiella pneumonia is "currant jelly" sputum.

IN A NUTSHELL

Lobar pneumonia:

- *Called "lobar" because it involves the entire lobe*
- *Most often due to Streptococcus pneumoniae*
- *Characterized mainly by an intra-alveolar exudate that results in consolidated lobe(s) of the lung*
- *Red hepatization followed by grey hepatization*

IN A NUTSHELL

Interstitial pneumonia:

- *Most commonly due to viruses and Mycoplasma pneumoniae*
- *Inflammation is found in the lung interstitium and alveolar septae; there is no alveolar exudate*
- *Involves one or more lobes*

f. **Aspiration pneumonia** results from aspiration of oral secretions or gastric contents. It is seen in **alcoholics and other debilitated patients** with neurologic or anatomic impairment affecting the swallowing mechanism. A chemical pneumonitis results, often with secondary bacterial infection from mouth anaerobes, causing necrosis and abscess formation.

g. **Pulmonary abscess** refers to an area of inflammation with a central region of liquefaction necrosis. It occurs at any age but is more common in young adults (men > women). It is rare in infants.

1. **Pathogens** include aerobic and anaerobic Streptococcus, *S. aureus*, Gram-negative rods, and mouth anaerobes, including Bacteroides, Fusobacterium, and Peptostreptococcus.

2. **Routes of infection**
   a. **Aspiration** of gastric contents and mouth flora
   b. Bacterial pneumonia **(inhalation)**
   c. Septic **emboli** from the venous circulation or the right side of the heart
   d. **Neoplasia** with postobstructive pneumonia
   e. Miscellaneous **trauma**, extension of infection from other organs, hematogenous spread, or cryptogenic (no identifiable cause)

3. **Clinical features** include fever, paroxysmal cough with **foul-smelling**, purulent or sanguineous sputum, and weight loss. Clubbing can occur within weeks of abscess formation. 10-15% have underlying carcinoma. With appropriate antibiotics, 75% of pulmonary abscesses resolve without sequelae. An **air-fluid level** is often seen on chest x-ray.

4. **Complications** include respiratory failure, extension of infection into the pleural space, and embolization to the brain and meninges.

h. **Pulmonary tuberculosis** (TB) primarily affects the lungs and is caused by **acid-fast mycobacteria.** Almost all cases are caused by Mycobacterium tuberculosis. Atypical mycobacteria can cause infection, especially in the immunocompromised host. Because *M. tuberculosis* is a **strict aerobe,** reactivation tends to occur in the apex of the lung and renal cortex. There is an increased incidence in areas with poor sanitary conditions, poverty, overcrowding, malnutrition, and limited access to medical care. The emergence of AIDS and other immunosuppressed states has led to a resurgence in the incidence of TB. Of concern now is the occurrence of **multiple drug-resistant TB.**

1. **Primary pulmonary TB**
   a. **Pathology.** The lung is the usual location of initial infection, typically the lower part of the upper lobe or the upper part of the lower lobe. Parenchymal or subpleural lesions occur associated with enlarged, ipsilateral caseous lymph nodes, which are "draining" the parenchyma. The **"Ghon complex"** refers to radiographic

evidence of a calcified peripheral lesion in conjunction with a calcified hilar lymph node.

b. **Clinical features.** Most patients are asymptomatic, and the lesions become fibrotic and calcified over time. It is the macrophage that leads to phagocytosis of tubercle bacilli, epithelioid giant cell fusion, and **granuloma formation** with central **caseous necrosis.** The tubercle bacilli survive in granulomas for years, only to reactivate when the patient's immune system is depressed (e.g., elderly, malnourished, HIV).

2. **Secondary pulmonary TB.** Most cases represent **reactivation** (rather than reinfection) of old TB that had disseminated at the time of primary TB. Reactivation occurs often in areas of high oxygen tension, such as the **lung apices.** Only 5–10% of patients exposed to TB develop reactivation. Reactivation TB usually occurs in debilitated elderly patients.

   a. **Pathology**

      (1) **Grossly,** there is a small focus of consolidation, usually less than 3 cm, in the lung apex. Hilar lymph nodes are also involved, developing foci of tuberculous activity. Parenchymal lesions can develop small areas of caseous necrosis that may not cavitate. The usual course is fibrous encapsulation, leading to fibrocalcific scars and pleural adhesions. A thick, collagenous wall may totally enclose caseous debris. This may never resolve and can remain as a granular lesion.

      (2) **Microscopically,** characteristic **granulomas** composed of epithelioid cells, with occasional Langhans' giant cells, are seen.

   b. **Complications** include hemoptysis, resulting from ulceration of the bronchial mucosa; pleuritis; tuberculous pneumonia; and bronchopleural fistula with empyema.

3. **Late progressive pulmonary TB** shows progression of an early tuberculous apical lesion to a fibrocaseous area with cavitation. Spread is through erosion into an airway to other regions of the lung, resulting in multiple lesions that may cavitate. Spread may also occur via the lymphatic system or blood, leading to distant dissemination. The pleura is often involved and may lead to exudative pleural effusion, frank tuberculous empyema, or massive obliterative fibrous pleuritis. Bronchi are also involved as a result of seeding and can cause mucosal ulcers. Pathology reveals caseating granulomas.

4. **Miliary TB** is due to spread via blood or lymphatics. Disease may remain confined to the lung but usually disseminates widely. For example, erosion into a pulmonary artery leads to lung lesions; erosion into a pulmonary vein leads to systemic lesions. Extrapulmonary sites of involvement include the renal cortex, lymph nodes, genital tract, peritoneum, bone marrow, adrenal gland, pericardium, and meninges.

Clinical Correlate

Legionella pneumophila infection is a result of inhalation of the aerosol from contaminated water, most commonly found in air conditioning systems.

i. **Legionella infections.** *Legionella pneumophila* (a Gram-negative bacillus) is the etiologic agent of these infections. It is usually found in soil or water. Transmission is via **inhalation** into the lungs. Major environmental sources include **water reservoirs and cooling units** of air conditioning systems that may contain blue-green algae and amoebae, among which Legionella can survive for prolonged periods.

1. **Clinical features.** Community outbreaks traced to an infected water source reveal two patterns of illness.
   a. **Pontiac fever** is a mild, nonfatal, systemic febrile illness.
   b. **Legionnaire's disease** is a severe pneumonia with 15%–20% mortality. After approximately 5 days of incubation, patients develop fever, dry cough, malaise, chest and abdominal discomfort, confusion, and occasionally, diarrhea. Frequently, pulse-temperature dissociation exists (a high temperature with no increase in pulse). Severe cases have blood-tinged sputum, dyspnea, high fevers, and impressive systemic symptoms. Death may occur due to progressive ventilatory failure or from a shock-like syndrome with disseminated intravascular coagulation (DIC) and renal failure.

2. **Complications**
   a. Inflammation of small pulmonary arteries and veins can lead to thrombosis.
   b. Abscess formation is frequent, but the abscesses are small.
   c. Organization and scarring secondary to destructive lesions can lead to ventilatory impairment.
   d. Fibrinous pleuritis is usually mild with serous effusion.
   e. Bacteremia is always a risk.

j. **Diphtheria** (due to *C. diphtheriae*) and **whooping cough** (due to *B. pertussis*) both cause toxin-mediated upper respiratory tract infections that can be accompanied by lower respiratory tract infection. The diphtheria toxin induces necrosis of the epithelium of the upper respiratory tract, resulting in the formation of a "diphtheric pseudomembrane."

Note

COPD is a group of disorders that includes:

- Emphysema
- Chronic bronchitis
- Asthma
- Bronchiectasis

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

COPD is a group of disorders characterized by **increased resistance to airflow** during both inspiration and expiration, due to airway obstruction. The obstruction can occur at any level from the trachea to terminal bronchioles. This group represents the most common form of pulmonary disease and includes emphysema, chronic bronchitis, asthma, and bronchiectasis.

A. **Emphysema** refers to distention of air spaces distal to the terminal bronchiole with destruction of alveolar septae, probably secondary to ischemia.

1. **Incidence.** Emphysema is associated with **cigarette smoking**, urban living, and pollution. Cigarette smoke causes an increase in elastase

availability (released by neutrophils and macrophages) and a decrease in antielastase activity (due to oxidant effects). Men are affected more frequently than women.

2. **Types**
   a. **Centrilobular emphysema** affects the **central and proximal** part of a lobule; distal alveoli are not involved. It is more common and usually more severe in the upper lobes. Inflammation surrounding bronchi, bronchioles, and alveoli is common.
   b. **Panacinar emphysema** causes a uniform enlargement of lobules, including terminal and respiratory bronchioles as well as distal alveoli. It is more common and more severe in the lower lobes. **Alpha$_1$-antitrypsin deficiency** is thought to lead to an imbalance between protease and antiprotease activity. This imbalance then leads to panacinar emphysema by young adulthood, especially in the lower lungs.
   c. **Paraseptal emphysema** involves the **distal region of the acinus**, sparing terminal bronchioles and respiratory bronchioles. It is most severe along the pleura, septae, and the lobule edge. It commonly occurs adjacent to areas of fibrosis, scarring, or atelectasis, and is more severe in the upper lung. Paraseptal emphysema forms multiple confluent distended air spaces. It may be the cause of spontaneous pneumothorax (collapsed lung) in young adults.
   d. **Irregular emphysema** describes irregular acinus involvement. It is associated with scarring.
   e. **Bullous emphysema** refers to large, balloon-like distended air spaces in the lung periphery, which can lead to pneumothorax.
   f. In **interstitial emphysema**, an alveolar tear allows air into the connective tissue stroma of the lung, mediastinum, or subcutaneous tissue.
3. **Pathology**
   a. **Centrilobular emphysema**
      (1) **Grossly**, the lungs may not be particularly enlarged or pale unless disease is well advanced. The upper two-thirds are more severely involved.
      (2) **Microscopically**, central airspaces (respiratory bronchioles and alveolar ducts) are destroyed with sparing of peripheral alveoli; inflammation around bronchi and bronchioles is common.
   b. **Panacinar emphysema**
      (1) **Grossly**, panacinar emphysema causes hyperinflated lungs with increased crepitance. Involved areas are pale as a result of blood vessel destruction and compression.
      (2) **Microscopically**, there is little inflammatory involvement of septae or alveoli associated with their destruction.
4. **Clinical features** include dyspnea with or without cough, weight loss, **barrel-chest** due to hyperinflation, pursed-lip breathing, prolonged

expiratory time, and **cor pulmonale** (right-sided heart failure). "**Pink puffers**" are patients who overventilate to maintain oxygenation despite the elevated work of breathing. X-rays reveal **hyperinflation** with flattened diaphragms.

5. **Pathogenesis.** There are two theories.
   a. **Protease-antiprotease theory**, as described above.
   b. Loss of bronchial cilia as a result of smoking leads to mucus plugging and **alveolar overdistention**. Alveolar overdistention, resulting from obstruction, can compromise the septal blood flow, leading to ischemia and alveolar destruction. Inflammation and mucus plugging may exacerbate the obstruction.
6. **Complications** include **cor pulmonale** as a result of increased pulmonary vascular resistance, ventilatory failure, polycythemia, and pneumothorax.

B. **Chronic bronchitis** is a common disorder that can lead to obstructive airway disease. Chronic bronchitis is a **clinical diagnosis**; that is, persistent cough with sputum production for at least three months for two consecutive years. Sputum varies from uninfected mucus (simple chronic bronchitis) to purulent (mucopurulent chronic bronchitis).

1. **Pathogenesis.** There are two major factors.
   a. **Chronic irritation** from inhaled substances (e.g., nitrogen dioxide, sulfur dioxide) may cause inflammation.
   b. **Recurrent infections** do not initiate bronchitis, but they do perpetuate it, and result in acute exacerbations. Common organisms include *Haemophilus influenzae*, *S. viridans*, and *S. pneumoniae*. Smoking can lead to both irritation and infection. Smoke destroys the lung's ciliary tree, damages the mucosa, and interferes with WBC function. It is believed that changes in the small airways are important in the pathogenesis of bronchitis. Small airway obstruction represents the earliest manifestation of COPD. Inflammation and mucus plugging increase resistance to air flow in these usually low-resistance airways. Continued exposure to irritants and repeated infection eventually lead to chronic bronchitis.
2. **Pathology**
   a. **Grossly**, lungs are boggy, hyperemic, and hyperinflated with **copious mucus plugging** the airways.
   b. **Microscopically**, there is hypertrophy of the submucosal glands first in the large airways then in smaller airways. Bronchial epithelium may exhibit squamous metaplasia or dysplasia. Mucus plugging, inflammation, edema, smooth muscle hypertrophy, and fibrosis are all common.
3. **Clinical features**. There is a **productive cough** with copious sputum production, dyspnea, barrel chest, cyanosis, hypercapnia, hypoxia, and

In a Nutshell

Chronic bronchitis

- *Is a clinical diagnosis of persistent cough with sputum production for at least 3 months for 2 consecutive years*
- *Is associated with infections, cigarette smoking, air pollution, and various genetic factors*
- *Can present with mucus plugging, inflammation, edema, fibrosis, and smooth muscle atrophy*

frequent infection. Patients are classically known as **"blue bloaters"** because they are constantly cyanotic.

4. **Complications. Respiratory failure** usually occurs during a bout with an acute infection. **Cor pulmonale** may occur as a result of pulmonary hypertension (increased resistance of pulmonary vasculature as a result of alveolar destruction and hypoxic vasoconstriction). Dysplasia of bronchial epithelium may lead to cancer.

C. **Asthma** is characterized by enhanced airway reactivity, leading to intermittent episodes of **reversible paroxysmal airway narrowing.**

1. **Types**
   a. **Extrinsic asthma (allergic, atopic).** Attacks are triggered by environmental antigens (e.g., dust, pollen, food). There is frequently a family history of **atopy** (e.g., rhinitis, asthma, and eczema). Bronchospasm is mediated by a **type I immunoglobulin E (IgE) hypersensitivity** response to a particular antigen. Histamine, leukotrienes (LTC_4, LTD_4, and LTE_4), prostaglandin D_2 (PGD_2), chemotactic factors, and platelet activation all lead to airway-constricting inflammation and increased vascular permeability. Serum IgE levels are elevated, and a positive skin test may be demonstrated to the offending antigen.
   b. **Intrinsic asthma (idiosyncratic).** Exacerbations frequently follow a viral infection, which causes inflammation and a lowering of the vagal threshold for irritants. Other causes of increased airway reactivity include stress, pollution, occupational exposure, exercise, and cold weather. There is no family history, skin tests are negative, and IgE levels are normal.
   c. **Aspirin-induced asthma** may be seen in adults. There is a classic triad of **nasal polyps, rhinitis, and bronchoconstriction.**

2. **Pathology**
   a. **Grossly**, asthma causes hyperinflated lungs with small areas of atelectasis. Bronchi and bronchioles are occluded by thick, tenacious mucus plugs.

3. **Clinical features** include cough, dyspnea, and **wheezing**. X-ray reveals hyperinflation. If airway obstruction is severe, the patient may not be able to ventilate, leading to respiratory failure (increased Pco_2 and decreased Po_2). Between attacks, patients are asymptomatic.

D. **Bronchiectasis** is an abnormal, permanent dilatation of airways due to **chronic necrotizing infection** and obstruction.

1. **Pathogenesis**
   a. **Bronchial obstruction** (e.g., tumor, foreign body, COPD, mucus plug) leads to atelectasis and airway smooth muscle relaxation.
   b. **Infection** further weakens the airway wall. Organisms include *Staphylococcus*, *Streptococcus*, enteric anaerobes, and *H. influenzae*. Patients are susceptible to recurrent infection due to impaired

IN A NUTSHELL

Some microscopic pathologic findings in asthma:

- *Mucus plugs containing Curschmann's spirals and Charcot-Leyden crystals*
- *Eosinophilic infiltrate*
- *Edema*
- *Submucosal gland hypertrophy*
- *Bronchial wall muscle hypertrophy*

defense against pathogens, caused by cough, injury to the mucociliary apparatus, and impaired phagocytosis.

c. Examples of disorders in which chronic infection leads to bronchiectasis include:

(1) **Cystic fibrosis**, which is characterized by exocrine gland dysfunction, leading to viscous sputum.

(2) **Kartagener's syndrome**, one of several immotile cilia syndromes, is characterized by a triad of **sinusitis, bronchiectasis, and situs inversus**. Absence of pulmonary cilia interferes with bacterial clearance.

2. **Pathology**

a. **Grossly**, bronchiectasis predominantly affects the lower lobes. Dilated airways may be cylindroid, fusiform, or saccular. The lumen is filled with a purulent exudate and the mucosa is edematous and ulcerated.

3. **Clinical features** include cough, fever, and foul-smelling purulent sputum, which is most copious in the morning due to pooling. Clubbing and frequent pneumonia may also be seen.

4. **Complications** include lung abscess, pneumonia, empyema, and septic emboli.

RESTRICTIVE LUNG DISEASE

This is a group of diseases characterized by **decreased lung compliance**, i.e., stiff lungs. The decreased compliance results in small lung volumes with augmented air flow rates. Varying pathologic processes can result in restriction, including extrinsic disease (neuromuscular, chest wall, myasthenia) and intrinsic lung disease. Intrinsic lung processes include interstitial and infiltrative disease, adult respiratory distress syndrome (ARDS), pneumoconiosis, and granulomatous disease.

A. **Adult respiratory distress syndrome (ARDS)** is the final common pathway of **acute diffuse alveolar damage** (both physiologic and histopathologic). It can be caused by a variety of insults, including sepsis/shock, pancreatitis, burns, trauma, drug overdose, pneumonia, and toxins.

1. **Clinical features** include the rapid onset of severe respiratory insufficiency, resulting from alveolar flooding with impaired ventilation (decreased Po_2, increased Pco_2).

B. **Pneumoconiosis** refers to the presence of environmental "dust" in the lung and the lung's response to this foreign entity. It applies to any aerosol, whether in the form of fumes or particulate matter. Development of disease depends upon the amount of exposure, the size and shape of the particles, and the solubility and cytotoxicity of the offending material. All can result in progressive massive fibrosis with diffuse scarring and restrictive lung disease.

1. **Coal workers' pneumoconiosis** occurs after prolonged periods (> 10 years) of exposure to coal dust containing both carbon and silica.
   a. **Clinical features.** Most are asymptomatic or have a slight cough productive of **blackened sputum.** X-ray reveals diffuse nodularities ("tattooing"). A small number of cases go on to develop progressive disease with dyspnea, chronic cough with blackened sputum, poorly localized chest pain, and frequent infections. If exposure continues, **progressive massive fibrosis** with large blackened scars (usually in the upper regions of various lobes) with cor pulmonale can develop, and the pleura can become retracted and thickened if near fibrotic lesions.
   b. **Pathology. Microscopically, "coal dust macules"** are formed initially by the aggregation of macrophages, creating intensely pigmented areas.
2. **Anthracosis** is due to the inevitable inhalation of some carbonaceous particles by city dwellers, cigarette smokers, and miners.
   a. **Clinical features.** Deposition of **carbon dust** can be seen as black pigment in lung parenchyma, pleura, and lymph nodes. When isolated, it is not associated with symptomatic disease.
   b. **Pathology.** Macrophages aggregate into small, peribronchiolar regions in an attempt to phagocytose the dust.
3. **Silicosis.** Chronic silicosis occurs with prolonged exposure to silica dust (mining, glass production, sand blasting, farming, road construction), causing an insidious disease that can progress to respiratory failure and death.
   a. **Clinical features.** Patients with silicosis are at increased risk of developing TB. There is no associated increased cancer risk.
   b. **Pathology.** Collagenous fibrotic nodules form wherever the silica is deposited, probably due to macrophage release of lysosomal enzymes and production of **fibroblast growth factor (FGF).**
4. **Asbestosis** is a disease caused by a family of fibrous silicates commonly found in shipyards, insulation, and roofing industries.
   a. **Clinical features.** Many years after exposure, patients complain of dyspnea, chronic dry cough, recurrent respiratory infections (especially viral), and weight loss. Respiratory failure can occur many years after exposure has ceased. Patients with asbestos exposure are at increased risk of developing bronchogenic cancer as well as **mesothelioma** (pleural and peritoneal). Smoking causes a multiplicative increase in the risk of developing lung cancer. Patients with asbestosis are also at risk of developing renal and gastrointestinal carcinoma.
   b. **Pathology.** Smaller asbestos fibers that reach smaller airways and alveoli are phagocytosed by macrophages after being covered with hemosiderin and glycoprotein (**ferruginous body**).

NOTE

Silica dust in the lungs is ingested by alveolar macrophages, which become damaged. There is then a release of the macrophages' lysosomal enzymes and production of FGF, resulting in fibrotic silicotic nodules.

5. **Berylliosis** is due to heavy exposure to airborne beryllium or its salts. Because of its high tensile strength and resistance to heat and fatigue, beryllium is still used in the electronic, ceramic, aerospace, and nuclear energy industries. Disease due to beryllium probably represents a type IV hypersensitivity reaction, with noncaseating granuloma formation and eventual fibrosis. There is an increased incidence of bronchogenic cancer in patients with berylliosis.

C. **Goodpasture's syndrome** is a necrotizing hemorrhagic interstitial pneumonia that can lead to **hemoptysis** (coughing up blood) and **rapidly progressive glomerulonephritis** (with crescent formation). The disease appears to involve antibody recognition of a common pulmonary and renal basement membrane antigen.

1. **Clinical features.** Goodpasture's syndrome usually occurs in young individuals (20s and 30s) and is more common in men. Death usually occurs as a result of complications of renal failure, but massive hemoptysis can be responsible.

2. **Pathology**

a. **Grossly,** heavy lungs with areas of red-brown consolidation are seen.

In a Nutshell

Goodpasture's syndrome:
Antibodies against glomerular and pulmonary basement membranes result in a hemorrhagic pneumonitis and glomerulonephritis. Immunofluorescence reveals linear deposits of IgG along the glomerular basement membrane. If you see a patient with both hemoptysis and hematuria, think Goodpasture's.

VASCULAR DISORDERS

A. **Pulmonary congestion and edema** result from an accumulation of fluid and protein within the pulmonary interstitium and alveolar space as a result of hemodynamic (Starling's) derangements or from increased capillary/alveolar permeability.

1. Most commonly, **pulmonary edema** develops when there is an increase in pulmonary capillary pressure as with left heart failure. Volume overload of the nephrotic syndrome and decreased lymphatic drainage also lead to transudation of fluid across the alveolar membrane. As fluid accumulates in the interstitium, interendothelial junctions stretch, leading to increased permeability to both fluid and macromolecules. The lymphatic flow must be increased tenfold before the lung's drainage mechanism is overwhelmed, leading to edema. It is only after even higher capillary pressures are achieved that fluid moves from the interstitium into the alveolar space.

2. **Alveolocapillary permeability.** Edema results after injury to both capillary endothelial and alveolar epithelial cells. Fluid and protein accumulate initially in the interstitium and subsequently in the alveolar space. **Noncardiogenic pulmonary edema** can result from septic shock, pancreatitis, burns, toxin inhalation, oxygen toxicity, narcotic overdose, pneumonia, organic solvent hypersensitivity, and other causes. Pathologically, the lungs are heavy, wet, and subcrepitant, mostly involving the bases. Alveolar capillaries are engorged, and the alveolar space contains a granular pink precipitate. Alveolar microhemorrhage

In a Nutshell

Cardiogenic pulmonary edema:
- *Left ventricular failure*
- *Mitral stenosis*

Noncardiogenic pulmonary edema:
- *Septic shock*
- *Pancreatitis*
- *Burns*
- *Toxin inhalation*
- *O_2 toxicity*
- *Narcotic overdose*
- *Pneumonia*
- *Organic solvents*

and hemosiderin-containing macrophages are present. If the process becomes chronic, macrophages with hemosiderin are abundant, and alveolar wall fibrosis results in firm, brown lungs ("brown induration"). These patients are particularly susceptible to bronchopneumonia.

B. **Pulmonary hypertension.** The pulmonary circulation is characterized by low pressure and low resistance, which protect the right ventricle from excessive work. Pulmonary hypertension usually occurs as a result of elevated pulmonary vascular resistance.

1. **Primary pulmonary hypertension** has an unclear etiology, although there are numerous theories. It generally affects young women 20–40 years of age. Some theories include:
   a. **Multiple small pulmonary emboli,** which become organized and incorporated within arterial walls
   b. **Neurohormonal-induced vascular hyperreactivity,** causing chronic vasoconstriction and pulmonary hypertension
   c. **Immune complex-mediated disease**
   d. **Diet or medicinal products,** such as appetite suppressants, which may cause direct endothelial damage

2. **Secondary pulmonary hypertension** results from known diseases, causing elevated pulmonary vascular resistance and pulmonary pressures.
   a. **Increased pulmonary blood flow** may be due to atrial septal defect, ventricular septal defect, patent ductus arteriosis, or Eisenmenger's complex.
   b. **Hypoxic vasoconstriction** may be seen in COPD and interstitial lung disease.
   c. **Elevated left heart pressures,** transmitted back to the right side of heart, may occur in congestive heart failure, mitral stenosis, and left atrial myxoma.
   d. **Destruction of pulmonary vessels** may occur in schistosomiasis, necrotizing vasculitis, multiple pulmonary emboli, sickle-cell anemia, scleroderma, and COPD.

3. **Pathology.** A variety of vascular lesions with much overlap between primary and secondary hypertension is seen.
   a. In **primary hypertension,** medium-sized muscular arteries develop medial hypertrophy, intimal thickening and fibrosis with adventitial fibrosis, and internal and external elastic membrane thickening and reduplication. Small arteries and arterioles are most affected with medial thickening. A "plexiform lesion" may form, consisting of cellular intraluminal angiomatous tufts.
   b. **Secondary changes** are similar to those in the primary disease but may have organized thrombi and diffuse atherosclerotic changes without calcification or ulceration.

In a Nutshell

Pulmonary embolism:

- *Very common occurrence*
- *Occurs during times of venous stasis, especially during prolonged bed rest or sitting; CHF and in primary venous disease*
- *Most often originates from a "DVT" or deep venous thrombosis in the lower extremities or pelvic area*
- *Risk factors include: obesity, cancer, pregnancy, oral contraceptives, hypercoagulability, multiple fractures, and prior DVT*
- *If you are given a question on the exam where a bedridden patient (often postsurgical) develops sudden shortness of breath, think pulmonary embolism. Diagnosis would be confirmed with a V/Q (ventilation/perfusion) scan.*

4. **Clinical course.** Patients become symptomatic only after the disease is well advanced. They usually present with dyspnea and fatigue. Occasionally, syncope or angina can be the initial manifestation. Respiratory failure or decompensated cor pulmonale result in death within several years of presentation.

C. **Pulmonary thromboembolism and infarction** is an underdiagnosed entity (500,000 annually; 10% fatal), resulting in occlusion of a pulmonary artery by an **embolic blood clot.** Thrombosis on top of a nonocclusive embolus may lead to complete arterial obstruction. The usual sources of emboli are the **deep veins of the leg.** However, a clot can also develop in the pelvic veins and right heart.

1. **Risk factors** include bed-bound conditions, obesity, cancer, pregnancy, oral contraceptives, hypercoagulability, and prior deep venous thrombosis.
   a. **Large emboli** may occlude the main pulmonary artery or its major branches or lodge in the pulmonary artery bifurcation, leading to a "saddle embolus." Sudden death can follow from blockage of blood flow out of the right ventricle or from acute right heart failure (acute cor pulmonale).
   b. **Small emboli** occlude smaller vessels. Fewer than 10% of pulmonary emboli cause infarction as a result of bronchial artery collateral flow to the lung parenchyma. Under these conditions, hemorrhage with parenchymal preservation rather than infarction occurs. If the collateral circulation is compromised, even small emboli can cause infarction.
2. **Pathology.** Characteristically, infarctions extend to the lung periphery, forming a wedge-shaped, pleural-based infiltrate. Initially, the infarct is hemorrhagic with ischemic necrosis ("red infarct"). Fibrinous exudate forms on the apposed pleural surface. RBCs lyse within 48 hours, and eventually fibrous replacement begins at the margins, leading to scar formation.
3. **Clinical features** of a pulmonary embolus depend on its size.
   a. **Small emboli** cause transient cough, dyspnea, tachycardia, hyperventilation, and possibly chest pain. Infarction may produce fever, worsening chest pain, and hemoptysis in addition to dyspnea and tachypnea.
   b. **Large emboli** can produce sudden death with a clinical syndrome similar to an acute myocardial infarction (chest pain, severe dyspnea, shock, fever).

D. **Fat embolism** is characterized by progressive respiratory insufficiency, mental deterioration, and occasionally renal insufficiency. These emboli usually develop 1–3 days after a **long bone fracture.**

1. **Pathogenesis** is controversial and probably multifactorial.

a. Release of fat globules from the marrow may simply occlude vessels in the lung and brain. Smaller globules may fit through the pulmonary vasculature and cause systemic emboli.
b. Chylomicrons may coalesce with stress, leading to vessel occlusion.
c. DIC may cause obstructive symptoms, exacerbated by fat emboli.
d. Free fatty acids may cause microvascular toxic injury, leading to capillary block.

2. **Prognosis.** Mortality is high (10–15%).

I. **Amniotic fluid embolism.** Release of thrombogenic amniotic fluid into the maternal circulation during delivery causes widespread thrombosis and occlusion of pulmonary capillaries. DIC may follow. There is a high mortality rate.

LUNG TUMORS

Most lung tumors represent metastatic lesions. Of the primary lung neoplasms, most are **bronchogenic carcinomas.**

A. **Benign neoplasms**

1. **Hamartomas** are the most common benign pulmonary neoplasm. They are **mesenchymal neoplasms,** composed of a mixture of tissues usually found in the lung (cartilage, smooth muscle, collagen) in a disorganized array. They can become extremely large despite their benign nature and can remain clinically silent because of their peripheral location. Calcification resembling "popped popcorn" occurs in 5–20% of hamartomas.
2. **Bronchial adenomas** arise from bronchial mucous glands.
3. **Leiomyomas** arise from smooth muscle, usually in an endobronchial location.
4. **Hemangiomas** are usually peripheral and often subpleural.
5. **Lipomas** are usually endobronchial and can occur on either side of the bronchial cartilage.
6. **Chondromas** are derived exclusively from formed bronchial cartilage.

B. **Bronchial carcinoids** comprise up to 5% of all primary lung tumors. They are a disease of young adults (35–45 years of age). Smoking does not appear to be an independent risk factor. The cells are derived from a precursor cell, closely related to the Kulchitsky **neuroendocrine argentaffin cell** and contain neurosecretory granules. The release of neuroendocrine substances leads to the carcinoid syndrome.

1. **Clinical features.** Eighty percent of bronchial carcinoids are central lesions that are "radiographically silent" but can lead to bronchial obstruction, causing cough, fever, chest pain, and localized wheeze. Hemoptysis is present in approximately 50%, reflecting central origin

and hypervascularity. Complete obstruction can lead to bronchiectasis and parenchymal necrosis distal to the obstruction. Twenty percent are peripheral lesions that are usually clinically silent; they are detected fortuitously on routine chest x-ray as a slightly lobulated nodule. Calcification is rare. Only 3.5% develop the carcinoid syndrome with diarrhea, cutaneous flushing, wheezing, heart disease (valvular fibrosis), abdominal pain, and telangiectasia.

C. **Bronchogenic carcinoma** is the leading cause of cancer death among both men and women. The female preponderance has increased, most probably as a result of increased smoking among women in the past few decades. Bronchogenic carcinoma occurs most commonly in patients 40–70 years of age. **Adenocarcinoma** is the most frequent type of bronchogenic carcinoma, surpassing squamous cell carcinoma. Carcinoma of the lung begins as an area of cellular hyperplasia and atypia that causes thickening of the bronchial mucosa. Eventually, an irregular elevation forms that can elevate or erode the lining epithelium. Continued progression can follow one of three paths: **intraluminal growth, infiltrative peribronchial growth, and intraparenchymal cauliflower-like growth** that pushes normal tissue away. When bulky, hemorrhage or necrosis can convert the usually grey-white firm mass to a yellow-white mottled and softer mass. Spread to hilar, mediastinal, bronchial, and tracheal lymph nodes is common (50%). Metastasis via lymphatics or blood occurs relatively early. Only approximately 25% of lung cancers are operable when discovered.

1. **Types**

   a. **Adenocarcinoma** (35%) usually forms peripheral tumors that arise from distal airways and alveoli, although occasionally they occur proximally, arising from submucosal glands or epithelium. Adenocarcinoma occurs equally in men and women and is less closely associated with smoking than squamous cell.

   b. **Squamous cell** (25%) arises from bronchial epithelium, following years of mucosal alterations, including metaplasia, dysplasia, and carcinoma in situ. The tumor starts as a small red granular plaque or as a focus of whitish leukoplakia and progresses to a large intrabronchial mass. Cavitation may occur in the lung distal to the mass. Squamous cell carcinoma is most closely related to **cigarette smoking**. It tends to metastasize locally and somewhat later than the other lung tumors. It is more common in men and is usually centrally located.

   c. **Small cell carcinoma** (25%), forms proximal, large, soft, grey-white masses that can narrow bronchi circumferentially simply by extraluminal tumor bulk. There is rapid growth and early dissemination so that, if untreated, the median survival is less than three months.

   d. **Large cell carcinoma** (15%) forms peripheral, anaplastic lesions that can become quite large and active.

Note

Small cell carcinoma cells secrete the hormones ACTH and ADH. This may give rise to a Cushing's syndrome or syndrome of inappropriate ADH (SIADH), respectively. Squamous cell carcinoma may secrete a parathyroid hormone-like substance that may cause hypercalcemia.

- e. **Bronchioalveolar carcinoma** (5%) is a subset of adenocarcinoma that arises from terminal bronchioles or alveolar walls.

2. **Major risk factors**
   - a. **Cigarette smoking.** The incidence of lung cancer is related to the number of cigarettes smoked per day, the duration of cigarette use, the depth of inhalation, and the type of cigarette used. Histologic changes in the bronchial epithelium caused by smoking include:
     (1) Loss of bronchial cilia
     (2) Basal epithelial hyperplasia
     (3) Nuclear hyperchromatism
   - b. **Occupational exposure,** including uranium mining, metal work, painting, and radiation, all may increase the risk of cancer.
   - c. **Air pollution.** Reducing agents (sulfur dioxide and carbonaceous particulate matter) appear to be carcinogenic, whereas oxidants are not.
   - d. **Genetics.** There may be a familial predisposition to lung cancer, particularly with deletions or mutations to p53 or the retinoblastoma gene.

3. **Clinical features.** There are two modes, early and late, depending upon cell type and site of origin. Staging of disease is by the size of the tumor, number of affected nodes, and distant metastasis (TNM system). In the early stage of disease, intrabronchial lesions cause mild cough or a change in the character of a chronic cough. Partial obstruction may produce focal emphysema. Total occlusion leads to postobstructive atelectasis or pneumonia with fever, chills, sputum production, localized wheeze, hemoptysis, or abscess formation. In the late mode, there is a wide spectrum of presentations.
   - a. Nonspecific systemic symptoms include weight loss, anorexia, fatigue, weakness, and nausea.
   - b. Intrathoracic spread can lead to Horner's syndrome with secondary cervical sympathetic nerve involvement, **superior vena cava syndrome,** dysphagia with secondary esophageal obstruction, hoarseness with secondary recurrent laryngeal nerve involvement, diaphragmatic paralysis with secondary phrenic nerve damage, and **Pancoast tumor** (causing ulnar nerve pain and Horner's syndrome).
   - c. Extrathoracic extension may involve prescalene lymph nodes, brain, liver, adrenal, and, most commonly, **bone metastases.**
   - d. The systemic syndromes, or **paraneoplastic syndromes,** may occur before the lesion is visible on x-ray.
     (1) **Neuromuscular syndromes** include cerebral encephalopathy and cortical cerebellar degeneration (small cell), peripheral neuropathy with pain, paresthesias, myasthenia (Eaton-Lambert syndrome), and proximal muscle neuromyopathy.

NOTE

Superior vena cava (SVC) syndrome may be a presentation of bronchogenic carcinoma. In this syndrome, obstruction of the SVC by tumor results in dilatation of head and neck veins, facial swelling, and cyanosis.

Clinical Correlate

Sputum cytology, transbronchial biopsies, and open biopsies are all used to diagnose lung cancer. Pathologists are also asked to evaluate resection margins following surgery as well as to detect the presence of lymph node metastases. Evaluation of liver and bone marrow biopsies are required in the setting of metastatic disease for the purpose of staging.

(2) **Hematologic/vascular syndromes** include anemia unrelated to therapy or bone marrow infiltration, coagulopathy (Trousseau's syndrome), migratory thrombophlebitis, DIC, noninfectious endocarditis, and arterial embolization.

(3) **Dermatologic signs** are dermatomyositis, hyperpigmentation, and acanthosis nigricans.

(4) **Skeletal and connective tissue syndromes** include hypertrophic pulmonary osteoarthropathy (periosteal new bone formation, clubbing, and arthritis), which is sometimes caused by squamous cell carcinoma. Vasomotor instability with blanching of hands and feet may also be seen.

MEDIASTINAL MASSES

Mediastinal masses often present as an unexpected finding on routine chest x-ray. Symptoms are due to either compression or invasion of neighboring structures. Vascular lesions may present as "masses" in all parts of the mediastinum and include congenital vascular rings, double superior vena cavae, aortic malformations, aneurysms, and dilatations, aneurysm or dilatation of major aortic branches, and dilated pulmonary arteries. Other masses include diaphragmatic herniations and pulmonary lobar sequestrations. The mediastinum can be divided into three compartments, each with characteristic lesions:

A. **The anterior mediastinum** ranges from the root of the neck, extending down to include the region between the sternum (anteriorly) and pericardial surface (posteriorly).

1. **Thymoma** is the most common anterior mediastinal mass. There are four cell types: epithelial, lymphocytic, spindle, and mixed. Benign thymomas have a thick fibrous capsule and do not invade. Malignant thymomas lack a capsule and do invade.
2. **Teratomas** are tumors derived from pluripotential precursor cells.
   a. **Mature teratomas (dermoid cysts)** generally show ectodermal differentiation, although elements from other germ layers may be present. They are generally benign, although approximately 1% undergo malignant transformation.
   b. **Immature teratomas** have a fetal or embryonic appearance microscopically; primitive neuroepithelial cells are frequently encountered. Immature teratomas may behave aggressively; tumor behavior correlates with histologic grade.
3. **Lymphoma.** The most common lymphoma is nodular sclerosing Hodgkin's disease. Tracheal compression occurs in 20%.
4. **Cysts** of pericardial, bronchogenic, or thymic origin are also rarely seen.
5. **Intrathoracic goiter** is an unusual finding.

B. **The middle mediastinum** includes the pericardium and its contents, lower trachea, carina and main bronchi, and lymph nodes.

1. **Cysts**
   a. **Pericardial cysts** are usually located in the cardiophrenic angle. They occasionally communicate with the pericardial space and are composed of one mesothelial layer, covering a thin fibrous wall.
   b. **Bronchogenic cysts** are lined with ciliated columnar epithelium with mucous glands and cartilage in the wall.
   c. **Enteric cysts** are lined by squamous epithelium and smooth muscle without cartilage.
2. **Lymphoma,** *both Hodgkin's and nonHodgkin's types, may involve* middle mediastinal nodes.
3. **Primary mediastinal carcinoma** may arise from cyst epithelium.
4. **Granulomatous lesions.** Histoplasmosis, sarcoidosis, and TB may all involve middle mediastinal nodes, usually because they drain primary lesions in the lungs.

C. **The posterior mediastinum** includes the posterior pericardium to the anterior vertebral column and posterior ribs, including the paravertebral gutters.

1. **Neurogenic tumors** are almost always benign in adults, although 10% have an intraspinal component.
   a. **Schwannomas** (neurilemmomas) are benign nerve sheath tumors of Schwann cells.
   b. **Neurofibromas** are benign nerve sheath tumors of fibroblasts.
   c. **Ganglioneuromas** are benign nerve cell tumors of sympathetic ganglion cells. They occur primarily in the second and third decades.
   d. **Ganglioneuroblastomas** are malignant tumors of sympathetic neurons; they are common in children and infants.
   e. **Neuroblastoma** is also common in children and infants and is highly malignant.

DISEASES OF THE PLEURA

A. **Effusions** are abnormal **accumulations of fluid within the pleural space;** they are a common manifestation of both systemic and intrathoracic disease. The normal pleural space contains no more than 15 ml of serous fluid that lubricates the pleural surface. The factors that determine whether pleural fluid accumulates include oncotic pressure in the pleural microcirculation and surrounding tissue, permeability of the pleural microcirculation, pressure in the pleural microcirculation and surrounding tissue, intrathoracic negative pressure, and lymphatic drainage. Pleural

effusions can be divided into **transudates** (low lactate dehydrogenase, low protein) and **exudates** (high lactate dehydrogenase, high protein).

1. **Noninflammatory pleural effusions (transudates)**
   a. **Hydrothorax. Noninflammatory serous fluid** collects in the pleural cavity as a result of CHF (increased pressure), renal failure (fluid overload, increased pressure), cirrhosis (fluid overload, decreased oncotic pressure), or nephrotic syndrome (fluid overload, decreased oncotic pressure). The fluid is clear and straw-colored.
   b. **Hemothorax** follows hemorrhage into the pleural space, often the result of a rupturing aortic aneurysm of iatrogenic causes, such as biopsies.
2. **Inflammatory pleural effusions (exudates)**
   a. **Serofibrinous pleuritis** is caused by **inflammatory diseases** within the lung such as TB, pneumonia, lung infarcts, lung abscess, and bronchiectasis. Systemic disease such as rheumatoid arthritis, systemic lupus erythematosus, uremia, and diffuse infections can also cause serous or serofibrinous pleuritis. The fluid consists of relatively clear, straw-colored fluid with small strands of yellow fibrin and few WBCs.
   b. **Suppurative pleuritis (empyema)** is a **purulent exudate** with bacterial or fungal seeding of the pleural space, usually by contiguous spread from the lung. Occasionally, infection can come from blood or lymphatics. It is characterized by **yellow-green pus** with masses of polys and other leukocytes. Empyema infrequently resolves but usually organizes with the formation of tough fibrous adhesions that can obliterate the pleural space or form a pleural "peel," preventing pulmonary expansion. Calcification is typical of tuberculous empyema.

B. **Pneumothorax** is an accumulation of **air or gas in the pleural cavity**, leading to **collapse of the underlying lung** as a result of increased surrounding pressure (pleural pressure is usually negative). Pneumothorax is frequently due to spontaneous rupture of an alveolus or bleb or to a communication between an abscess and either the pleural space or interstitium. It is most common in patients with emphysema, asthma, and TB. **Traumatic pneumothorax** results from puncture of the chest wall with communication between the pleural space and external environment. When air can enter the pleural space but not exit during expiration, pressure builds, leading to a **tension pneumothorax** with **tracheal deviation**, respiratory compromise, and hemodynamic instability.

C. **Tumors**

1. **Metastatic involvement** of the pleura is most common, usually from the breast or lung.
2. **Malignant mesothelioma** is a rare tumor that arises from parietal or visceral pleura. It is associated with **asbestos exposure** after a pro-

Bridge to Cardiovascular

Now may be a good time to review the Starling equation from cardiovascular physiology: Transudates result from ↑ P_c, ↓ π_c, or a combination of the two.

In a Nutshell

Transudate	Exudate
• *Specific gravity less than 1.012*	• *Specific gravity greater than 1.020*
• *Noninflammatory edema fluid resulting from changes in hydrostatic or osmotic pressure intravascularly*	• *Inflammatory edema fluid with increased vascular permeability*
• *↓ protein in fluid*	• *↑ protein in fluid*
	• *↓ glucose in fluid*
	• *↑ inflammatory cells in fluid*

longest latent period of 25–45 years. In contrast to bronchogenic carcinoma, in which smoking and asbestos exposure act synergistically, smoking does not increase the risk of malignant mesothelioma. The malignant mesothelioma is a diffuse lesion that spreads over the lung surface, causing a pleural effusion and invasion of thoracic structures. The lung is encased by a thick layer of gray-pink tumor, composed of mesenchymal stromal cells or even papillary, epithelial-like cells. Patients complain of chest pain and dyspnea. Prognosis is poor.

LARYNGEAL DISEASES

A. **Inflammation.** **Laryngitis** is usually part of an inflammatory process of the lung and lower respiratory tract. It may also be involved with diffuse infections, such as TB, syphilis, diphtheria, and local disease of the mouth and throat. Although trivial in the adult, laryngeal inflammation can lead to upper airway obstruction in children.

B. **Tumors**

1. **Benign neoplasms**
   a. **Polyps** usually occur on the true vocal cords as smooth, round nodules that may be pedunculated or sessile. Polyps are composed of loose connective tissue and covered by squamous epithelium that can ulcerate when traumatized by the opposite vocal cord. They are associated with heavy smoking and vocal cord overuse.
   b. **Papilloma** is a true neoplasm, usually a soft, friable nodule on the true vocal cords. Papillomas frequently ulcerate and bleed with manipulation. They are composed of multiple finger-like projections composed of fibrous tissue covered with squamous epithelium. Papillomas rarely undergo malignant transformation.

2. **Malignant tumors** are uncommon except for those arising from the surface epithelium. Most occur on the vocal cords, although they can occur anywhere. Ninety-five percent are **squamous cell carcinomas**, which can cause hoarseness, difficulty swallowing, pain, hemoptysis, and eventually, respiratory compromise. Ulceration can lead to superinfection. Complications arise due to direct extension, metastases, and infection. Risk factors include cigarette smoking, alcohol, and frequent cord irritation.

b. **Microscopically**, neuronal loss occurs mainly in the cortex but also in many subcortical nuclei. The following features are characteristic, though not pathognomonic:
   (1) **Neurofibrillary tangles** are intracytoplasmic, skein-like structures composed of paired helical filaments.
   (2) **Granulovacuolar degeneration** describes small cytoplasmic vacuoles containing a central granule.
   (3) **Senile plaques** are abnormal, enlarged, presynaptic axon terminals surrounding a central core of extracellular amyloid-like substance.
   (4) **Hirano bodies** are found in some cases.

c. It has been proposed that loss of cholinergic neurons in the nucleus basalis of Meynert is in part responsible for memory impairment and other cognitive deficits.

IN A NUTSHELL

Alzheimer's pathology:
- *Gross cortical atrophy*
- *Microscopic changes*
  - *Neurofibrillary tangles*
  - *Senile plaques*
  - *Hirano bodies*

B. **Pick's disease** is a rare form of dementia, which causes lobar atrophy (affecting both grey and white matter), predominantly in the frontal and temporal lobes. Familial cases are common.

IN A NUTSHELL

Pick's disease is similar to Alzheimer's disease but with atrophy localized to the frontal and temporal lobes.

C. **Parkinson's disease** (paralysis agitans) is an idiopathic disorder that usually begins after age 40 and afflicts 1% of the population older than 50.

1. **Clinical features** include bradykinesia (difficulty initiating and slowness of voluntary movement), rigidity, resting tremor, flexed posture, expressionless (masked) facies, and festinating (shuffling) gait. Dementia may occur.

2. **Etiology**. Symptoms are primarily from **dopamine depletion in the caudate and putamen**, the termination of the nigrostriatal tract. The cause of death of substantia nigra dopaminergic neurons is unknown.

3. **Pathology**
   a. **Grossly, depigmentation of the substantia nigra** (which contains the somata of dopaminergic neurons from which the nigrostriatal tract originates) and locus ceruleus is evident.

4. **Parkinsonism** includes disorders displaying the clinical features of Parkinson's disease. This classification is now recognized as encompassing several routes of pathogenesis. The final common pathway for the recognized etiologies listed below is thought to be nigrostriatal dopamine depletion or blockade of postsynaptic receptors. Causes include:
   a. Neuroleptics (e.g., phenothiazines)
   b. Encephalitis, particularly viral
   c. Carbon monoxide/manganese poisoning
   d. Strokes
   e. Methylphenyltetrahydropyridine (MPTP), which is found in some synthetic heroin

IN A NUTSHELL

Parkinson's symptoms:
- *Bradykinesia*
- *Rigidity*
- *Resting tremor*
- *Festinating gait*
- *Masked facies*
- *Dementia*

Parkinson's disease is characterized by a loss of dopaminergic neurons in the substantia nigra, which projects to the striatum (caudate nucleus and putamen).

D. **Huntington's disease** is characterized by **autosomal dominant inheritance, choreoathetosis**, and **dementia**.

In a Nutshell

Huntington's disease is an autosomally dominant disease characterized by the degeneration of neurons of the caudate nucleus. The gene is located to the short arm of chromosome 4.

1. **Incidence.** The onset is usually between 25 and 55 years of age and tends to be about the same in each afflicted family.
2. **Pathology**
   a. **Grossly,** there is striking degeneration of the medium-sized, spiny neurons of the **caudate nucleus** with less severe involvement of the putamen and cerebral cortex.

E. **Progressive supranuclear palsy** is a degenerative disorder characterized by ophthalmoplegia (affecting vertical before horizontal gaze), pseudobulbar palsy, axial dystonia, and bradykinesia. Mild dementia often develops.

1. **Incidence.** Onset is usually between the fifth and seventh decades of life.
2. **Pathology**
   a. **Grossly,** there is widespread neuronal loss and gliosis in subcortical sites with sparing of the cerebral and cerebellar cortices.

F. **Friedreich's ataxia** is an inherited disorder (usually autosomal recessive).

1. **Incidence.** Onset is usually between ages 5 and 25.
2. **Clinical features.** Most patients are unable to walk within 5–15 years of onset because of progressive ataxia. Associated features include pes cavus (hollowing of the instep), diabetes, kyphoscoliosis, diminished proprioception, tremors, decreased or absent tendon reflexes, Babinski's sign, and cardiomyopathy.

G. **Motor system disease** refers to a group of overlapping degenerative disorders characterized by some combination of **muscle weakness, atrophy,** and **spasticity;** these symptoms result from loss of motor cells in the spinal cord, brain stem, cerebral cortex, and cerebellum. These disorders include **amyotrophic lateral sclerosis** (ALS; Lou Gehrig's disease).

Clinical Correlate

In ALS, both upper and lower motor neurons degenerate. Symptoms are mixed: atrophy and fasciculation indicate lower motor neuron degeneration; spastic paralysis, increased muscle tone, and hyperreflexia indicate upper motor neuron degeneration.

VASCULAR LESIONS

A. **Cerebral infarction** refers to necrosis of neural parenchyma secondary to inadequate blood or oxygen supply.

1. **Etiology**
   a. **Thrombosis** usually results from atherosclerosis. Diabetes, smoking, family history, age, hypertension, and alcohol are important risk factors. Thrombosis is also caused by arteritis, vascular trauma, and a hypercoagulable state. It usually occurs in large- and medium-sized vessels.
   b. **Emboli** may arise from a mural thrombus of the left ventricle, aortic or carotid plaques, septic emboli, and fat and air emboli. They usually occur in medium-sized vessels.
   c. **Lacunar infarcts** are clues to the occlusion of deep penetrating arteries and are associated with hypertension. They are named for small cavities (lacunae) formed in the deep white or gray matter.

The nervous system is affected by all of the same processes that affect other organ systems: genetic malformations, degeneration, infectious diseases, vascular insufficiency, and neoplasms.

Degenerative disorders of the central nervous system (CNS) are often due to the accumulation of metabolic products, sometimes from an inherited disorder (e.g., Tay-Sachs disease) and sometimes from a problem acquired or manifested later in life (e.g., Alzheimer's disease). A great deal of progress has been made in determining the molecular basis of these diseases. Prenatal tests now exist for Tay-Sachs disease, Huntington's disease, and even for a genotype predisposing to Alzheimer's disease.

Vascular disease is of primary importance in the CNS. Again, arteriosclerosis and its attendant risk factors are the most common cause of vascular insufficiency and its resultant pathology, stroke. Infectious diseases of the CNS can have viral, bacterial, protozoal, or fungal etiologies. Some of the "slow virus" diseases such as kuru have now been shown to be due to prions, which are thought to be proteins that may fold into more than one configuration.

NONSPECIFIC NEURONAL AND GLIAL CHANGES

The following terms describe conditions that may be seen alone or in combination in many disorders that affect the central nervous system (CNS). They are presented here together for convenience, but will be discussed again throughout the chapter.

A. **Neuronal loss** is the endpoint of many disease processes. It usually requires at least a 30% loss of neurons before it is observable by light microscopy. In many cases, neuronal loss is accompanied by fibrous gliosis.

In a Nutshell

Signs of ischemic neuronal damage:
- *Nissl substance dissolution*
- *Cytoplasmic eosinophilia*
- *Nuclear condensation (pyknosis)*

8. **Ischemic neuronal damage** is an acute process that most commonly follows anoxia. It is characterized by retraction of the cell body (soma), disappearance of Nissl substance, cytoplasmic eosinophilia, and nuclear pyknosis (condensation, often with hyperchromasia).

C. **Neuronophagia** refers to neuronal phagocytosis, which often occurs with viral infections; the degenerating neuron is surrounded by monocytes and microglia (CNS macrophages).

D. **Central chromatolysis** (axonal reaction) refers to the reaction of the cell body following a lesion of the lower motor neuron (LMN) axon. The soma swells, Nissl substance disappears (especially around the nucleus), and there is peripheral displacement of the nucleus.

E. **Neuronal atrophy** results from a variety of slowly progressive degenerative processes. The soma shrinks, there is increased cytoplasmic basophilia, nuclear pyknosis, and increased neurofibril and lipofuscin pigment (the "wear and tear" pigment, which accumulates in degenerating and aged neurons and other tissues).

In a Nutshell

Gliosis is the scarring process of the CNS. Glial scars are formed by astrocytes (and sometimes by fibroblasts).

F. **Gliosis.** In gliosis, injury to the CNS stimulates hypertrophy and hyperplasia of astrocytes shortly after exposure to a variety of noxious agents. The cell body, nucleus, and processes of the astrocyte swell. In the chronic stage, glial fibers accumulate as the cell body shrinks. Roughly five days after infarction, swollen astrocytes with eosinophilic cytoplasm proliferate around the necrotic lesion.

DEGENERATIVE DISORDERS OF THE CNS

Degenerative disorders of the CNS are a mixed group of disorders that tend to begin insidiously and progress gradually. They may cause dementia, disorders of movement and posture, ataxia, weakness, or sensory changes.

A. **Alzheimer's disease** is the most common form of dementia. Presenile and senile forms have been distinguished on the basis of age, although both share common clinical and pathologic features and are considered together.

1. **Incidence.** Most cases occur after the age of 40. There is a female predominance.
2. **Etiology** remains unknown, although it has been ascertained that genetic factors are involved in a small number of cases.
3. **Clinical features.** Early symptoms include impairment of short-term memory, abstract thinking, problem solving, and visuospatial orientation, as well as emotional and social changes (e.g., irritability). Symptoms progress and are later accompanied by aphasia and apraxia; ultimately, the patient enters a vegetative state.
4. **Pathology**
   a. **Grossly,** diffuse cortical atrophy occurs with relative sparing of primary motor and sensory areas. Gyri are thin and sulci are wide.

2. **Clinical features** vary with etiology and location.
   a. **Thrombosis** follows a variable course, often stuttering and often preceded by **transient ischemic attacks (TIAs)**, which cause focal neurologic dysfunction lasting up to 24 hours.
   b. **Emboli** often produce their maximal deficit within 1 minute; signs and symptoms depend on the specific arterial territory affected.

B. **Intracranial hemorrhage.** Bleeding within the cranial cavity may occur in the epidural, subdural, or subarachnoid spaces, or in neural parenchyma. Epidural and subdural hemorrhages are discussed under trauma.

1. **Intraparenchymal bleeds** are usually the result of **hypertension** (called hypertensive, primary, or spontaneous intracerebral hemorrhage) and are the most common cause of death from stroke.
   a. **Clinical features**
      (1) There is a sudden headache and abrupt onset of neurologic deficit.
      (2) Edema may be massive, and herniation can occur.
      (3) The CSF is usually bloody, especially in hypertensive hemorrhage with dissection of blood into the ventricular system.

2. **Saccular (berry) aneurysms** are the most common cause of nontraumatic subarachnoid hemorrhage.
   a. **Etiology** is usually attributed to congenital defects in the arterial media, acquired factors such as atherosclerosis and hypertension, or both.
   b. **Pathology**
      (1) Ninety percent of saccular aneurysms are in the anterior part of the **circle of Willis**, especially at bifurcations. In order of frequency, sites of rupture are the posterior and anterior communicating arteries and the bifurcation of the middle cerebral artery.
   c. **Clinical features.** Rupture usually causes a **severe headache**, which may be followed by no deficit or may be followed by coma. Rupture often occurs during exertion but may occur spontaneously.

C. **Arteriovenous malformations (AVMs)** are developmental abnormalities (non-neoplastic) that directly connect arterial and venous circulations without capillaries. These fistulae vary in size and may be found throughout the CNS. Ninety percent are found in the cerebral hemispheres. There is a male predominance.

IN A NUTSHELL

Thrombotic infarcts, characterized by permanent neural damage, are often preceded by TIAs, which are temporary syndromes resembling mini-strokes.

IN A NUTSHELL

Intraparenchymal bleeds, often caused by hypertension, are the most common cause of stroke fatality.

IN A NUTSHELL

Ruptured berry aneurysms are the most frequent cause of subarachnoid hemorrhage; they often occur at bifurcations of the anterior circle of Willis.

CLINICAL CORRELATE

Patients with subarachnoid hemorrhages often describe having the worst headache of their lives.

BRAIN TRAUMA

A. **Concussion** is a transient paralysis of cerebral function immediately after head trauma (typically a blunt, nonpenetrating injury such as a blow with a fist) that is not associated with structural damage. Although impairment of consciousness is brief, symptoms (e.g., headache, dizzi-

IN A NUTSHELL

- *Concussion → no structural damage*
- *Contusion → "brain bruise" from blunt head trauma*

neni may persist. Duration of post-traumatic amnesia is the best index of the severity of injury.

B. **Contusion** is a bruise of the brain parenchyma that typically involves the summit of the gyrus. The bruise produces a wedge-shaped defect of necrosis and petechial hemorrhages with the base near the meninges and the apex towards the white matter.

C. **Skull fractures** may be of no clinical significance or they may be responsible for important sequelae, including contusion (usually with depressed fractures), CSF leakage (meningeal tear), or epidural hematoma (vascular tear).

1. **Linear fractures** are seen as lucent lines with well-defined borders. Both tables of the skull are involved.
2. **Depressed fractures** cause indentation of the skull and are often associated with contusion.
3. **Compound fractures** have a communication with the outside through an associated tear of the scalp or paranasal sinuses. Osteomyelitis may develop.
4. **Basilar skull fractures** are usually linear and may not be seen on x-ray. CSF leak and cranial nerve palsies may develop.

D. **Hemorrhage** following head trauma may occur into the epidural, subdural, or subarachnoid spaces or within the parenchyma of the brain.

1. **Epidural (extradural) hemorrhage** occurs into the space between the dura and the skull; bleeding may arise from arteries, veins, or both. Most cases follow trauma to the lateral skull, resulting in **laceration of the middle meningeal artery**, although frontal and occipital lesions also occur. Skull fracture is present in 80–90% of cases. Classically, the head trauma is associated with momentary loss of consciousness, followed by a lucid (asymptomatic) period of 1–48 hours. The patient then develops symptoms of elevated intracranial pressure (e.g., headache, changes in mental status, nausea, vomiting) and possibly focal findings (e.g., hemiparesis). Herniation of the medial temporal lobe, coma, and death may result if the collection of blood is not surgically evacuated.
2. **Subdural hematoma** results from bleeding into the space between the dura and arachnoid.
   a. **Acute subdural hematomas** almost always result from severe head trauma, causing **tears in the bridging veins**; they are associated with contusion. Large hematomas are usually fatal; smaller ones may lead to symptoms after a latent interval of days to weeks. Treatment consists of surgical evacuation of the clot.
   b. **Chronic subdural hematoma.** The diagnosis of a chronic subdural hematoma is often difficult because many patients are elderly or alcoholic, and head trauma may be minor or forgotten. Anticoagulation and coagulopathy are predisposing factors.

In a Nutshell

- *Epidural hematomas lie between the skull and the dura. Due to their arterial origin, they grow rapidly and constitute a serious emergency.*
- *Subdural hematomas lie between the dura and the arachnoid. They originate from the bridging veins and therefore develop more slowly than do epidural hematomas.*

Clinical Correlate

Because of cortical atrophy due to age, bridging veins are more fragile in the elderly. Thus, elderly persons are more more likely to develop subdural hematomas than are younger persons.

Symptoms may develop weeks to months after trauma. Headache, drowsiness, asymmetric signs, and fluctuation of symptoms are often present. Herniation, coma, and death may result from compressive effects of an enlarging hematoma.

3. **Subarachnoid hemorrhage** results from bleeding into the space between the arachnoid and pia (i.e., subarachnoid space). Severe head trauma or rupture of an aneurysm can produce subarachnoid hemorrhage.
4. **Intracerebral hemorrhage** results from bleeding into the parenchyma of the brain. Although this is an unusual complication of head trauma, it is present in almost half of fatal cases.

E. **Traumatic spinal cord lesions**

1. **Etiology.** Trauma may be penetrating (producing laceration and hemorrhage) or compressive (causing contusion and ischemia). Vertebral bodies may or may not be displaced.
2. **Clinical features** include weakness, paresthesias, and paralysis, depending on the level of the spinal cord involved.
3. **Pathology.** The injured cord undergoes necrosis and hemorrhage and then, ultimately, cavitation and gliosis.

BRAIN EDEMA

Cerebral edema is an important complication of many neurologic diseases. There are three types of brain edema.

A. **Vasogenic edema** results from increased permeability of endothelial cells in brain capillaries. It occurs with trauma, infarction, tumor, infection, hemorrhage, and lead encephalopathy.

B. **Cytotoxic edema** results from the swelling of neurons, glia, and endothelial cells in brain capillaries. It occurs with infarction, hypoxia, or hyponatremia.

C. **Interstitial edema** occurs in obstructive hydrocephalus with leakage of CSF into the periventricular white matter.

In a Nutshell

- Vasogenic edema → interstitium swells
- Cytotoxic edema → cells swell

TUMORS

A. **Overview**

1. **Types.** CNS tumors may be classified as primary or secondary. Secondary tumors include metastatic or craniovertebral bone tumors. Primary tumors may be divided by tissue of origin.
2. **Incidence.** Neoplasm is the second most common cause of mortality from intracranial disease (stroke is first). CNS tumors are found in about 1% of routine autopsies and constitute roughly 9% of all neoplasms.

a. **Neural tube gliomas** include astrocytomas, glioblastomas, ependymomas, oligodendrogliomas, medulloblastomas, gangliomeuromas, and certain pineal tumors.
b. **Neural crest tumors** include meningiomas, schwannomas, and neurofibromas.
c. **Mesodermal tumors** include CNS lymphomas, hemangioblastomas, lipomas, and chordomas.
d. **Ectodermal tumors** include craniopharyngiomas and pituitary adenomas.
e. **Germ cell tumors** include germinomas and teratomas.

I. **Clinical syndromes.** Brain tumors produce progressive cerebral dysfunction. Symptoms may be generalized (if they result from diffuse compromise) or focal. Since the volume of the intracranial cavity is fixed, tumor growth and edema may cause compression or displacement of parenchyma as well as increased intracranial pressure. Obstructive hydrocephalus may result from a block in normal CSF flow. Elevated intracranial pressure may produce headache, nausea, vomiting or papilledema, and autonomic changes (e.g., hypertension, bradycardia, respiratory changes). Pressure gradients in different intracranial compartments can lead to brain herniation. Focal symptoms include aphasia, hemiparesis, and visual field cuts. Generalized or focal seizures occur in roughly 35% of brain tumors. Behavioral changes are common. Stroke-like syndromes may result from hemorrhage into a tumor.

NOTE

Brain tumors produce symptoms directly by invading tissue or indirectly by increasing intracranial pressure.

CLINICAL CORRELATE

Signs and symptoms of increased intracranial pressure:

- *Headache*
- *Nausea and vomiting*
- *Papilledema*
- *Autonomic changes*

NEUROCUTANEOUS DISORDERS

Neurocutaneous disorders or "phakomatoses" are localized tumors and/or tumor-like lesions of the skin, eye, and nervous system.

A. **Neurofibromatosis** has been described above. Neurofibromas rarely become neurofibrosarcomas.

1. **Clinical features** include:
   a. **Café au lait (pigmented skin lesions) spots**
   b. **Neural tumors** (e.g., neurofibromas)
   c. **Lisch nodules** (benign, pigmented hamartomas of the iris)

B. **Tuberous sclerosis** involves multiple organs but commonly presents as a result of CNS disease, seizures, and mental retardation. Adenoma sebaceum of the face, ashleaf spots, shagreen patches of skin, and subungual angiofibromata may be evident. Multifocal areas of cerebral cortex may be involved with "tubers," which are potato-like masses of giant neurons and astrocytes. The condition is associated with giant-cell astrocytomas, gliomas, and gangliogliomas, and rarely involves the infratentorial CNS or spinal cord.

C. **Retinocerebral angiomatosis (von Hippel-Lindau disease)** is an autosomal dominant disorder involving:

1. **Hemangioblastomas** of the retina or cerebellum with other hemangioblastomas in the cerebrum or spinal cord
2. **Abdominal masses**, such as pheochromocytoma
3. **Cysts** of the kidney, pancreas, and liver, and renal cell carcinoma

D. **Encephalofacial angiomatosis (Sturge-Weber syndrome)** involves the association of an extensive **capillary-venous malformation** of one cerebral hemisphere with an ipsilateral cutaneous **port-wine stain** (nevus flammeus) in the trigeminal region of the face.

IN A NUTSHELL

von Hippel-Lindau disease:
- *Autosomal dominant*
- *Hemangioblastomas*
- *Pheochromocytoma*
- *Renal, pancreatic, hepatic cysts*
- *Renal cell carcinoma in up to 50% of patients*

DEMYELINATING DISEASES

Demyelination may occur primarily (as in multiple sclerosis) or secondary to wallerian degeneration due to axonal death.

A. **Multiple sclerosis (MS)**

1. **Incidence**
   a. MS usually presents between the ages of 20 and 40.
   b. There is a slight female predominance.
2. **Clinical features**
   a. The course is characterized by **spontaneous exacerbations and remissions**.
   b. Ninety percent of patients develop **pyramidal tract dysfunction** (hyperreflexia, weakness, spasticity). Dysfunction is generally multifocal.
   c. Cerebellar dysfunction (e.g., dysarthria, tremor, ataxia) is also common.
   d. Disturbances of extraocular muscles result from lesions of the medial longitudinal fasciculus; disturbances of visual acuity result from lesions of the optic nerve.
3. **Etiology**. There is a presumed autoimmune etiology, possibly influenced by a viral infection. Antibody to measles virus is often detected in the CSF.
4. **Pathology**
   a. **Grossly, plaques are evident in the white matter** (frequently periventricular) or in the corpus callosum. They are also found in the optic nerves and spinal cord.

IN A NUTSHELL

The course of multiple sclerosis is characterized by spontaneous appearance and remission of symptoms.

IN A NUTSHELL

Grossly, MS brains show plaques of demyelination composed of immune cells and glial cells in the white matter.

B. **Devic's disease** (neuromyelitis optica) refers to demyelination confined to the optic nerves and spinal cord. It is characterized by blindness, paralysis, and loss of sphincter control.

C. **Postinfectious/postvaccinial encephalomyelitis**

1. **Pathology.** This form of demyelinating disease causes acute widespread, perivenular demyelination associated with mononuclear infiltration; infiltration follows certain viral illnesses and vaccinations.
2. **Etiology** is thought to be autoimmune (rather than primary) destruction of myelin by viral infection of the neurons.

IN A NUTSHELL

Guillain-Barré syndrome is an autoimmune, postinfectious, peripheral demyelinating disorder. Limb paralysis and autonomic failure may result.

D. **Guillain-Barré syndrome** is a demyelinating illness of autoimmune etiology that **affects peripheral nerves** following certain viral illnesses or vaccinations. It usually presents with limb weakness, but facial and ocular muscles may be involved early. Guillain-Barré syndrome may cause complete paralysis, autonomic dysfunction, and respiratory failure. **CSF protein gradually becomes markedly elevated.** Symptoms usually resolve completely, but prolonged respiratory assistance may be required. Peripheral nerves show demyelination and an accumulation of lymphocytes and macrophages.

NUTRITIONAL AND TOXIC DISORDERS

A. **Thiamine (vitamin B_1) deficiency.** Thiamine is crucial to cellular energy production. Deficiency is due to dietary insufficiency. In the United States, deficiency is usually due to the malnutrition of **chronic alcoholism.** Two neurologic diseases result:

1. **Beriberi peripheral neuropathy** is an axonal degeneration with secondary demyelination. It is caused by an unknown mechanism.
2. **Wernicke's encephalopathy** is characterized by confusion, ocular disturbance, and ataxia of gait.

IN A NUTSHELL

Neurologic sequelae of thiamine deficiency:

- *Beriberi: peripheral neuropathy*
- *Wernicke-Korsakoff: memory gait, and eye movement disturbances*

B. **Vitamin B_{12} deficiency** is almost always secondary to **malabsorption** rather than to dietary deficiency (except in strict vegetarians). The most common cause is **pernicious anemia,** which results in pathology in the peripheral and optic nerves as well as in the spinal cord and brain.

IN A NUTSHELL

Vitamin B_{12} deficiency results in CNS and PNS pathology due to both demyelination and axonal degeneration.

C. **Ethanol.** Pathology is usually the result of nutritional deficiency, hypoxia, or hepatic disease. The following diseases may accompany alcoholism.

1. **Alcoholic cerebellar degeneration** causes cerebellar atrophy, predominantly in the anterior superior vermis, particularly affecting the Purkinje cells. It occurs mainly in men and is characterized by severe ataxia of the lower extremities.
2. **Central pontine myelinosis** is a condition of localized pontine demyelination. It may also be seen in severe malnutrition and with sudden shifts in serum sodium. It may be asymptomatic or cause severe brain stem dysfunction, quadriparesis, coma, and death.
3. **Alcoholic polyneuropathies** are characterized by axonal degeneration of peripheral nerves, gradual development of paresthesias, weakness, and pain.

4. **Fetal alcohol syndrome (FAS)** describes fetal damage resulting from alcohol use during pregnancy. The amount required to produce the syndrome remains controversial. Features of the syndrome include mental retardation, microcephaly, incoordination, hypotonia, irritability, hyperactivity, and a characteristic facies.

D. **Methanol intoxication** produces **metabolic acidosis** (with an anion gap) and **visual disturbances.** The metabolism of methanol to formaldehyde (and less so, to formic acid) is responsible for the ocular toxicity.

INFECTIOUS DISORDERS

A. **Bacterial infections**

1. **Acute pyogenic meningitis**
   a. **Pathogenesis.** Infectious agents are relatively specific to the patient's age, although overlap occurs.
      (1) For neonates, *Escherichia coli*, Group B Streptococci, and *Listeria monocytogenes* predominate.
      (2) For infants and children, *Streptococcus pneumoniae* is the most common infectious cause in those that have received the vaccine for *H. influenzae*. *H. influenzae* will predominate in nonvaccinated children.
      (3) In young adults, *Neisseria meningitidis* causes the most cases.
      (4) In the middle-aged and elderly, Pneumococcus predominates.
   b. **Clinical features** include fever, malaise, headache, nuchal rigidity, photophobia, and altered mental status.

2. **Brain abscesses** are localized, walled-off areas of intraparenchymal purulent exudate.
   a. **Etiology.** Brain abscesses may result from:
      (1) Extension of otitis, mastoiditis, or sinusitis
      (2) Contamination of surgical wounds
      (3) Penetrating head injuries
      (4) Hematogenous dissemination from infected heart and lung sites
   b. **Clinical features.** There may be focal or generalized signs. Death follows herniation or, more rarely, rupture with ensuing meningitis and ventriculitis.
   c. **Pathogenesis.** Common organisms include anaerobic Streptococci, Staphylococci, Bacteroides, Gram-negative Bacilli, and less often, Nocardia and Citrobacter.

3. **Neurosyphilis** (tertiary syphilis) follows an asymptomatic meningitis.
   a. **Meningovascular syphilis** involves infiltration of meninges and vessels with chronic inflammatory cells; the resultant arterial fibrosis and infarction is responsible for many of the clinical manifestations, such as hydrocephalus and cranial nerve palsies.

CLINICAL CORRELATE

Methanol poisoning is treated with ethanol. Ethanol competes with methanol for alcohol dehydrogenase and prevents the formation of formaldehyde.

NOTE

Meningitis is an inflammation of the meninges' layers, not the brain parenchyma.

IN A NUTSHELL

Cerebral abscess is a localized parenchymal infection walled off from the rest of the brain. Symptoms may be focal or generalized.

IN A NUTSHELL

Tertiary syphilis involves the meninges and brain parenchyma, as well as the spinal cord (tabes dorsalis).

b. **General paresis** is characterized by meningeal fibrosis and atrophy; it is most severe in the frontal and temporal lobes. Histologic examination reveals neuronal loss, astrocytosis, rod-shaped microglial cells, and spirochetes.

c. **Tabes dorsalis** involves thoracolumbosacral chronic meningeal inflammation with initial injury to dorsal roots and secondary demyelination of the dorsal columns.

4. **Neurotuberculosis** results from hematogenous dissemination of tuberculosis. It is characterized by a thick exudate at the base of the brain or over the dorsal surface of the spinal cord.

B. **Mycotic infections** occur commonly in patients with neoplasia, immunosuppression, and organ transplants.

1. **Candidiasis** is the most often encountered fungal infection at autopsy of the CNS. Virtually all cases result from hematogenous dissemination from distant sites in colonized patients. Lesions are composed of multiple small abscesses. The organisms appear as a **mixture of yeast and pseudohyphae,** a pathognomonic characteristic of Candida.

2. **Aspergillosis** is the second most common fungal infection of the CNS encountered at autopsy. It results from initial infection through **inhalation of airborne spores with hematogenous dissemination to the brain.** Thus, these infections rarely occur without overt infection elsewhere, especially in the lung.

3. **Mucormycosis** may occur as a regional infection involving the nose, sinuses, and brain (as in **uncontrolled diabetes**), or as a systemic disease with hematogenous dissemination in compromised hosts. Lesions include purulent meningitis, cerebritis, and infarction secondary to arterial invasion and thrombosis.

4. **Cryptococcosis.** Approximately 50% of cases occur in immunocompetent individuals. Inhalation of spores, followed by hematogenous spread, leads most often to meningitis.

C. **Parasitic infections**

1. **Toxoplasmosis**

a. **Acquired toxoplasmosis** is caused by the protozoan *Toxoplasma gondii*. Acutely, there is destruction caused by intracellular, crescent-shaped trophozoites. Chronically, intracellular cysts containing organisms are formed and may remain viable in brain and muscle for years. Normal or immunocompromised adults acquire the organism by consumption of poorly cooked meat or by contamination with feces from infected cats. In severe cases, the brain is littered with multiple large foci of necrosis and many encysted organisms and free trophozoites.

b. **Congenital toxoplasmosis** complicates nearly 40% of primary infections in pregnancy. A maternal infection during the second

Note

Candida frequently causes infections in immunocompromised hosts.

In a Nutshell

Aspergillosis lesions of the CNS result from hematogenous spread. Aspergillosis tends to invade vascular walls and cause cerebral infarction.

In a Nutshell

T. gondii is acquired through contact with cats or infected meat. It is an important cause of CNS infection in both host and fetus (since it can cross the placenta).

to sixth month of gestation may result in infant convulsions, intracerebral calcification, hydrocephalus, and chorioretinitis.

D. **Viral infections**

1. **Meningoencephalitis** may be caused by many agents, but the morphologic features are similar.
   a. **Pathology**. The brain is edematous, containing focal areas of necrosis and even hemorrhage.
   b. **Enteroviruses** are common causes of viral CNS infections. Prior to immunization, poliomyelitis was a prominent example. Today, coxsackievirus (especially group B) and echoviruses are common.
   c. **Arenaviruses** are associated most commonly with lymphocytic choriomeningitis.
   d. **Arboviruses** produce Eastern, Western, Venezuelan, St. Louis, Japanese, and California encephalitis. The St. Louis variety is common in older individuals and carries a mortality of 20%.
   e. **Paramyxoviruses**
      (1) **Mumps** causes meningitis in nearly 25% of patients. A rare meningoencephalitis that appears to be immune-mediated may occur.
      (2) **Measles** (rubeola) is responsible for many cases of postinfectious encephalomyelitis and in a rare, persistent form, **subacute sclerosing panencephalitis (SSPE)**. SSPE mainly affects children. With regard to the pathogenesis of SSPE, damage is caused by an immune reaction to the measles virus.
   f. **Rubella virus** causes the congenital rubella syndrome: low birth weight, cardiac defects, cataracts, chorioretinitis, and neurologic abnormalities.
   g. **Rabies virus** causes pain and paresthesia at the original wound, followed by abnormal behavior, hyperactivity, autonomic dysfunction, and laryngeal muscle spasm. **Negri bodies** (eosinophilic, oval cytoplasmic inclusions) are characteristic.
   h. **Herpesvirus**
      (1) **Herpes simplex** is the most common cause of **sporadic encephalitis**, which can be fatal if untreated. Pathologic changes have a predilection for the frontal and temporal lobes.
      (2) **Varicella zoster** produces a benign cerebellar ataxia and postinfectious encephalomyelitis. The latter entity is characterized by perivenular demyelination. Latent virus may persist in sensory ganglia; reactivation leads to **herpes zoster (shingles)**, which commonly affects thoracolumbar dermatomes and the ophthalmic division of the trigeminal nerve.
      (3) **Cytomegalovirus** may involve the cerebrum with disseminated "glial nodules" that consist of nodular infiltrates of histiocytes; these are usually seen in immunosuppressed individuals.

In a Nutshell

Negri bodies = rabies

In a Nutshell

Herpes encephalitis is often a result of HSV-1 infection. It is treated with acyclovir.

Bridge to Immunology

Prions are proteins without a nucleic acid component. They arise by variable or alternate folding of a particular class of normal proteins. This variable folding causes them to "crystallize" easily, producing plaques. The variable folding pattern is very stable, so these proteins appear infectious, surviving the gastrointestinal tract if ingested and causing normal proteins to "crystallize" with them when they are absorbed into the brain.

2. **Transmissible subacute spongiform encephalopathy** is thought to be caused by virus-like agents (prions) with a very long incubation period ("slow viruses").
   a. **Creutzfeldt-Jakob disease (CJD)**
      (1) **Clinical features** include personality changes, incoordination, myoclonus, dementia, and death (within 3 years).
   b. **Kuru** affects tribal people of the mountains of Papua, New Guinea. The incidence has greatly diminished since the practice of cannibalism has ceased.
      (1) **Clinical features** include ataxia, tremor, and death (within one year). Dementia is not prominent.

Male Reproductive Pathology 7

The most common clinical findings in male reproductive pathology are solid tumors of the testes, prostate, and penis. Prostate carcinoma, in fact, is the second most common cause of cancer in men. Since the majority of the tumors are well differentiated and respond to chemotherapy, radiation therapy, or to surgery, it is important to be able to identify the tumors early on in the course of the disease, through the use of screening tests, tumor markers, and clinical signs and symptoms. This chapter will focus on these diseases, as well as on other disorders that commonly affect the male reproductive system.

TESTES

A. **Cryptorchidism**

1. **Clinical features.** Cryptorchidism is the **failure of normal descent of intra-abdominal testes** into the scrotum. It affects approximately 1% of the adult male population, more often on the right side than the left, and may be unilateral or bilateral. Bilateral cryptorchidism can cause infertility by elevating body temperature to a level that interferes with spermatogenesis. Maldescended testes are also susceptible to trauma and have a greatly increased incidence of testicular cancer.

2. **Pathogenesis.** Cryptorchidism may be a mechanical, hormonal, or idiopathic congenital anomaly.

B. **Germ cell tumors.** Approximately 95% of testicular tumors are germ cell tumors. They are the **most common malignancy in men 15–34** years of age. Although its etiology is unknown, cryptorchidism increases the likelihood of malignancy 14-fold. Infection, trauma, and genetic factors also influence incidence. Generally, germ cell tumors begin as a painless testicular enlargement, with potential for widespread dissemination, usually via the lymphatics to iliac and para-aortic nodes. See summary in Table 7-1.

Table 7-1. Testicular tumors

Tumor	Presentation	Pathology
Germ cell		
Seminoma	Radiosensitive	Bulky and homogeneous
Embryonal carcinoma	Often metastatic	Hemorrhagic nodules
Choriocarcinoma	Highly malignant; elevated HCG	Cyto- and syncytiotrophoblast
Yolk sac tumors	Infants and children; elevated AFP	Nonencapsulated
Teratoma	Mature or immature	Variety of tissues
Nongerm cell		
Interstitial (Leydig) cell tumors	May produce estrogens or androgens	Usually unilateral
Sertoli cell tumors	May produce estrogens or androgens	Usually unilateral
Lymphoma	Older men	Often disseminated

C. **Nongerm cell tumors**

1. **Interstitial (Leydig) cell tumors**
   a. **Clinical features.** Leydig cell tumors can produce androgens, estrogens, or corticosteroids. In children, they often present with masculinization or feminization and in adults with gynecomastia.
   b. **Course and prognosis.** They are usually benign and only 10% are invasive. Surgery may be curative.

2. **Sertoli cell tumors**
   a. **Clinical features.** Sertoli cell tumors can produce small amounts of androgens or estrogens, but usually not enough to cause endocrinologic changes. They may present with testicular enlargement.
   b. **Course and prognosis.** Over 90% of these tumors are benign.

3. **Lymphomas** are the most common testicular cancer in elderly men. The tumors are rarely confined to the testes.

D. **Inflammatory lesions**

1. **Mumps**
   a. **Clinical features.** Orchitis develops in approximately 25% of patients over age 10, usually within a week after parotid swelling. Orchitis is less common in patients under 10 years old.
   b. **Pathology**
      (1) Mononuclear inflammatory infiltrates predominate in the acute phase.
      (2) Atrophy is rare.
   c. **Course.** Mumps rarely leads to sterility. However, should atrophy follow, it may predispose patients to testicular neoplasm.

2. **Gonorrhea**
   a. **Clinical features.** A neglected urethral gonococcal infection may spread to the prostate, to the seminal vesicles, and to the epididymis, but rarely to the testes.
   b. **Pathology.** There may be purulent inflammation or abscesses.
3. **Syphilis**
   a. **Clinical features.** Acquired or congenital syphilis may involve the testes.
   b. **Pathology.** There are two forms: gummas or a diffuse interstitial lymphocytic plasma cell infiltrate.
   c. **Course.** Syphilis can lead to sterility; Leydig cell involvement can cause a loss of libido.
4. **Tuberculosis**
   a. **Clinical features.** TB usually spreads from the epididymis; this is almost always associated with foci of TB elsewhere.
   b. **Pathology.** Caseating granulomata are the classic finding, as with TB dissemination elsewhere.
5. **"Nonspecific"** inflammation is usually caused by Chlamydia trachomatis spread from the epididymis.

E. **Torsion**

1. **Clinical features.** Twisting of the spermatic cord may compromise both arterial supply and venous drainage. Torsion may be precipitated by sudden movement, trauma, or congenital anomalies.
2. **Course.** If not surgically corrected early, torsion may result in testicular infarction with resultant loss of function.

PROSTATE

A. **Benign prostatic hyperplasia (BPH)**

1. **Clinical features.** Benign prostatic hyperplasia (BPH) is characterized by the formation of large nodules in the periurethral region (median lobe) of the prostate, which may narrow the urethral canal to produce varying degrees of urinary obstruction. Patients often present with **difficulty urinating.** It is increasingly common after age 45, and the incidence increases steadily with age (e.g., 90% of men after age 70).
2. **Pathogenesis.** The mechanism is poorly understood, but the blocking of androgens seems to reduce the incidence.
3. **Course.** The course can follow an asymptomatic pattern, or it could result in urinary symptoms and urinary retention, leading to secondary bladder changes, such as smooth muscle hypertrophy. Currently, it is thought that this disease does not predispose to prostatic carcinoma.

NOTE

The "H" in BPH more accurately represents hyperplasia than hypertrophy, although you may see either term still used.

CLINICAL CORRELATE

The urinary symptoms of BPH include frequency, nocturia, and problems initiating and stopping the urinary stream.

NOTE

Although prostate cancer is more common than lung cancer, mortality from lung cancer is more than twice the mortality from prostate cancer.

CLINICAL CORRELATE

An elderly man with osteoblastic metastases visible on x-ray should be considered to have prostate carcinoma until proven otherwise.

B. **Carcinoma**

1. **Clinical features.** Prostatic carcinoma is the second most common cancer in men. Prostate cancer usually occurs after age 50, and the incidence increases steadily with age. In addition to clinically significant tumors, a high incidence of small "incidental" or "latent" carcinomas is discovered at autopsy in men over age 50. The disease may present with urinary problems or a palpable mass on rectal examination.
2. **Pathogenesis** is unknown. The tumor is age related, associated with race (more common in African Americans than in Caucasians, relatively rare in Asians), and is under endocrinologic and environmental influences.
3. **Pathology**
   a. **Grossly,** prostate cancer is found usually in peripheral tissue and is firm and "gritty" as a result of fibrosis.
   b. **Microscopically,** most are **adenocarcinomas.**
4. **Course and prognosis**
   a. **Staging of prostatic tumors** depends upon the size of the tumor, the degree of infiltration to local tissues, and the degree of metastasis.
   b. **Metastases** may occur via the lymphatic or hematogenous route; bone is commonly involved with **osteoblastic metastases,** typically in the pelvis and lower vertebrae.
   c. **Tumor markers. PSA (prostate-specific antigen)** is an enzyme produced by normal, hyperplastic, and malignant prostate glands. It is elevated in both hyperplasia and cancer, but usually more so in the latter. Elevated PSA together with an enlarged prostate on digital rectal exam is highly suggestive of carcinoma.
   d. **Survival** is correlated with stage and grade. Unfortunately, most patients present with advanced disease and have a 10-year survival rate of less than 30%.
   e. **Treatment** involves surgery, radiation, and hormonal modalities (orchiectomy and estrogenic drugs).

C. **Infections**

1. **Acute prostatitis**
   a. **Clinical features.** This condition usually results from a bacterial infection of the prostate. Pathogens are often organisms that cause urinary tract infection. ***Escherichia coli*** is the most common, followed by other Gram-negative rods. Infection may follow manipulation of the prostate or urethra (e.g., cystoscopy, catheterization).
   b. **Pathogenesis.** Bacteria spread by direct extension from the posterior urethra or the bladder. Lymphatic or hematogenous spread can also occur.
   c. **Course.** Appropriate antibiotic therapy is usually curative.

2. **Chronic prostatitis**
   a. **Clinical features.** Chronic prostatitis is a common cause of recurrent urinary tract infections in men. There are two types: bacterial and nonbacterial. Both forms may be asymptomatic or may present with lower back pain and urinary symptoms.
   b. **Pathogenesis.** Bacterial infection may be a sequela of acute prostatitis; nonbacterial infections are most often caused by *Ureaplasma* and *Chlamydia trachomatis*.

PENIS

A. **Congenital malformations**
   1. **Hypospadias and epispadias**
      a. **Clinical features.** These are malformations of the urethral groove and canal. They are often associated with cryptorchidism and other congenital anomalies.
      b. **Pathology.** In hypospadias, the urethra opens onto the ventral surface of the penis. In epispadias, the urethra opens onto the dorsal surface.
      c. **Course.** Both of these malformations may cause infertility.
   2. **Phimosis.** In this condition, the prepuce orifice is too small to be retracted normally. It interferes with hygiene and can also predispose to bacterial infections.

B. **Infections**
   1. **Condyloma acuminatum**
      a. **Clinical features.** This is a benign lesion of **papillomavirus** origin, which may occur on any mucous membrane.
   2. **Syphilis.** Syphilis is a sexually transmitted or congenital disease caused by the spirochete ***Treponema pallidum***. The acquired form initially presents with cutaneous manifestations followed by widespread dissemination. The disease occurs in stages.
      a. **Primary syphilis** has an average 3-week incubation during which spirochetes spread throughout the body. Painless **chancre sores** form and heal within 1–3 months.
         (1) **Grossly,** chancres usually occur on the glans penis in men and the vulva or cervix in women. Occasionally, they appear on other mucous membranes, such as the oral cavity. They appear as single, firm, red papules that may ulcerate.
         (2) **Microscopically,** there is a mononuclear infiltrate with obliterative endarteritis. Plasma cells are very prominent. Special stains may show treponemes.
      b. **Secondary syphilis** usually develops 1–2 months after the primary stage. There is a **local or generalized rash** lasting 1–3 months. The

rash can involve the palms and soles as well as mucous membranes. **Condyloma lata** can appear on the penis.

(1) **Grossly**, condyloma lata are flat, brown red papules on the penis or other mucous membranes. They may form large plaques or ulcerate.

(2) **Microscopically**, there is an obliterative endarteritis and plasma cell infiltrate. Treponemes are present.

c. **Tertiary syphilis** develops in one-third of untreated patients. It may affect the central nervous system (CNS), heart, and skin. **Neurosyphilis** has a varied presentation, including meningovascular, tabes dorsalis, and general paresis. CNS gummas are rare. An **obliterative endarteritis** can occur, involving the vasa vasorum of the aorta, which can lead to the formation of an **aneurysm**. Elastic stains show destruction of fibers. In other tissues the characteristic lesion is the **gumma**.

(1) **Grossly**, gummas may be single or multiple. They have rubbery, necrotic central focus that is variable in size. They are most common in the liver, testes, and bone.

(2) **Microscopically**, gummas are composed of **mononuclear cells surrounding a center of coagulative necrosis.** Gummas resemble caseating granulomas but usually do not have multinucleated giant cells and do not have any stainable acid-fast organisms. Treponemes are rare.

d. **Serologic tests for syphilis**

(1) **VDRL** tests for nonspecific antibodies evoked by spirochetal infection; these antibodies react with **cardiolipin**, a lipoid substance from beef heart. The VDRL becomes positive a few weeks after primary infection and may remain persistently elevated. **"False positives"** may occur in many acute illnesses, as well as in chronic mononucleosis, leprosy, hepatitis, and autoimmune disorders.

(2) **Fluorescent treponemal antibody (FTA)** tests for specific spirochetal antigens. It can confirm the presence of active syphilis in a patient with a positive VDRL.

3. **Chancroid**

a. **Clinical features.** This is a sexually transmitted infection caused by *Haemophilus ducreyi*. Patients have a **painful chancre** and regional **lymphadenopathy**.

4. **Lymphogranuloma venereum (LGV)**

a. **Clinical features.** LGV is a sexually transmitted disease caused by *Chlamydia trachomatis*. It is rare in the United States but common in tropical areas. LGV can present with genital or anorectal lesions or regional lymphadenopathy.

b. **Course.** Scarring and fibrosis can follow chronic infection. Subsequent lymphatic obstruction can lead to edema and elephantiasis of the lower extremities and external genitalia.

Note

Chancroid is not caused by the same etiologic agent as chancre (syphilis). Chancroid is caused by H. ducrei, whereas chancre is caused by T. pallidum.

5. **Genital herpes**
   a. **Clinical features.** There are two subtypes: **herpes simplex (HSV I)** and **herpes genitalis (HSV II)**, causing an overlapping spectrum of disease.
   b. **Pathology**
      (1) **Grossly,** HSV I and II cause vesicles on the external genitalia and mucous membranes; ulcerations can also develop.
      (2) **Microscopically,** epithelial cells show cytopathic changes. Cell fusion leads to **giant cells** or polykaryons, which can be seen on a smear of blister fluid or **Tzanck smear.**
   c. **Course.** HSV infections **tend to recur.** The virus can remain latent in nerve ganglia. **Acyclovir** may prevent or decrease the frequency of recurrences.

C. **Carcinoma**

1. **Bowen's disease** is **carcinoma in situ** and can be associated with visceral malignancy. It usually occurs in men or women over age 35. In men, it tends to involve the shaft of the penis and the scrotum.

2. **Squamous cell carcinoma**
   a. **Clinical features.** Squamous cell carcinoma of the penis accounts for 1% of cancers in men in the United States, usually ages 40–70. Circumcision decreases the incidence. **Human papilloma virus infection** is closely associated with the development of squamous carcinoma.
   b. **Course and prognosis.** Squamous carcinoma is usually slow growing and nonpainful; patients often delay seeking medical attention. Metastases can go to local lymph nodes. The prognosis depends on the degree of advancement of the tumor; limited have a greater than 80% 5-year survival rate.

CLINICAL CORRELATE

HSV I usually appears above the waistline; HSV II typically appears below.

NOTE

Squamous cell carcinomas, particularly those associated with papilloma viruses, show a markedly higher incidence in HIV infection. Its configuration is often papillary. Patients can also have perianal carcinomas or papillomas.

Papillomaviruses (types 16 and 18) are most often associated with squamous carcinoma.

Each organ in the female reproductive system is susceptible to specific disease states, including cancers, benign hyperplasia, and infection. Gynecologic malignancies account for a large majority of cancers in women. Breast cancer is the second leading cause of cancer death in women in the U.S., and cervical cancer is the sixth leading cause. Since many gynecologic disorders present with similar symptoms of menstrual irregularities, nonmenstrual vaginal bleeding or discharge, and pelvic pain, it is important to be able to recognize the features that differentiate one disease state from another. This chapter will focus on these disorders and will highlight the risk factors and clinical and pathologic features that distinguish them.

UTERUS

A. Endometrium

1. Endometritis

a. **Acute endometritis** is relatively uncommon. It is caused by bacterial infection of the endometrium, usually **following childbirth or abortion.** It may be related to retained products of conception. The usual pathogens are group A β-hemolytic Streptococci and Staphylococci, producing a nonspecific interstitial inflammation with neutrophils.

b. **Chronic endometritis** may occur postabortion or postpartum but is also related to the use of intrauterine devices (IUDs), tuberculosis (TB), or pelvic inflammatory disease (PID). There is a chronic inflammatory infiltrate with plasma cells in the interstitium.

2. Endometriosis

a. **Clinical features.** Endometriosis refers to **ectopic endometrial tissue outside the uterine cavity,** most often in the ovaries, uterine ligaments, rectovaginal septum, pelvic peritoneum, postlaparoto-

Note

Endometriosis is characterized by cyclic bleeding from the ectopic endometrial tissue, resulting in "chocolate cysts"—brown blood-filled spaces.

Note

In postmenopausal women, endometrial hyperplasia is often due to exogenous estrogen administration. Occasionally, well-differentiated adenocarcinoma arises in this setting. It regresses when estrogen therapy is stopped.

Clinical Correlate

Risk factors for endometrial carcinoma:

- *Prolonged estrogen stimulus*
- *Obesity*
- *Diabetes*
- *Hypertension*

my ovary, vagina, vulva, and appendix. It occurs in women of reproductive age and is rare over age 50. It is commonly associated with infertility. Depending on the location of ectopic tissue, it may cause dysmenorrhea, pelvic pain, dyspareunia, pain on defecation, dysuria, and an inability to conceive.

b. **Course and prognosis.** Infertility may result from fibrosis and scarring of tubes and ovaries.

3. **Endometrial hyperplasia**

a. **Clinical features.** Hyperplasia may occur in both perimenopausal and postmenopausal women. It may present with abnormal or excessive uterine bleeding, often associated with states of **elevated estrogen production** (e.g., prolonged estrogen therapy, adrenocortical hyperfunction, certain ovarian tumors). It may be a precancerous lesion.

4. **Endometrial polyps**

a. **Clinical features.** These are most common in perimenopausal or postmenopausal women. They usually present with **uterine bleeding.**

b. **Pathology**

(1) **Grossly,** polyps may be single or multiple and are usually less than 3 cm. They are often sessile but may be pedunculated.

(2) **Microscopically,** there are two types: functional endometrium and hyperplastic (cystic or adenomatous) endometrium.

c. **Course and prognosis.** Malignant transformation is rare.

5. **Endometrial carcinoma**

a. **Clinical features.** This disease primarily occurs in the postmenopausal age group. It is associated with obesity, diabetes, hypertension, and infertility. It may be asymptomatic or present with abnormal uterine bleeding/discharge.

b. **Pathogenesis** is thought to be the result of **prolonged estrogen stimulation.** There is a correlation with prolonged estrogen therapy, estrogen-secreting neoplasms, and endometrial hyperplasia (which may also be a result of estrogen stimulation).

c. **Pathology**

(1) **Grossly,** tumors are either polypoid or diffuse and may become fungating and necrotic.

(2) **Microscopically,** one sees primarily **adenocarcinomas,** showing glandular patterns with varying degrees of differentiation.

d. **Course and prognosis.** There is early spread by contiguous growth through the myometrium, into the broad ligament, and then to nearby portions of the gastrointestinal and urinary tract. Later, lymphatic and hematogenous spread occur. Survival depends on the stage at diagnosis. Treatment is usually surgery, with or without radiation.

B. Myometrium

1. Leiomyoma (fibroids)

a. **Clinical features.** These are **benign smooth muscle neoplasms** representing the most common tumor in women and occurring generally in the third and fourth decades. Incidence is increased in African American women. There is a possible role of estrogens in the pathogenesis. They may present with excessive menstrual bleeding, abnormal uterine bleeding, pain, infertility, or urinary symptoms.

b. **Course and prognosis.** Malignant transformation is rare. They may require surgical removal for bleeding or infertility.

FALLOPIAN TUBES (UTERINE TUBES, OVIDUCTS)

A. Inflammation

1. **Pelvic inflammatory disease (PID)**

a. **Clinical features.** Inflammation begins in the vulva or accessory glands (Bartholin's glands or Skene's ducts) and may spread upward throughout the reproductive system. The most common organism is ***N. gonorrhoeae***, but Staphylococcus, Streptococcus, coliforms, *Clostridium perfringens*, Mycoplasma, Chlamydia, and anaerobes may be seen. PID may occur spontaneously, postabortion, or postpartum. Presentations include abdominal/pelvic pain, menstrual irregularities, dysmenorrhea, and fever.

b. **Course and prognosis.** Complications are severe and include sepsis, peritonitis, adhesions with intestinal obstruction, and infertility from tubal scarring or tubo-ovarian abscess. Early diagnosis and appropriate antibiotic therapy are essential.

B. **Tumors** in the fallopian tubes are rare.

CERVIX

A. Inflammation

1. **Acute and chronic cervicitis**

a. **Clinical features.** Various forms of cervicitis are common and are of variable clinical significance. The most common pathogens are Streptococcus, Enterococci, *Escherichia coli*, and Staphylococcus; others include Gonococci, *Trichomonas vaginalis*, Candida and Herpes (usually HSV II). Infection may follow intercourse, childbirth, and gynecologic instrumentation. Predisposing influences include high estrogens, alkaline mucus, and congenital anomalies.

b. **Course and prognosis.** Cervicitis may be asymptomatic or present with a vaginal discharge. It is important to distinguish it from cervical cancer, usually by Pap smear or biopsy.

B. **Tumors**

1. **Cervical polyps**
   a. **Clinical features.** Polyps are common in the fourth and fifth decades. They may present with irregular vaginal bleeding.
   b. **Pathology**
      (1) **Grossly**, polyps are usually single, arise in the endocervical canal, and may be sessile or pedunculated.
   c. **Course and prognosis.** They may be removed by curettage.
2. **Squamous cell carcinoma of the cervix**
   a. **Clinical features.** This is the sixth most common cause of cancer death in women. It may occur at any age from the second decade onward, but it is most common in the fourth and fifth decades.
   b. **Pathogenesis.** There is an increased risk associated with early onset of sexual relations and multiple sexual partners. **Human papillomaviruses,** particularly types 16 and 18, are clearly associated with squamous carcinoma. Other types are associated with benign papilloma. In patients infected with HIV, cervical cancer due to papillomaviruses is increasing in incidence.
   c. **Pathology**
      (1) **Grossly**, advanced, invasive cervical cancer may be fungating, ulcerating, or infiltrative.
      (2) **Microscopically**, koilocytosis and squamous vacuolizations are seen. Cervical cancer is viewed as the end stage of progression of atypia in cervical epithelium, or cervical intraepithelial neoplasia (CIN). Premalignant squamous epithelium begins to show atypical features (pleomorphism, loss of polarity, frequent mitoses, and increased nuclear/cytoplasmic ratio) but maintains differentiation in the upper cell layers.
   d. **Course and prognosis.** Cervical cancer spreads by contiguous growth to involve urinary structures and bowel. Lymphatic or hematogenous dissemination may occur. Mortality is declining as a result of early recognition of the precursor dysplastic cervical epithelium via the **Pap smear,** which should be a part of every woman's yearly physical examination from reproductive age onward. The cure rate for carcinoma *in situ* may be as high as 100%. More advanced disease has a much lower cure rate (10–15% if metastasis has occurred) and may require both surgery and irradiation.

Clinical Correlate

Risk factors for cervical carcinoma:

- *Early sexual activity*
- *Multiple sexual partners*
- *Lower socioeconomic group*

Clinical Correlate

Now that we appreciate the importance of papillomaviruses as causative agents of cervical cancer, in situ hybridization studies for specific viral DNA may be done on suspicious lesions.

Clinical Correlate

The recommended frequency of Pap smears is under discussion. Sexually active women should probably have a Pap smear every year. Sexually inactive women may only need a smear every 3 years. Women with suspicious findings should have repeat Pap smears perhaps as often as every 3–6 months. Repeatedly suspicious or positive smears should lead to cervical biopsy for definitive diagnosis.

VAGINA

A. **Congenital anomalies**

1. **Gartner's duct cysts**
   a. **Clinical features.** These cysts must be distinguished from tumor masses.

b. **Pathology**

(1) **Grossly**, 1–2 cm submucosal cysts on the lateral vaginal walls are present.

(2) **Microscopically**, the cysts may have cuboidal, columnar, transitional, or a mixed epithelial lining. There is no atypia.

B. **Inflammation** may be due to various pathogens.

1. ***Trichomonas vaginalis*** is a flagellated protozoan. It typically causes a "strawberry red" vaginal mucosa and microscopic, suppurative inflammation.
2. ***Candida albicans*** (monilia) causes a thick, white exudate.
3. **Herpes simplex vaginitis** may accompany vulvar infection. It may lead to neonatal infection during delivery. The organism is usually herpes simplex virus (HSV) II.
4. ***Gonococcus*** may cause vulvovaginitis in children as well as adults.

C. **Tumors**

1. **Squamous cell carcinoma**
   a. **Clinical features.** This tumor is quite rare, comprising less than 1% of female genital cancers. It may present with irregular bleeding, spotting, or discharge but is occasionally asymptomatic until advanced.
   b. **Course and prognosis.** Squamous carcinoma of the vagina spreads by local extension to the cervix, rectum, and bladder. Late lymphatic or hematogenous spread may occur.
2. **Adenocarcinoma**
   a. **Clinical features.** Adenocarcinoma is very rare; of the vaginal cancers, 85% are squamous and 1% are adenocarcinoma. It is much more common in young women whose mothers were treated during pregnancy with **diethylstilbestrol (DES)**. Because DES is no longer used to treat threatened abortion, this cause of adenocarcinoma has almost disappeared.
   b. **Course and prognosis.** Tumors grow by contiguous spread; later, they grow by lymphatic or hematogenous spread. Treatment includes surgery with or without radiation. DES-related tumors have an 80% five-year survival.

OVARIES

A. **Overview.** The most common ovarian lesions are cysts and tumors. Ovarian cancer is the fifth most common cancer in women, accounting for 6% of all female cancers. Eighty percent of ovarian tumors are benign. The benign tumors tend to occur earlier (in the third through the fifth decades), whereas the malignant tumors are more common in older women (in the fifth through the seventh decades). **Family history, early**

CLINICAL CORRELATE

DES therapy in pregnant women increases the incidence of vaginal neoplasms in their daughters. Vaginal adenosis is a benign condition that is thought to be a precursor of clear cell adenocarcinoma in these women.

menarche, and nulliparity are risk factors. There is an increased incidence in children with gonadal dysgenesis. Tumors are **often asymptomatic until large.** Then they may present with abdominal pain, distension, vaginal bleeding, and gastrointestinal or urinary symptoms. Ovarian tumors are classified into four groups: surface epithelial tumors, germ cell tumors, sex cord/stromal tumors, and metastatic tumors involving the ovary.

B. **Surface epithelial tumors**

1. **Overview.** 60% of ovarian tumors arise from surface epithelium. There are variable presentations. In addition to abdominal discomfort, vaginal bleeding, and gastrointestinal/genitourinary symptoms, patients may present with malignant ascites from peritoneal seeding or with an acute abdomen from torsion of a large tumor or rupture of a cyst. Unfortunately, these slow-growing tumors are often asymptomatic until the disease is far advanced.

C. **Germ cell tumors**

1. **Overview.** These constitute 15–20% of all ovarian neoplasms; **most (over 95%) are benign cystic teratomas.** They occur primarily in young women and children. Presentations vary. Germ cell tumors are divided into four groups: teratomas, dysgerminomas, endodermal sinus (yolk sac) tumors, and "other," a group that includes choriocarcinoma, embryonal carcinoma, polyembryoma, and mixed germ cell tumors.

2. **Teratomas**

   a. **Mature (benign) teratomas** are also called **dermoid cysts** because they are lined by skin and adnexae and are **often filled with sebaceous secretions and hair.** There is a high incidence in women of reproductive age. They may present with an abdominal mass, pain, and gastrointestinal or menstrual abnormalities.

   (1) **Grossly,** they are usually unilateral, small, unilocular cysts that may have a mixture of hair, tooth structures, and bone.

   (2) **Microscopically,** they are usually composed of cysts, lined by stratified squamous epithelium and structures derived from **multiple germ layers,** including endoderm, mesoderm, and ectoderm.

   (3) The course is usually benign. Surgical resection leads to cure. Torsion may occur.

   b. **Immature (malignant) teratomas** are rare, containing embryonic elements derived from all three germ layers.

   (1) **Grossly,** they form smooth, large masses that are primarily solid but may have cystic spaces. **Necrosis and hemorrhage are common.** As with the benign tumors, malignant teratomas may contain hair and bone.

   (2) **Microscopically,** they are composed of immature tissues differentiating into nerve, muscle, bone, and a variety of other tissues. The characteristic of malignancy is undifferentiated areas.

(3) These tumors are **fast-growing and invasive** with both lymphatic and hematogenous spread. Grading is based on degree of maturity of cells and presence of neural tissue: the more immature the cells and the more neuroepithelium, the higher the grade and the worse the prognosis.

D. **Sex cord-stromal tumors**

1. **Overview.** These tumors constitute only 5-10% of ovarian neoplasms. They occur at all ages and **produce steroid hormones** that may lead to endocrinologic syndromes. The three most important groups of these tumors are granulosa-theca cell, fibroma, and Sertoli-Leydig cells.

E. **Tumors metastatic to the ovary.** The most common sites of origin are other pelvic organs, upper gastrointestinal tract, and breast. **Krukenberg's tumor** is bilateral, metastatic, mucin-producing adenocarcinoma (usually signet-ring cells derived from the stomach).

F. **Cysts**

1. **Follicular cysts**
   a. **Clinical features.** These are often asymptomatic cysts, originating in unruptured or resealed follicles.
   b. **Pathology**
      (1) **Grossly,** these cysts are usually in the cortex, multiple, filled with clear fluid, and approximately 1 cm in size.
      (2) **Microscopically,** granulosa lining cells may be identified in cysts with little fluid; with large amounts of fluid, pressure causes atrophy of lining cells.
   c. **Course and prognosis.** These cysts generally remain small. Some may produce estrogens and cause endometrial hyperplasia.

2. **Luteal cysts**
   a. **Clinical features.** These benign cysts are less common than follicular cysts.
   b. **Pathology**
      (1) **Grossly,** cysts are usually approximately 2 cm and yellow.
      (2) **Microscopically,** the cystic lining is luteal tissue, comprising large cells filled with smooth endoplasmic reticulum (like normal corpus luteum cells).

3. **Polycystic ovaries**
   a. **Clinical features.** Polycystic ovaries may be associated with three clinical syndromes: **virilism, excessive menstrual bleeding,** or the **Stein-Leventhal syndrome,** which is characterized by secondary amenorrhea, obesity, hirsutism, infertility, and bilaterally enlarged, polycystic ovaries. They are most common in young women in the second and third decades.
   b. **Pathology**
      (1) **Grossly,** the ovaries are enlarged, with a thick, white outer covering and multiple cysts.

IN A NUTSHELL

Polycystic ovaries:
- *Occur mainly in young women*
- *Associated with:*
  - *Amenorrhea*
  - *Infertility*
  - *Obesity*
  - *Hirsutism*
  - *↑ LH secretion*

(2) **Microscopically**, cysts are lined with granulosatheca cells.

c. **Pathogenesis** is thought to be an abnormality in the hypothalamic-pituitary axis: the ovary is continuously stimulated by FSH, and LH cysts form. Luteinized theca cells make androgens, accounting for the masculinization symptoms.

d. **Course and prognosis.** Wedge resection (by removing cysts and theca cells) may restore normal menses and fertility.

BREAST

A. Acute mastitis

1. **Clinical features.** Fissures in nipples during early nursing or from skin disorders may predispose to bacterial infection of the breast. Usual pathogens are ***Staphylococcus aureus*** and Streptococcus.
2. **Pathology.** Mastitis is usually unilateral, with pus in the ducts. Necrosis may occur.
3. **Course.** Antibiotics and surgical drainage may be adequate therapy, but necrosis and subsequent fibrosis of a localized area of breast tissue may occur.

B. Mammary duct ectasia (plasma cell mastitis)

1. **Clinical features.** This disorder generally occurs in the fifth decade in multiparous women. It presents with pain, redness, and swelling around the areola.
2. **Pathology.** Involvement is usually unilateral, causing a thickened, indurated area of the breast with thick secretions.
3. **Course.** Skin fixation, nipple retraction, and axillary lymphadenopathy may occur and must be distinguished from malignancy.

C. Fibrocystic disease (cystic hyperplasia)

1. **Clinical features.** This is the **most common breast disorder;** it is responsible for 50% of breast surgery, affecting approximately 10% of women. It usually develops during reproductive life and represents a distortion of the normal breast changes associated with the menstrual cycle. Patients often have lumpy, tender breasts.
2. **Pathogenesis** is thought to be due to high estrogen levels, e.g., estrogen therapy or estrogen-secreting neoplasm, coupled with progesterone deficiency.
3. **Pathology.** Several morphologic patterns are recognized.
   a. **Fibrosis** usually affects women 35–49 years of age and is not premalignant.
   b. **Cystic disease** usually affects women 45–55 years of age and may predispose to malignancy.

Table 8-1. Features distinguishing fibrocystic disease from breast cancer

Fibrocystic Disease	Breast Cancer
Often bilateral	Often unilateral
May have multiple nodules	Usually single
Menstrual variation	No menstrual variation
Cyclic pain and engorgement	No cyclic pain or engorgement
May regress during pregnancy	Does not regress during pregnancy

i. **Sclerosing adenosis** usually affects women 35–45 years of age and probably does not predispose to cancer.

ii. **Epithelial hyperplasia** occurs in women over 30 years of age (usually 35–45) and represents an increased cancer risk.

4. **Course and prognosis.** Fibrocystic disease is clinically important because it may be mistaken for cancer, and it may predispose to cancer, particularly the epithelial hyperplasia variant. Table 8-1 lists the features that differentiate the two diseases.

D. **Gynecomastia**

1. **Clinical features.** Gynecomastia is an **enlargement of the male breasts** that occurs in various clinical situations (e.g., Klinefelter's syndrome; testicular tumors [particularly Sertoli-Leydig cell tumors], puberty, or old age) and is associated with **increased sensitivity to estrogens** (e.g., in hepatic cirrhosis, the liver cannot properly metabolize estrogens).

E. **Tumors**

1. **Fibroadenoma**

a. **Clinical features.** This is the **most common benign breast tumor.** It occurs in women of reproductive age, generally before age 30 and may be related to increased estrogen sensitivity. Fibroadenoma presents as a **single movable breast nodule** not fixed to the skin.

b. **Pathology**

(1) **Grossly,** there is a small, freely movable nodule, often in the upper outer quadrant. Size may range up to 10 cm. The tumors are usually round and encapsulated with a gray-white cut surface.

(2) **Microscopically,** fibroadenomas form glandular epithelial-lined spaces with a fibroblastic stroma. Stromal proliferation may collapse gland lumina, or alternatively, glandular proliferation may predominate with scanty connective tissue stroma. Usually, there is a network of ducts within a proliferated, edematous stroma.

c. **Course.** Fibroadenomas may show menstrual variation and increased growth during pregnancy. Postmenopausal regression is usual. Surgery is required for definitive diagnosis.

2. **Cystosarcoma phyllodes (Phyllodes tumor)**
   a. **Clinical features.** These are fibroadenoma-like tumors that have become large, cystic, and lobulated. They are distinguished from fibroadenomas by the nature of the stromal component. When hypercellular, the term "cellular fibroadenoma" is used. When the stroma is both hypercellular and highly atypical, the tumor is called a sarcoma.

3. **Intraductal papilloma**
   a. **Clinical features.** This forms a solitary lesion within a duct or cyst and is most common in women 35–50 years of age. It may present with **nipple discharge** (serous or bloody), nipple retraction, or as a small subareolar mass.
   b. **Course.** Current evidence suggests that single intraductal papillomas are benign, but multiple papillomas are associated with an increased risk of cancer.

4. **Carcinoma of the breast**
   a. **Incidence.** Breast carcinoma is the second most common cause of cancer death in women, surpassed recently by lung cancer. It is rarely seen in women under age 25.
   b. **Etiology.** Risk factors include increasing age (particularly after 40), nulliparity, family history (especially in premenopausal cancer), early menarche/late menopause, fibrocystic disease (especially epithelial hyperplasia), and a previous history of breast cancer. The lifetime risk of breast cancer for the average woman with no family history is 8–10%.
   c. **Clinical features**
      (1) Locations of breast carcinoma are: 50% in the upper outer quadrant, 20% in central area, and 10% in other quadrants. Ninety percent arise in ductal epithelium, while 10% arise in the lobules. Carcinoma is slightly more common in the left breast (110:100); it is bilateral or sequential in 4% of cases.
      (2) Most patients present with a breast mass discovered either by self-examination or on a routine physical examination by a physician.
      (3) Depending on the size and invasiveness of the tumor, other clinical patterns may occur. The tumor may grow into the thoracic fascia to become fixed to the chest wall; it may extend into the skin, causing **dimpling and retraction**; it may cause obstruction of subcutaneous lymphatics, causing an orange-peel consistency to skin called **"peau d'orange"**; or it may invade Cooper's ligaments within ducts to cause **nipple retraction**.
   d. **Pathogenesis** is multifactorial: genetic (e.g., family history), environmental (e.g., radiation), and viral (e.g., mammary tumor virus in mice) influences may be involved. A possible hormonal role has been intensively studied, yielding the finding that "unopposed

IN A NUTSHELL

Risk factors for breast cancer:

- *Increasing age (40+)*
- *Nulliparity*
- *Family history*
- *Early menarche*
- *Late menopause*
- *Fibrocystic disease*
- *Previous history of breast cancer*
- *Obesity*
- *High-fat diet*

estrogen" over prolonged periods may lead to ductal hyperplasia and malignant transformation.

e. **Metastatic tumors to the breast** are rare. The most common are leukemia, lymphoma, lung cancer, and melanoma.

f. **Diagnosis. Mammography**, a radiologic evaluation of the breast, is part of the clinical investigation of a breast mass. Sixty percent of breast cancers have foci of calcification.

g. **Metastases.** Most breast cancers disseminate via lymphatic or hematogenous routes to axillary, supraclavicular, and internal thoracic nodes or the nodes of the contralateral breast. The direction of spread depends on the anatomic location and lymphatic drainage of the primary tumor.

h. **Staging of breast carcinomas** is based upon the size of the tumor and the degree to which the tumor has spread to the surrounding tissues.

i. **Prognosis** depends on many factors, including the type and stage of the carcinoma. Overall 5-year survival is 50%.

j. **Treatment**

(1) **Surgery. Segmental mastectomy** (can be local excision, quadrant excision, partial removal of breast tissue, or "lumpectomy"), where only the tumor and its surrounding tissue is removed. **Simple mastectomy** is the removal of breast tissue; **modified radical mastectomy** is the removal of the breast tissue, axillary nodes, and pectoralis fascia; and **radical mastectomy** is the removal of breast tissue, axillary nodes, pectoralis fascia, and pectoral muscles. Therapy usually includes some **combination of surgery, radiation, and chemotherapy.**

(2) **Estrogen receptors.** The presence of cytoplasmic estrogen receptors may be a useful predictor of response to "hormonal therapy." Approximately two-thirds of breast cancers are estrogen-receptor-positive; most of these will regress when patients are given anti-estrogen compounds such as **tamoxifen.** In fact, patients who are both estrogen- and progesterone-receptor-positive have the best response to tamoxifen. **Adjuvant chemotherapy** is clearly of benefit in postmenopausal cancer but not in premenopausal cancer.

Note

The American Cancer Society recommends annual mammography for all women over the age of 40.

The kidney is a complex organ often affected by a variety of acquired and congenital disorders. Common disorders include glomerulonephritis and neoplasms such as Wilms' tumor and renal cell carcinoma. Because the kidney plays such a central role in homeostasis, damage to the organ can have far-reaching effects. For example, since the kidney is involved in blood pressure regulation through the renin-angiotensin system and in the regulation of red blood cell (RBC) production through its synthesis of erythropoietin, renal disease can cause both hypertension and anemia.

The kidney is also frequently affected by systemic disease, such as autoimmune disorders, amyloidosis, septicemia, and diabetes. In fact, renal failure is one of the most common causes of death in systemic lupus erythematosus and diabetes.

This chapter will focus on the disease processes associated with the kidney as well as disorders of the rest of the urinary system.

CONGENITAL ANOMALIES OF THE KIDNEY

A. **Agenesis.** Bilateral agenesis is incompatible with life. Unilateral agenesis may have adequate renal function but may develop progressive glomerular sclerosis.

B. **Hypoplasia** is the failure of the kidneys to develop to normal weight; it is usually unilateral. There are a decreased number of calyces and lobules.

C. **Horseshoe kidney** is a fusion of the kidneys, usually at the lower pole. It is found in 1 in 750 autopsies. Patients have normal renal function but may be predisposed to renal calculi.

D. **Abnormal locations.** The most common abnormal location is the pelvic kidney. There is normal function; however, tortuosity of ureters may predispose to pyelonephritis.

CYSTIC DISEASE

A. **Childhood polycystic disease**

1. **Incidence.** This is a rare autosomal recessive disease.
2. **Clinical features.** Patients present in infancy with progressive renal failure; if the infant survives, he may develop hepatic fibrosis and portal hypertension.
3. **Pathology**
   a. **Grossly,** there are bilaterally enlarged kidneys with smooth surfaces. The cut section shows a sponge-like appearance, with multiple small cysts in the cortex and medulla.
   b. **Microscopically,** there is a cylindrical dilatation of tubules.
   c. Most cases also have multiple hepatic cysts.

B. **Adult polycystic disease**

1. **Incidence.** This disease affects 1 in 500 people, showing **autosomal dominant** inheritance. It has a negative family history in 25% of cases, implying a new mutation.
2. **Clinical features.** Patients usually have normal renal function until middle age, at which time they present with renal insufficiency, hematuria, flank pain, and hypertension. Extrarenal manifestations include liver cysts, berry aneurysm in the circle of Willis, mitral valve disease, and colonic diverticula. Most patients develop hypertension, and 50–75% develop end-stage renal failure by their seventh decade.
3. **Pathology**
   a. **Grossly,** there is marked bilateral enlargement with large cysts bulging through the surface.
   b. **Microscopically,** functioning nephrons are present between the cysts. Cysts involve less than 10% of nephrons, but they gradually expand and compress the rest of the kidney, interfering with its function. This is the reason why kidney function can remain normal for many years.

Note

Adult polycystic disease → think liver cysts and berry aneurysms in addition to renal cysts.

HYPERTENSION

Hypertension is defined as an elevated blood pressure greater than 140/90. Primary (essential) hypertension has an unknown etiology and represents 90% of cases. Secondary hypertension makes up the remaining 10% of cases and may be secondary to renal, vascular, endocrine, or neurogenic disorders.

A. **Essential hypertension**

1. **Etiologies**
   a. **Environmental factors.** High dietary sodium in predisposed patients exacerbates the problem. Obesity, stress, and oral contraceptives may contribute to the development of hypertension.

b. **Physiologic theories**
   (1) A defect in sodium excretion would raise blood pressure by a loss of autoregulatory function (i.e., loss of ability to respond to elevated blood pressure by excreting excess sodium and water).
   (2) An increase in peripheral resistance could come from increased sympathetic tone.

2. **Pathology.** There is frequently a hyaline deposition in arteriolar walls, narrowing the lumen. High blood pressure may cause atrophy and scarring of the glomeruli and tubules.

B. **Secondary hypertension**

1. **Etiologies**
   a. **Renal disease.** Chronic renal disease, acute glomerulonephritis, and renin-producing tumors all lead to high blood pressure.
   b. **Vascular disease.** Coarctation of the aorta and renal artery stenosis both reduce renal blood flow, leading to increased renin production and hypertension.

2. **Pathogenesis of renal hypertension**
   a. **Increased renin secretion**
      (1) Renin, which is released from the juxtaglomerular apparatus, converts angiotensinogen to angiotensin I, which is converted to angiotensin II in the lung. Angiotensin II causes arteriolar constriction and stimulates aldosterone secretion by the adrenal cortex. Aldosterone causes sodium retention, which leads to an increased intravascular volume.
      (2) Malignant hypertension, unilateral renal artery stenosis, renin-producing tumors, vasculitis, and chronic renal failure all lead to increased renin production.
   b. **Decreased renal antihypertensive substances.** Prostaglandins and kinins typically lower blood pressure; however, they cannot be synthesized normally in renal failure.
   c. **Renal artery stenosis** is a potentially curable form of hypertension. It stimulates renin secretion because of reduced blood flow past the juxtaglomerular apparatus.
      (1) **Pathology.** It is most commonly caused by atherosclerosis (in patients > 50 years) or fibromuscular dysplasia (in patients < 30 years). The kidney exhibits ischemic atrophy with interstitial atrophy and a chronic inflammatory infiltrate.
      (2) **Diagnosis** is made by **arteriography.** Not all anatomic lesions have functional significance.

C. **Malignant hypertension** is a syndrome of severe hypertension (blood pressure is usually > 200/140, but there is no absolute limit) and acute end-organ damage. It usually occurs in patients with long-standing, poorly controlled hypertension. The five-year mortality rate is 66–79%.

NOTE

Factors that may raise blood pressure:
- ↑ Glucocorticoids, T_3, T_4
- ↑ Norepinephrine, epinephrine, growth hormone
- ↑ Aldosterone

1. **Clinical features**
   a. There may be manifestations of **increased intracranial pressure**, including papilledema (with retinal hemorrhages and exudates), headache, vomiting, and scotomas. Symptoms may progress to loss of consciousness and seizures and may also cause subarachnoid or intracerebral bleeds.
   b. **Cardiac failure.** Left ventricular dysfunction may occur early.
   c. **Malignant nephrosclerosis** may lead to proteinuria, hematuria, and sometimes acute renal failure. Patients with renal failure have a higher mortality rate.

GLOMERULAR DISEASES

A. Overview

1. **Glomerular response** to damage can take several forms.
   a. **Cellular proliferation** may include mesangial, epithelial, and endothelial cells.
   b. **Thickening of the basement membrane** of the glomerular capillaries most often results from subepithelial deposition of fibrin and immune complexes, followed by secretion of more basement membrane material by endothelial and epithelial cells.
   c. **Leukocytic infiltration.** Neutrophils and monocytes may be attracted by antigen–antibody (Ag–Ab) complexes.
   d. **Sclerosis and hyalinization** are due to an accumulation of eosinophilic material, composed of plasma proteins and mesangial matrix. This may lead to irreversible injury.

2. **Pathogenesis**
   a. **Antiglomerular basement membrane antibodies.** Nephritis results from antibodies against fixed antigens in the glomerular basement membrane, and is the basic mechanism of **Goodpasture's syndrome**, which also includes antibodies against the basement membrane in pulmonary alveoli.
   b. **Antibodies against other antigens.** Glomerulonephritis may result from antibodies against other fixed antigens or antibodies in glomeruli.
   c. **Circulating immune complexes.** Ag–Ab complexes become trapped within glomeruli, causing glomerular injury. Antigens may be exogenous (e.g., serum sickness) or endogenous (e.g., systemic lupus erythematosus with DNA–anti-DNA complexes).
   d. **Mediators of injury.** After Ag–Ab interaction, injury may result from a variety of mechanisms, including activation of the complement system, macrophages, and the coagulation system, and attraction of neutrophils and monocytes.

Note

Goodpasture's: *antiglomerular basement membrane and antialveolar basement membrane*
Goodpasture's is also discussed in the Respiratory Pathology chapter.

B. **Clinical syndromes in glomerular disease**

1. **Nephritic syndrome.** Patients with acute nephritis present with **proteinuria, hematuria, red blood cell (RBC) casts**, and varying degrees of renal insufficiency and hypertension.
2. **Nephrotic syndrome** is a clinical tetrad of generalized **edema, severe proteinuria, hypoalbuminemia**, and **hyperlipidemia**. It results from a loss of the charge barrier of the glomerular basement membrane (GBM) with an increased permeability to albumin. This leads to massive proteinuria and edema. The most common cause of nephrotic syndrome in children is **lipoid nephrosis (minimal change disease)**; in adults, the most common cause is **membranous glomerulonephritis**.
3. **Rapidly progressive glomerulonephritis (RPGN).** Also called "crescentic GN," RPGN is a syndrome of rapidly deteriorating renal function that accompanies glomerular injury. Clinically, patients present with a nephritic urine sediment and renal failure.

C. **Glomerulonephritis**

1. **Acute poststreptococcal glomerulonephritis**
   a. **Clinical features.** This disease affects children more frequently than adults and usually occurs 1–2 weeks after streptococcal infection of the throat or skin. Laboratory studies show **elevated antistreptolysin O (ASLO)** titers and **low serum complement**.
   b. **Pathogenesis.** The mechanism is immune-related; the disease is probably due to immune complex deposition.
2. **Lipoid nephrosis (minimal change disease)**
   a. **Clinical features.** This is the most common cause of nephrotic syndrome in children. Its peak incidence is 2–3 years of age, and it may be associated with food allergy, certain medications, or hematologic malignancies.
   b. **Prognosis.** Renal function does not usually deteriorate. This syndrome is usually steroid-responsive, especially in children. Complete recovery is expected.
3. **Membranous glomerulonephritis**
   a. **Clinical features.** This is the most common cause of nephrotic syndrome in adults, but it is rare in children. There is usually an insidious onset of proteinuria. Hematuria and mild hypertension may occur. There may be a genetic predisposition. Most cases are idiopathic but some are associated with infection, drugs, tumors, and systemic disease.
4. **Membranoproliferative glomerulonephritis (MPGN)**
   a. **Clinical features.** Two-thirds of patients have the nephrotic syndrome; the rest have non-nephrotic range proteinuria or a mixed nephritic/nephrotic picture. MPGN accounts for 5–10% of cases of idiopathic nephrotic syndrome in adults and children. MPGN may

be secondary to many systemic disorders, including complement deficiency, chronic infections, and chronic lymphocytic leukemia.

b. **Prognosis** is poor, and treatment is controversial. The disease is slowly progressive. Half of all patients die of chronic renal disease within 10 years of the diagnosis.

f. **Focal segmental glomerulosclerosis**

a. **Clinical features.** It accounts for 10–15% of cases of nephrotic syndrome in children and adults. As compared with lipoid nephrosis, these patients more often have hematuria, hypertension, impaired GFR, and nonselective proteinuria.

b. **Pathogenesis.** The mechanism is probably immunologic (possibly an aggressive variant of lipoid nephrosis) or a secondary reaction of residual nephrosis to nephron loss. Intravenous drug abuse is implicated in some patients.

c. **Prognosis** is poor; some patients, especially children, respond to steroids. More than 50% of patients develop end-stage renal disease within 10 years of diagnosis. There is a high rate of recurrence in transplants.

g. **Anti-GBM antibody disease**

a. **Clinical features.** This disease causes **rapidly progressive glomerulonephritis (RPGN).** When accompanied by pulmonary involvement, it is known as **Goodpasture's syndrome.**

b. **Pathogenesis.** The mechanism involves antibodies directed against a collagen component of basement membranes.

h. **Chronic glomerulonephritis**

a. **Clinical features.** This is the final stage of many forms of glomerular disease, so the rate of development is variable. Patients may present with anemia, anorexia, malaise, nausea, vomiting, proteinuria, hypertension, and azotemia.

b. **Pathogenesis.** The mechanism depends on the underlying etiology. It may follow RPGN, membranous glomerulonephritis, MPGN, IgA nephropathy, focal segmental glomerulosclerosis, and others. It is rare after poststreptococcal glomerulonephritis. Twenty-five percent of patients with chronic glomerulonephritis have no documented history of acute glomerulonephritis.

c. **Prognosis** is poor. Patients usually progress to end-stage renal disease.

d. **Pathology**

(1) **Grossly,** shrunken kidneys are seen.

D. **Hereditary nephritis (Alport's syndrome)** is a hereditary abnormality of collagen, resulting in renal disease, deafness, and ocular abnormalities (e.g., dislocated lens, corneal dystrophy, cataracts).

1. **Incidence.** It is primarily an X-linked disorder; women are carriers with mild forms and men develop the full-blown syndrome.

Note

- *"Focal" refers to involvement of only some glomeruli.*
- *"Diffuse" means all glomeruli are involved.*
- *"Segmental" means only parts of the glomerulus are involved.*
- *"Global" means the entire glomerulus is involved.*

Note

Plasmapheresis involves filtering of plasma to remove Ag-Ab complexes.

2. **Clinical features.** Patients have hematuria and proteinuria, which slowly progress to renal failure.

E. **Glomerular injury in systemic disease**

1. Systemic lupus erythematosus
2. Amyloidosis
3. Diabetes mellitus
4. Goodpasture's syndrome
5. Wegener's granulomatosis
6. **Bacterial endocarditis** may lead to **immune complex nephritis.** It produces focal, segmental necrotizing glomerulonephritis, MPGN, or rapidly progressive glomerulonephritis with crescent formation. It is associated with low serum complement levels and usually reverses with treatment of the infection.
7. **Multiple myeloma** is a hematologic malignancy characterized by **overproduction of monoclonal immunoglobulins** and often excess monoclonal light chains. The kidney in multiple myeloma can show a variety of pathologic lesions, including **tubular plugging by casts of myeloma protein (myeloma kidney),** amyloid, hypercalcemic nephropathy, and light-chain deposition disease.

ACUTE TUBULAR NECROSIS (ATN)

ATN is acute renal failure associated with reversible injury to the tubular epithelium. It is the most common cause of acute renal failure.

A. **Types**

1. **Ischemic ATN** is due to decreased blood flow caused by severe renal vasoconstriction, hypotension, or shock. It is the most common cause of ATN.
2. **Nephrotoxic ATN** is caused by heavy metals (e.g., mercury, lead, gold), drugs (e.g., polymyxin, methicillin, sulfonamides), organic solvents (e.g., carbon tetrachloride, chloroform, methyl alcohol), ethylene glycol, phenol, pesticides, or myoglobin.

B. **Pathogenesis.** Ischemia or toxins cause tubular damage and may lead to:

1. **Vasoconstriction** of preglomerular arterioles, leading to a decreased GFR
2. **Tubular obstruction** by casts formed from tubular debris. (Urinary obstruction causes increased intraluminal pressure and decreased GFR.)
3. **Back leakage of fluid** from the tubules into the interstitium, causing increased interstitial pressure and tubular collapse
4. **Decreased glomerular** capillary permeability

C. **Clinical features.** ATN has four phases:

1. In the **initial phase**, the precipitating event (e.g., shock, toxins) occurs.
2. During the **oliguric phase**, there is decreased urine output. Uremia, fluid overload, and hyperkalemia may occur.
3. During the **diuretic phase**, there is a gradual increase in urine volume. Hypokalemia, electrolyte imbalances, and infection may occur.
4. In the **recovery phase**, there is an improved concentrating ability, normalization of blood urea nitrogen (BUN) and creatinine, and restoration of tubular function as new epithelial cells grow in.

D. **Prognosis** is excellent if the patient survives the disease responsible for the ATN.

TUBULOINTERSTITIAL DISEASE

Note

Tubulointerstitial disease usually affects females more than males because the female urethra is shorter.

A. **Pyelonephritis** is an infection of the renal pelvis, tubules, and interstitium, i.e., everything but the glomerulus.

1. **Etiology.** Etiologic agents are usually Gram-negative bacilli (e.g., *Escherichia coli*, Proteus, Klebsiella, Enterobacter) or *S. faecalis*. In general, etiologic agents are organisms derived from the patient's fecal flora.
2. **Pathogenesis**
   a. **Ascending infection** is the most common route. The sequence of events is as follows:
      (1) First, there is colonization of the distal urethra and vaginal introitus by bacteria.
      (2) Bacteria enter the bladder, facilitated by urethral instrumentation, short urethras, or urethral trauma during intercourse.
      (3) There is an inability to clear urine from the bladder. Urinary stasis is caused by bladder obstruction or inability to fully empty the bladder as seen during pregnancy, bladder diverticula, or benign prostatic hypertrophy.
      (4) Proliferation of bacteria in the urine leads to **cystitis**, infection of the urinary bladder, causing frequency, urgency, dysuria, and suprapubic pain. Systemic signs (e.g., fever) are uncommon.
      (5) **Vesicoureteral reflux (VUR)** allows bacteria to ascend to the kidneys; during micturition, urine is forced up one or both ureters.
      (6) Intrarenal reflux permits spread of bacteria to the renal parenchyma.
   b. **Hematogenous infection** is much less common as a source of pyelonephritis.

3. **Acute pyelonephritis**
   a. **Pathogenesis.** Predisposing factors are urinary obstruction, vesicoureteral reflux, pregnancy, urethral instrumentation, diabetes mellitus, and other renal pathology.
   b. **Incidence.** Women predominate among patients under age 40. In later years, there is an increasing incidence in men due to benign prostatic hypertrophy.
   c. **Clinical features** include fever, malaise, dysuria, frequency, urgency, and **costovertebral angle tenderness.** Urine shows many WBCs and WBC casts. Urine culture typically shows greater than one million organisms per milliliter.

4. **Chronic pyelonephritis** is characterized by interstitial parenchymal scarring, which involves and deforms the calyces and pelvis.
   a. **Pathogenesis**
      (1) **Reflux nephropathy** is the most common type. It results from VUR and subsequent infection.
      (2) **Chronic obstructive nephropathy** results from infection superimposed on urinary obstruction.
   b. **Clinical features.** There may be an insidious or acute onset. Patients present with renal failure and hypertension. Pyelograms are diagnostic. Proteinuria is a poor prognostic sign.

5. **Toxic nephritis**
   a. **Acute allergic interstitial nephritis** is a hypersensitivity reaction to infection or drugs (e.g., NSAIDs, synthetic penicillins, sulfonamides, furosemide, rifampin), resulting in interstitial edema with a mononuclear infiltrate.
   b. **Analgesic nephritis** is interstitial nephritis and renal papillary necrosis, induced by large doses of analgesic combinations (usually phenacetin and aspirin).

6. **Other forms of tubulointerstitial nephritis**
   a. **Gouty nephropathy** is the deposition of urate crystals in tubules.
   b. **Acute urate nephropathy** is due to precipitation of crystals in the collecting ducts, causing obstruction.
   c. **Hypercalcemia** results in calcium deposition in the kidney and stone formation.
   d. **Multiple myeloma.** Some **Bence-Jones proteins** are directly toxic to tubular epithelium and also lead to cast formation and urinary obstruction.

VASCULAR AND ISCHEMIC DISEASE

A. **Renal infarcts**

1. **Pathogenesis.** Ischemia may be caused by embolization of mural thrombi or valvular vegetations of the left heart, aortic dissection, or paradoxical embolization from aortic aneurysm.

NOTE

Anytime there is fluid stasis, bacteria can multiply.

2. **Pathology.** There are sharply demarcated pale regions, usually wedge-shaped, that undergo necrosis with subsequent scarring.
3. **Clinical features.** Infarcts may be asymptomatic or they may cause pain, hematuria, and hypertension.

B. **Diffuse cortical necrosis**

1. **Pathogenesis.** Disseminated intravascular coagulation (DIC) or vasoconstriction can lead to ischemia of the entire cortex.
2. **Pathology.** Ischemic necrosis of the renal cortex may develop.
3. **Clinical features** are acute anuria and uremia.

C. **Renal vein thrombosis**

1. **Pathogenesis.** Thrombosis of one or both renal veins may occur. This condition is associated with the nephrotic syndrome, particularly membranous glomerulonephritis, although a causal relationship is not established. Renal cell carcinoma may also provoke vein thrombosis as a result of direct invasion by tumor.
2. **Clinical features.** Thrombosis may present with hematuria, flank pain, and renal failure.
3. **Pathology**
   a. **Grossly,** the kidney is enlarged, and the vein contains a thrombus.

D. **Sickle cell anemia.** Blood in the vasa recta tends to sickle in response to the hypertonic, hypoxic milieu of the renal medulla. This produces patchy papillary necrosis and occasional cortical scarring.

UROLITHIASIS

A. **Incidence.** Urolithiasis occurs in up to 6% of the population; men are affected more often than women.

B. **Pathogenesis.** There is a familial predisposition, which depends on the type of stone.

1. **Calcium-containing stones** (75–80%). Most patients have hypercalciuria without hypercalcemia; 20% have hyperuricosuria.
2. **Magnesium-ammonium phosphate ("struvite") stones** (15%) occur after infection by **urea-splitting bacteria** (such as Proteus), which transform urea into ammonia.
3. **Uric acid stones** (5%) are seen in gout, leukemia, and in patients with acidic urine.
4. **Cystine stones** (1%) are associated with an inborn error of metabolism (e.g., cystinuria, an autosomal recessive amino acid transport disorder). They are very rare.

Bridge to Microbiology

When you see Proteus, think: urea-splitting, stone-forming, and alkaline urine.

C. **Pathology.** Most stones are unilateral and are formed in the calyx, pelvis, and bladder.

D. **Clinical features.** Calcium stones are radiopaque; they are the only ones that can be seen on x-ray.

OBSTRUCTIVE UROPATHY AND HYDRONEPHROSIS

A. **Etiologies** include urolithiasis, benign prostatic hypertrophy, pregnancy, neurogenic bladder, tumor, inflammation, and congenital anomalies (e.g., posterior urethral valves, strictures).

B. **Pathogenesis.** **Hydronephrosis** is the persistence of glomerular filtration despite urinary obstruction, causing dilation of calyces and pelvis and reabsorption of the filtrate into the vascular system. A high pressure in the collecting system causes atrophy and ischemia.

C. **Pathology.** There is dilatation of the pelvis and calyces with blunting of renal pyramids, leading to progressive parenchymal atrophy.

D. **Clinical features**

1. **Unilateral hydronephrosis** may remain asymptomatic as the kidney atrophies.
2. **Bilateral, incomplete hydronephrosis** causes the patient to lose concentrating ability, causing urinary frequency, polyuria, nocturia, and hypertension.
3. **Bilateral, complete hydronephrosis** causes anuria, uremia, and death if untreated.

TUMORS OF THE KIDNEY

A. **Benign tumors**

1. **Cortical adenomas** are a common finding at autopsy. Histologically, they may be identical to renal cell carcinoma and are distinguished by size (adenomas are less than 3 cm).
2. **Angiomyolipomas** are hamartomas, composed of fat, smooth muscle, and blood vessels.
3. **Renal fibroma (hamartoma)** is an incidental finding at autopsy. They are small gray nodules within the pyramids.

B. **Malignant tumors**

1. **Renal cell carcinomas** are adenocarcinomas, arising from the proximal convoluted tubule.
   a. **Incidence.** They form 90% of all renal cancers in adults. Men and women have about equal incidence. They are most common from ages 50–70.

b. **Pathogenesis.** There is a moderate association with smoking and a familial predisposition.

c. **Pathology.** Histology may be identical to adenoma, but tumors are prone to metastases if larger than 3 cm.

(1) **Grossly,** tumors are 3–15 cm yellow lesions found most commonly in the upper pole; they are usually solitary. Commonly, there are areas of necrosis and hemorrhage. The tumor often invades the renal vein and extends into the vena cava and heart.

d. **Clinical features**

(1) There is a "classic" triad of hematuria, palpable mass, and costovertebral pain that occurs in only 10% of cases; hematuria is most important.

(2) Renal cell carcinomas may remain asymptomatic until they are very advanced. They also may cause paraneoplastic syndromes from ectopic hormone production: polycythemia (erythropoietin production), hypertension (renin production), Cushing's syndrome (corticosteroid synthesis), hypercalcemia (PTH-like hormone), and feminization or masculinization (gonadotropin release).

(3) They also may cause amyloidosis, a leukemoid reaction, or eosinophilia.

e. **Metastases.** There is a high incidence of metastasis on initial presentation. Sites include lungs, bones, lymph nodes, liver, adrenals, brain, and the opposite kidney. Metastases are mainly hematogenous and lymphatic.

f. **Prognosis.** Five-year survival depends on stage, but it is especially poor (25–50%) if the tumor extends into the renal vein.

2. **Wilms' tumor (nephroblastoma)** is a tumor derived from mesonephric mesoderm and composed of epithelium, bone, cartilage, and muscle.

a. **Incidence.** This is a rather common childhood malignancy with peak incidence at age 2.

b. **Clinical features.** Patients present with an abdominal mass as well as hypertension, nausea, hematuria, or intestinal obstruction.

c. **Pathology**

(1) **Grossly,** most tumors are unilateral but may be bilateral if familial.

(2) Tumor cells contain microdeletions in chromosomes. The gene has been localized to chromosome 11p.

d. **Metastases.** Areas include lymph nodes, lungs, liver, and adrenals.

e. **Prognosis.** There is a 90% survival rate when patients are treated with surgery, chemotherapy, and radiotherapy.

3. **Carcinomas of renal pelvis**

a. **Incidence.** These make up 5–10% of primary renal tumors.

b. **Clinical features.** They usually present early with hematuria, and they may cause hydronephrosis and flank pain.

URETERS

A. **Congenital anomalies**

1. **Double ureters** form when ureters join at some point before the junction to the bladder (Y-shaped) or enter the bladder separately. This anomaly is associated with double renal pelves or an abnormally large kidney.
2. **Aberrant renal vessel.** Usually, an aberrant artery arises from a renal artery of the aorta and supplies the lower pole. It may cause ureteropelvic obstruction.

B. **Ureteritis** is an inflammation of the ureter, usually as a result of urinary tract infections.

C. **Ureteral obstruction** results in hydroureter and hydronephrosis.

1. **Internal obstruction**
   a. **Renal calculi** are the most common cause.
   b. **Strictures** may be congenital or acquired (e.g., postsurgical, inflammatory).
   c. **Hematomas** may result from bleeding in the kidney or proximal ureter.
   d. **Tumors** form intraluminal masses and thickening of the ureteral wall.
2. **External obstruction**
   a. **Inflammation** leads to scar formation.
   b. **Pelvic tumors** may compress or invade the ureteral wall.
   c. **Sclerosing retroperitonitis** is a fibrosis of retroperitoneal structures, possibly caused by an autoimmune mechanism.
   d. Pregnancy does not cause obstruction but does cause dilation of the ureters by an unknown mechanism.

D. **Tumors.** Primary tumors are rare. Benign tumors rarely cause obstruction; malignant tumors are usually associated with bladder carcinomas.

BLADDER

A. **Congenital anomalies**

1. **Diverticula** are pouch-like evaginations of the bladder wall. They occur in older men and women. They may lead to urinary stasis and infection.
   a. **Congenital** diverticula are due to abnormal development of musculature and are usually single.
   b. **Acquired diverticula** result from obstruction of the urethra or bladder neck.

2. **Exstrophy of bladder** is due to the absence of the anterior musculature of the bladder and abdominal wall as a result of the failure of down-growth of mesoderm over the anterior bladder. It is usually the site of severe chronic infections, and it leads to an increased incidence of adenocarcinoma.
3. **Patent urachus** is a fistula that connects the bladder with the umbilicus.
4. **Urachal cysts** are due to the persistence of the central urachus. Carcinomas may develop in these cysts.

B. **Cystitis**

1. **Etiology.** Organisms responsible are usually the patient's fecal flora (e.g., Escherichia coli, Proteus, Klebsiella, Enterobacter, Streptococcus faecalis, or Staphylococcus).
2. **Clinical features.** Cystitis causes frequency, urgency, dysuria, and suprapubic pain. Systemic signs (e.g., fever, malaise, chills) are uncommon with lower urinary tract infections.

C. **Bladder obstruction**

1. **Etiology**
   a. In **men**, prostatic enlargement as a result of benign hyperplasia or carcinoma is the most common cause.
   b. In **women**, cystocele of the bladder is the most common cause.
2. **Pathology.** Thickening and hypertrophy of the smooth muscle of the bladder wall leads to trabeculation. This may cause the development of diverticula.

D. **Miscellaneous lesions**

1. **Fistulas.** The most common fistula is a vesicovaginal fistula, which often results from irradiation or malignancy.
2. **Calculi** are usually asymptomatic, though they may cause inflammation of the bladder wall. They may form in the bladder or more proximally in the genitourinary tract.

E. **Tumors.** Ninety percent of primary bladder neoplasms are derived from transitional bladder epithelium called **urothelium**.

1. **Papillomas** are uncommon and may present with hematuria.
2. **Carcinomas**
   a. **Etiology.** Risk factors include:
      (1) Exposure to industrial chemical compounds (the risk may be increased 50 times with prolonged exposure)
      (2) Infection with **Schistosoma haematobium**
      (3) Cigarette smoking
   b. **Types. Transitional cell carcinoma** of the urothelium forms 90% of cases. Other forms, including squamous cell carcinomas and adenocarcinomas, are rare.

c. **Incidence.** Urothelial cell cancer causes 3% of all cancer deaths in the United States in both men and women. The peak incidence is between 40 and 60 years of age.

d. **Clinical features.** Bladder cancer usually presents with painless hematuria. It may also cause dysuria, urgency, frequency, hydronephrosis, and pyelonephritis.

e. **Prognosis.** Bladder cancer has a high incidence of recurrence. The prognosis depends on grade and stage; overall 5-year survival is 30%.

3. **Sarcomas** are large polypoid masses that protrude into the vesical lumen. They are usually leiomyosarcomas.

URETHRA

A. **Urethritis** presents with itching, pain, and urinary frequency. It may be gonococcal or nongonococcal. Organisms responsible for nongonococcal urethritis include Chlamydia, Mycoplasma, and enteric bacteria. **Reiter's syndrome** is the triad of urethritis, arthritis, and conjunctivitis.

B. **Tumors**

1. **Caruncles** are red, small, painful benign masses in the external urethral meatus of affected women.

2. **Carcinomas** are rare. They occur more frequently in the elderly, arising at the external meatus. They are wart-like, papillary growths, composed of malignant squamous cells, which may protrude into the lumen. They are often caused by papillomaviruses and are increasing in incidence among younger age groups as sexually transmitted diseases in immunocompromised hosts (i.e., patients with AIDS).

Disorders of the hemelymph system can result from underproduction or overproduction of the formed elements of the blood, hematologic malignancies, or autoimmune disorders. This chapter will discuss the different types of disorders, their clinical presentations, and their distinguishing features. Disorders involving the spleen and thymus will also be reviewed.

POLYCYTHEMIA

Polycythemia is an increase in concentration of circulating erythrocytes. This increase may be primary or secondary, absolute or relative.

A. **Relative polycythemia** occurs due to loss or sequestration of intravascular volume without loss of RBCs. Volume loss may be due to decreased fluid intake, vomiting, diarrhea, burns, or adrenal insufficiency.

B. **Polycythemia vera**

1. **Clinical features.** Polycythemia vera is a **myeloproliferative syndrome** characterized by a marked increase in erythrocyte mass. It is most common in males age 40–60. The etiology is unknown but is probably due to a neoplastic hematopoietic stem cell. There are symptoms of increased blood volume, vascular stasis/thrombosis, or bleeding tendency. Patients may later develop anemia or acute leukemia due to "bone marrow burn-out." Folate deficiency may develop due to the hyperproliferative state.
2. **Pathology.** The peripheral smear shows a markedly increased number of RBCs, WBCs, and platelets. Erythropoietin levels are low. The bone marrow shows **erythroid hyperplasia** with excess normoblasts.

C. **Secondary polycythemia**

1. **Clinical features.** An increased RBC mass as a result of **increased erythropoietin levels** is seen. There are multiple etiologies, including high altitude with low O_2, cigarette smoking with high carbon monoxide levels,

respiratory disease, cardiac disease (e.g., right-to-left shunts, cardiac failure), hemoglobinopathies, renal disease (e.g., cysts, hydronephrosis), and malignancies (e.g., renal cell carcinoma, hepatoma, leiomyoma, adrenal adenoma, cerebellar hemangioblastoma).

2. **Pathology.** An isolated erythrocythemia without an increase in WBCs or platelets is noted.

THROMBOCYTOPENIA

Thrombocytopenia is a decrease in the platelet count (normal platelet count = 150,000–400,000/mm³).

A. **Clinical features.** There may be bleeding from small vessels, often skin, gastrointestinal tract, and genitourinary tract. The most common sign is the development of **petechiae** (minute pin-sized hemorrhages in the skin) and **purpura** (large red, nonblanching lesions). Petechiae develop before purpura, which are more often seen with combined deficiencies of platelets and plasma clotting factors.

B. **Classification**

1. Decreased production due to drugs, radiation, myelophthisis, aplastic anemia, or platelet maturation defect (due to vitamin B_{12} or folate deficiency)
2. Abnormal sequestration of platelets in the spleen in congestive splenomegaly
3. Dilutional (e.g., massive blood transfusion)
4. Increased destruction, e.g., DIC, TTP, ITP, drugs, or malignancy

C. **Idiopathic thrombocytopenic purpura (ITP)**

1. **Clinical features.** ITP is characterized by an increased **peripheral platelet destruction** in the spleen, often **immune-mediated.** The course may be acute and self-limited (most common form in children), often following a viral infection, or it may be chronic (most common form in adults). ITP may be primary or secondary to another disorder such as SLE, HIV infection, or hemolytic anemia. The disease may present with a long history of easy bruisability, mucous membrane bleeding, gastrointestinal or genitourinary bleeding, and petechiae. CNS bleeding may occur.

D. **Thrombotic thrombocytopenic purpura (TTP)**

1. **Clinical features.** This is a rare disease characterized by thrombocytopenic purpura, fever, renal failure, neurologic changes, and microangiopathic, hemolytic anemia. It appears most frequently in young women. The etiology is unknown.

PLATELET FUNCTION DEFECTS

A. **Clinical features.** These disorders are characterized by prolongation of the **bleeding time** in the presence of a normal platelet count.

B. **Classification.** Qualitative platelet defects may be congenital or acquired. They may be classified as follows:

1. **Defects of adhesion** (e.g., von Willebrand's disease, Bernard-Soulier disease)
2. **Defects of primary aggregation** (e.g., thrombasthenia)
3. **Defects of secondary aggregation and release** (e.g., aspirin, storage pool disease)

C. **von Willebrand's disease**

1. **Clinical features.** There is an autosomal dominant defect in von Willebrand's factor. This factor is necessary for adhesion of platelets to collagen. This results in **impaired platelet adhesion**, although the platelets themselves are intrinsically normal. It is characterized by spontaneous hemorrhage from mucous membranes, wounds, and excessive menstrual bleeding.
2. **Pathology.** Patients with von Willebrand's disease have a range of clinical syndromes but are usually diagnosed when they bleed after surgery or dental extraction. Von Willebrand's factor (vWF) is also the carrier molecule for factor VIII, so patients with vWF deficiency have low factor VIII levels and activity. As a result, they have a prolonged partial thromboplastin time (PTT) in addition to an elevated bleeding time.

DISORDERS OF EXCESS PLATELETS

These disorders are defined by the elevation of the platelet count above the normal range.

A. **Classification**

1. **Thrombocytosis** is a reactive disorder resulting from bleeding, hemolysis, inflammation, malignancy, iron deficiency, stress, or postsplenectomy.
2. **Essential thrombocythemia** is a primary **myeloproliferative disorder.** Thrombocythemia is also a prominent feature of chronic myelogenous leukemia (CML).

CLOTTING FACTORS DISORDERS

Clotting factors disorders are characterized by deficits of secondary hemostasis due to alteration of the plasma protein factors of the clotting system.

NOTE

Excess platelets do not necessarily cause thrombosis because in myeloproliferative disorders they may not function normally.

A. **Clinical features.** Bleeding in disorders of secondary hemostasis tends to be from small arteries or into deep structures such as joint spaces or the retroperitoneum. Trauma may precede the bleeding but hemorrhage is often delayed.

B. **Laboratory values.** The most common blood tests to assay for the presence of an intact clotting system are the **prothrombin time (PT)**, **partial thromboplastin time (PTT)**, and **thrombin time (TT)**.

1. PT measures factors (fibrinogen) I, II, V, VII, and X.
2. PTT measures XII, prekallikrein, high-molecular weight, kininogen, and factors I, II, V, VIII, IX, X, and XI.
3. TT measures factor I (fibrinogen).

C. **Hereditary deficiencies**

1. **Factor VIII:C deficiency (hemophilia A)** is an X-linked recessive disorder with an incidence of 1/10,000. It results from defective factor VIII:C or impaired conversion of precursor to factor VIII:C. Severe cases bleed in infancy at circumcision or may have multiple hemarthroses. Moderate cases have occasional hemarthroses. Mild cases may be missed until the patients bleed following a dental or surgical procedure. Bleeding may require treatment with cryoprecipitate or lyophilized factor VIII.
2. **Factor IX deficiency (Christmas disease, hemophilia B)** occurs approximately one-sixth as often as factor VIII deficiency. It is due to inactive or inadequate Factor IX and is also an X-linked recessive. The signs and symptoms are the same as hemophilia A. Since both hemophilia A and B have a prolonged PTT, these diseases must be distinguished by specific factor assays.

D. **Acquired disorders**

1. **Vitamin K deficiency.** Vitamin K is a fat-soluble vitamin produced by bacterial metabolism of ingested nutrients within the large intestine. It is essential in the **post-translational modification of factors II, VII, IX, and X,** as well as **proteins C and S.** Vitamin K deficiency may result from fat malabsorption, diarrhea, dietary deficiency (i.e., usually patients on parenteral feedings who are not receiving vitamin K supplements), antibiotics (which may kill gut flora), and some anticoagulant drugs (e.g., warfarin).
2. **Liver disease.** Factors II, V, VII, IX, X, XI, and XII are synthesized in the liver; liver disease can result in failure to synthesize these clotting factors, with a resultant bleeding diathesis.
3. **Disseminated intravascular coagulation (DIC)**
   a. **Clinical features.** This is an *acquired* **consumption deficiency of clotting factors and platelets,** often resulting in fatal thrombosis and hemorrhage. Coagulation system activation leads to microthrombus

Clinical Correlate

Proteins C and S are involved in normal clot lysis. People with deficiencies of these proteins may develop frequent deep venous thrombosis. In addition, factor V resistant to protein C has recently been recognized as an inherited cause of deep venous thrombosis.

formation with consumption of platelets, fibrin, and clotting factors in the vasculature; this leads to activation of the fibrinolytic system. Hence, morbidity from DIC may be related to either thrombosis (tissue hypoxia and infarction) or hemorrhage (coagulation factor consumption and fibrinolysis).

b. **Pathology**. There is diffuse thrombus formation, especially in the brain, heart, lung, kidneys, adrenals, spleen, and liver. There may be diffuse bleeding as well.

c. **Diagnosis**. DIC is diagnosed in the laboratory by demonstrating **low platelets, low fibrinogen**, and the presence of **fibrin degradation products**.

NON-NEOPLASTIC WHITE BLOOD CELL DISORDERS

A. **Leukopenia** is a decrease in the circulating WBC count. It may selectively involve one WBC line, such as lymphocytes (lymphopenia), or more commonly, neutrophils (neutropenia or granulocytopenia).

1. **Classification of neutropenias**

a. **Decreased neutrophil production** is seen in megaloblastic anemias, aplastic anemia, some leukemias and lymphomas, drug suppression of myeloid stem-cell differentiation, or autoimmune attack on stem cells.

b. **Increased destruction of neutrophils** is usually due to splenic sequestration, which is often immune-mediated (e.g., Felty's syndrome).

c. **Drug-induced neutropenia** may be seen in patients treated with alkylating agents, chloramphenicol, sulfonamides, chlorpromazine, and phenylbutazone. Mechanisms may include both decreased production and increased destruction. The problem is usually reversible if the drug is stopped.

2. **Clinical features** usually result from lack of immune defense provided by neutrophils.

a. **Constitutional symptoms** include fever, chills, malaise, fatigability, and a high susceptibility to infection, particularly Gram-negative septicemia.

b. **Prognosis** is often poor with death resulting from overwhelming infection; early diagnosis and antibiotic therapy for infections is required to avoid a fatal outcome.

3. **Pathology**

a. **Bone marrow findings** depend on the etiology of the neutropenia. The neutropenia may be hypercellular due to increased destruction or megaloblastic anemia, or hypocellular, due to decreased production. RBC and platelet lines may be affected. There may be increased numbers of lymphocytes and plasma cells that result from relative preservation.

CLINICAL CORRELATE

A low factor VIII level may be used to distinguish DIC from the coagulopathy of liver failure, which has similar features except for a normal to elevated factor VIII level.

Note that factor VIII is synthesized in the endothelium of vessels; the other clotting factors are synthesized in the liver.

b. **Infection.** Infected, necrotic ulcers may occur in the oral cavity, skin, vagina, anus, gastrointestinal tract, or, less commonly, in the lungs and urinary tract. Lymphadenopathy draining infected sites may be seen. Uninhibited by neutrophils, bacteria may form colonies.

B. **Leukocytosis** is an increase in WBC count.

1. **Classification.** Leukocytosis may occur in a variety of WBC lines.
   a. **Monocytosis** may be seen in tuberculosis, endocarditis, malaria, brucellosis, rickettsiosis, and monocytic leukemia.
   b. **Lymphocytosis** may be seen in tuberculosis, brucellosis, viral hepatitis, cytomegalovirus infections, infectious mononucleosis, chronic lymphocytic leukemia (CLL), and some lymphomas.
   c. **Eosinophilic leukocytosis** may be seen in neoplasms, allergy, asthma, collagen vascular diseases, and parasitic infections. Any skin rash may produce eosinophilia.
   d. **Polymorphonuclear leukocytosis (most common)** may be seen in acute infection, tissue necrosis, and "stress," and may be accompanied by immature forms in the peripheral blood (leukemoid reaction or "left shift"). Chronic myelogenous leukemia (CML) produces extreme leukocytosis with immature forms and eosinophils, as well as basophils.

C. **Nonspecific lymphadenitis**

1. **Clinical features.** Nonspecific lymphadenitis may be caused by drugs, toxins, or infection. It is common in the neck following dental or tonsillar infection and in the axillae or the inguinal regions following infections of the extremities. Enlarged abdominal lymph nodes (mesenteric adenitis) may cause abdominal pain resembling acute appendicitis. Lymphadenopathy may be generalized in systemic viral or bacterial infections. A syndrome of generalized lymphadenopathy may be a precursor to AIDS. It is associated with hyperglobulinemia and normal CD4 lymphocyte counts.

LYMPHOMAS

A. **Hodgkin's disease (Hodgkin's lymphoma)**

1. **Overview.** Hodgkin's disease is classically considered separately from other lymphomas (nonHodgkin's lymphomas) because its **spread is almost always in contiguity** (i.e., from one set of lymph nodes to the next). The spleen is involved before the liver. It almost never has a leukemic component. It has a high cure rate, and histologically, it is characterized by the presence of the **Reed-Sternberg giant cell** (RS cell). The RS cell is large (15–45 m), often with two or more nuclei, containing large "owl-eyed" nucleoli surrounded by a clear halo; cytoplasm is abundant. The presence of the RS cell is necessary but not sufficient to make the diagnosis of Hodgkin's disease.

Note

Leukocyte alkaline phosphatase is elevated in inflammatory leukocytosis. It is depressed in chronic myelogenous leukemia.

2. **Clinical features.** Hodgkin's disease may present with painless cervical adenopathy or with constitutional (hypermetabolic) symptoms: fevers, chills, night sweats, and weight loss.
3. **Pathology.** There are four variants recognized, in order of best prognosis to worst:
   a. **Lymphocyte predominance** shows a sea of lymphocytes with few RS cells, a variable number of histiocytes, little fibrosis, and no necrosis.
   b. **Nodular sclerosis** is more common in women and tends to involve mediastinal, supraclavicular, and lower cervical nodes. There is a mixed infiltrate composed of lymphocytes, histiocytes, a few eosinophils, plasma cells, and RS cells.
   c. **Mixed cellularity** shows a mixture of neutrophils, lymphocytes, eosinophils, plasma cells, and histiocytes. Many classic RS cells may be identified.
   d. **Lymphocyte depletion** shows rare lymphocytes and many RS cells with variable eosinophils, plasma cells, and histiocytes. Diffuse fibrosis may be seen.
4. **Course and prognosis** depends on multiple factors, including age (younger do better), the presence or absence of constitutional symptoms, histology (patients with lymphocyte predominance and nodular sclerosis do better than patients with mixed cellularity or lymphocyte depletion), and stage (the lower the stage, the better).

B. Non-Hodgkin's lymphomas (NHL)

1. **Overview.** This is a varied group of lymphoreticular neoplasms usually characterized by **lymphadenopathy** and **hepatosplenomegaly**. In most cases the disease is first discovered in only one chain of nodes—usually cervical, axillary, inguinal, femoral, iliac, or mediastinal. Unlike Hodgkin's disease, NHL do not produce RS cells, generally do not spread in contiguity, and they frequently have a leukemic or blood-borne phase.
2. **Incidence.** The peak incidence of age is in the late 50s. NHLs are rare and more aggressive in children and young adults. They may involve lymph nodes or lymphoid tissue in the gut, oropharynx, liver, spleen, and thymus. Presentations include local or generalized lymphadenopathy, abdominal or pharyngeal mass, abdominal pain, or gastrointestinal bleeding. Weight loss is common and is a sign of disseminated disease. NHLs are common in immunosuppressed patients, whether iatrogenic, congenital, or acquired as in AIDS.
3. **Types of Non-Hodgkin's lymphomas**
   a. **Well-differentiated lymphocytic lymphoma (WDLL)**
      (1) **Clinical features.** WDLL comprises approximately 5% of NHLs and is usually diffuse. It usually affects older patients who present with generalized lymphadenopathy and mild hepatosplenomegaly.

b. Poorly differentiated lymphocytic lymphoma (PDLL)

(1) **Clinical features.** PDLL comprises approximately 30% of NHLs. It may be nodular or diffuse. Patients are usually middle-aged or older. In 75% of cases, they present with lymphadenopathy and infiltration of bone marrow, liver, and spleen at the time of diagnosis.

c. Histiocytic lymphoma

(1) **Clinical features.** This is one of the most common NHLs. It is usually diffuse but may be nodular. Diffuse histiocytic lymphoma (DHL) may present with nodal involvement (usually on one side of diaphragm), extranodal involvement (gastrointestinal tract, skin, brain, bone), or, rarely, liver and spleen involvement.

d. Lymphoblastic lymphoma

(1) **Clinical features.** MLHL is often associated with a mediastinal mass (thymoma), suggesting a thymic origin for the neoplastic cells. These cells often express T-cell markers.

e. Undifferentiated lymphoma: Burkitt's

(1) **Clinical features.** This disease is endemic in Africa and sporadic in the United States. It usually affects children or young adults. Lymphadenopathy is a rare initial presentation. In Africa it often arises in the mandible or maxilla; in the United States, it often arises in the abdomen (gastrointestinal tract, ovaries, retroperitoneum). The etiology of Burkitt's lymphoma is thought to be related to **Epstein Barr virus (EBV).** EBV may act as a mitogen, initiating a sustained polyclonal activation of B cells. This eventually results in a neoplastic proliferation of a single B-cell clone after a chromosomal translocation occurs.

(2) **Pathology.** There is a uniform sea of moderately large cells with round nuclei, multiple nucleoli, moderate basophilic cytoplasm with lipid-containing vacuoles, frequent mitoses, and many macrophages with ingested debris, producing the so-called **"starry sky" pattern.** A leukemic phase is rare.

LEUKEMIAS

The leukemias are a group of malignant neoplasms of WBC precursors characterized by abnormal leukocytes in the peripheral blood, liver, spleen, and bone marrow. Most of the morbidity results from the functional impairment of WBC, RBC, and platelets, leading to infection, anemia, and bleeding.

A. Classification

1. **Acute leukemias** are characterized by the presence of **blasts in the peripheral blood** and lack of mature cells. They are usually rapidly fatal if left untreated (2–4 months). The two most common types are **acute lymphocytic leukemia (ALL)** and **acute myelogenous leukemia (AML). Acute monocytic leukemia (AMoL)** and **acute undifferentiated leukemia (AUL)** occur less frequently.

NOTE

The term "histiocytic" is actually a misnomer: the tumors are composed of monoclonal B cells, not cells of macrophage lineage.

IN A NUTSHELL

Acute leukemias have blasts in peripheral blood and decreased mature cells, whereas chronic leukemias have an increased number of mature WBCs in the peripheral blood.

2. **Chronic leukemias** are characterized by elevated numbers of more mature leukocytes in the peripheral blood. They have a longer course (if untreated, 3–10+ years). **Chronic myelogenous leukemia (CML)** and **chronic lymphocytic leukemia (CLL)** are the two most common forms. **Chronic monocytic leukemia (CMoL)** is much less common.

B. **Acute lymphocytic leukemia (ALL)**

1. **Clinical features.** ALL accounts for 60–70% of childhood leukemia. The peak incidence is at age 4; it is rare over age 50. ALL presents with fatigue, fever (secondary to neutropenia and infection), bleeding in the form of epistaxis, gingival petechiae, ecchymoses (secondary to thrombocytopenia); subarachnoid or cerebral hemorrhage may occur. Patients may have lymphadenopathy, hepatosplenomegaly, or bone pain from infiltration of these areas.

2. **Pathology.** Almost all patients present with anemia and thrombocytopenia on peripheral smear. The initial WBC count is variable and may be high, normal, or low, depending on the course of the disease. **Lymphoblasts** are prominent and mature WBCs are rare.

C. **Acute myelogenous leukemia (AML)**

1. **Clinical features.** AML represents approximately 20% of acute leukemia in children and is the most common acute leukemia in adults. Signs and symptoms resemble ALL, except that AML usually presents with lymphadenopathy or splenomegaly.

2. **Pathology.** One may see tissue infiltrates of neoplastic cells called chloromas. The primary cell type is variable.
   a. **Myeloblasts** have a round-oval nucleus, loose chromatin, two or more nucleoli, and pale blue cytoplasm. They may contain **Auer rods** (finely granular cytoplasmic bodies), which are abnormal fused lysosomal structures.

D. **Chronic myelogenous leukemia (CML)**

1. **Clinical features.** This is primarily a disease of middle age but may occur in children and young adults. Initial symptoms are often fatigue, fever, night sweats, weight loss. **Splenomegaly** is common and often massive enough to cause abdominal discomfort. Laboratory studies may show marked leukocytosis (50,000–500,000), **low-to-absent leukocyte alkaline phosphatase,** elevated serum vitamin B_{12} and vitamin B_{12}-binding protein, and high uric acid as a result of rapid cell turnover. After a variable remission period, patients may develop **blast crisis,** which is an acute resistant form of leukemia, leading to death. Approximately two-thirds of patients convert to AML and one-third to B-cell ALL.

2. **Pathology**
   a. The peripheral smear shows a very high WBC count. Segmented neutrophils, metamyelocytes, and myelocytes are predominant, but promyelocytes and blasts are also present. Eosinophils and basophils are present and often prominent. Lymphocytes are few. There is a moderate anemia with some anisocytosis. Platelets are usually increased, often markedly.
   b. The bone marrow is packed, often 100% cellular with hyperplasia of the granulocytic cell line.
   c. **The spleen may be massively enlarged** (up to 5 kg). Leukemic cells may obstruct vessels, leading to multiple splenic infarcts.
   d. Over 95% of patients with CML have the **Philadelphia chromosome (Ph')**, the result of translocation from the long arm of chromosome 22 to chromosome 9 in all dividing progeny of pluripotent stem cells.

E. **Chronic lymphocytic leukemia (CLL)**

1. **Clinical features.** This is a disease of patients usually over 60 years of age. It is common in the West and rare in Asians. There is usually an insidious onset, often discovered incidentally during routine blood testing. The patient may be asymptomatic or present with fatigue and weight loss; lymphadenopathy and hepatosplenomegaly are later findings. Patients may develop low levels of gamma globulins with resultant susceptibility to infection. Patients with CLL are also thought to have a higher incidence of visceral malignancy (e.g., gastrointestinal tract, lung, skin), and develop autoimmune hemolytic anemia more frequently than the normal population.

2. **Pathology.** The peripheral smear shows marked lymphocytosis (50,000–250,000). Normochromic, normocytic anemia is common and autoimmune hemolysis may occur. Platelets are initially normal, then decrease as the bone marrow is replaced by neoplastic cells.

F. **Adult T-cell leukemia/lymphoma**

1. **Clinical features.** This disease is endemic in Japan and sporadic in the West. It is caused by the **human T-cell leukemia/lymphoma virus (HTLV 1)**, a virus with some similarities to human immunodeficiency virus (HIV). Patients present with lymphadenopathy, hepatosplenomegaly, skin involvement, and hypercalcemia. The incubation period after exposure to the virus may be decades.

2. **Pathology.** The primary cell type is the CD4 T cell.

Note

The classical CLL cell is the CD5 B cell. CLL cells divide very slowly but do not undergo apoptosis and therefore accumulate endlessly.

In a Nutshell

Leukemia clues:

• Childhood lymphoblastic	→ ALL
• Myeloblasts	→ AML
• Auer rods	→ AML, promyelocytic
• DIC	→ Promyelocytic
• Elderly	→ CLL
• Massive splenomegaly	→ CML
• Philadelphia chromosome	→ CML
• HTLV-1	→ Adult T cell

PLASMA CELL DYSCRASIAS

A. **Hypergammaglobulinemia** is an increased serum level of immunoglobulin.

1. **Classification**

a. **Monoclonal immunoglobulin molecules**, or M components, belong to a single class, subclass, and type. Although complete immunoglobulin molecules circulate in the plasma and interstitium, fragments, such as immunoglobulin light chains, may be found in the urine. **Monoclonal gammopathies** may be malignant (e.g., multiple myeloma, Waldenström's macroglobulinemia, heavy-chain disease) or benign (e.g., monoclonal gammopathy of undetermined significance, MGUS).

b. **Polyclonal immunoglobulins** are usually due to antigenic stimulation. Liver disease also elevates immunoglobulins as a result of decreased catabolism. Polyclonal hypergammaglobulinemia typically occurs 1–2 weeks after an antigen stimulus. It may follow bacterial infection or occur with granulomatous disease, connective tissue disorders, and liver failure secondary to decreased catabolism. Pathology is variable and depends on the underlying disorder.

2. **Laboratory tests** show elevated serum globulins, an elevated erythrocyte sedimentation rate (ESR), and a positive serum protein electrophoresis. **Bence-Jones proteins** (free light chains) may be found in serum or urine. In myeloma, the free light chains are monoclonal; in inflammation, liver disease, or glomerulopathy, the free light chains are polyclonal.

3. **Clinical features**

a. **Hyperviscosity of blood** may lead to sludging and rouleaux formation with subsequent thrombosis, hemorrhage, renal impairment, CNS disturbances, and right-sided congestive heart failure.

b. **Cryoglobulins**, immunoglobulins that precipitate in the cold (usually M components), may lead to Raynaud's phenomenon, thrombosis, and gangrene.

c. **M components** may interfere with clotting, leading to gastrointestinal or retinal hemorrhage. They most often inhibit factors IX and X.

d. **The presence of immunoglobulins** with antibody activity in the serum may lead to immune-mediated destruction of RBCs, granulocytes, or platelets with resultant anemia, granulocytopenia, or thrombocytopenia.

B. **Multiple myeloma**

1. **Clinical features.** Multifocal plasma cell neoplasms in the bone marrow and, occasionally, soft tissues, produce **monoclonal immunoglobulins (IgG).** Signs and symptoms result from excess abnormal immunoglobulins causing hyperviscosity and from infiltration of various organs by neoplastic plasma cells. Immune-mediated destruction of blood cells and lack of normally functioning antibodies lead to

susceptibility to infection. Proteinuria may contribute to progressive renal failure. Infiltration of bone with plasma cell neoplasms may lead to **bone pain** and **hypercalcemia.** Over 99% of patients have elevated levels of serum immunoglobulins or urine Bence-Jones proteins, or both. **Serum protein (SPEP) electrophoresis** shows a homogeneous peak or "spike."

C. **Waldenström's macroglobulinemia**

1. **Clinical features.** These are neoplasms of lymphocytoid plasma cells that produce **monoclonal IgM.** The disease resembles lymphocytic lymphoma. Symptoms are due to hypergammaglobulinemia and tumorous infiltration. Most patients present with constitutional symptoms (i.e., fatigue, weakness, weight loss) but they may present with hepatosplenomegaly, lymphadenopathy, bone pain, and manifestations of hyperviscosity. Ten percent of patients have Bence-Jones proteins in urine. Almost all patients have an M-protein spike on serum protein electrophoresis.

2. **Pathology. Bone marrow** shows infiltrates of lymphocytes, plasma cells, lymphocytoid plasma cells, and related variants. There is **no bone erosion.**

D. **Monoclonal gammopathy of undetermined significance (MGUS)**

1. **Clinical features.** There is an asymptomatic elevation in serum immunoglobulins detected as an M-protein spike on serum electrophoresis.

2. **Pathology.** Patients have a low concentration of M protein, and the bone marrow contains less than 5% plasma cells.

3. **Prognosis.** This disorder was initially thought to be benign, but approximately 3% of patients a year with MGUS may later develop myeloma, lymphoma, amyloidosis, or Waldenström's macroglobulinemia.

Note

A major difference between multiple myeloma and Waldenström's macroglobulinemia is the lack of lytic bone lesions in Waldenström's.

DISORDERS OF THE SPLEEN

A. **Splenomegaly**

1. **Clinical features.** There are multiple etiologies for splenomegaly, including infections (e.g., mononucleosis, TB, CMV, malaria), congestion with portal hypertension (e.g., cirrhosis, portal vein thrombosis, right-sided CHF), inflammation (e.g., SLE and rheumatoid arthritis), lymphohematogenous disease (e.g., myeloma, lymphoma, leukemia), storage disease (e.g., Gaucher's, Niemann-Pick's), and others (e.g., infarcts, amyloid, tumor).

2. **Signs and symptoms.** The patient may complain of left upper-quadrant discomfort. Sequestration of blood elements by an enlarged spleen is known as **hypersplenism** and is characterized by splenomegaly, reduction of one or more blood cell lines with resultant anemia, leukopenia,

or thrombocytopenia, and resolution of the blood disturbance by splenectomy.

3. **Pathology** depends on the underlying disease. Congestive splenomegaly may lead to a large, firm, red spleen with a thick capsule.

B. **Splenic infarcts**

1. **Clinical features.** Infarcts initially present with splenomegaly, but then fibrosis and shrinkage occur. They may be caused by occlusion of the splenic artery or its branches but are most commonly caused by **embolisms from the heart**; thrombosis may occur. Occlusion of sinusoids by **sickled cells** also produces multiple microinfarcts, leading to autosplenectomy.

2. **Pathology.** Infarcts may be single or multiple, small or large. They are usually **pale and wedge-shaped** with a broad base at the periphery. Suppurative necrosis may develop, followed by scarring.

C. **Splenic neoplasms**

1. **Clinical features.** Most tumors involving the spleen are lymphohematogenous neoplasms, but others may occur.

2. **Primary neoplasms**
   a. **Benign.** Fibromas, osteomas, chondromas, lymphangiomas, and hemangiomas (often cavernous) are all rare.
   b. **Malignant.** Lymphomas are by far the most common; hemangiosarcomas are rare.

D. **Rupture**

1. **Clinical features.** Rupture is usually due to trauma but may be spontaneous in leukemia, malaria, typhoid fever, and infectious mononucleosis.

2. **Pathology.** There is usually massive intraperitoneal hemorrhage. The peritoneal cavity may be seeded with foci of splenic tissue.

E. Congenital anomalies of the spleen, including accessory spleens and abnormal lobulations, are common. Small accessory spleens can become clinically significant when they enlarge following a therapeutic splenectomy.

DISORDERS OF THE THYMUS

A. **Atrophy of the thymus** may be seen in several congenital abnormalities and with radiation, chemotherapy, and stress.

1. **Pathology**
   a. **Congenital immune deficiencies** as a result of adenosine deaminase deficiency or interleukin-2 (IL-2) receptor deficiency lead to the absence of lymphoid precursors and failure of the thymus to populate with thymocytes. **Severe combined immunodeficiency disorder** (SCID) results.

CLINICAL CORRELATE

Recall that patients undergoing splenectomy should receive vaccinations to protect them from encapsulated organisms. Vaccines for pneumococcus and H. influenzae are available.

FLASHBACK TO EMBRYOLOGY

Remember that the third pharyngeal pouch gives rise to the thymus gland, whereas the fourth pouch gives rise to the superior parathyroids.

   b. **Other congenital immune deficiencies**, such as **Nezelof's syndrome** and **DiGeorge syndrome**, lead to atrophy or failure to develop a thymus. In DiGeorge syndrome, a defect in the development of the third and fourth pharyngeal pouches also leads to the absence of the parathyroids, causing parathormone deficiency and tetany shortly after birth.

B. **Hyperplasia of the thymus** with germinal center formation may be seen in some autoimmune diseases, such as **myasthenia gravis**, where antibodies are made to acetylcholine receptors. Removal of the thymus often cures the disease.

C. **Epithelial thymomas** are benign in 90% of cases.

   1. **Pathology.** Most epithelial thymomas are lobulated and encapsulated and are composed of a mixture of epithelial cells and T lymphocytes.

   2. **Clinical features.** The mean age is 50. They may present incidentally on chest x-ray with cough, dyspnea, or dysphagia. There is an increased incidence of thymoma in patients with myasthenia gravis.

D. **Lymphomas** may originate in the thymus. The thymus may also be secondarily involved in Hodgkin's disease, non-Hodgkin's lymphomas, and acute lymphoblastic leukemia.

Musculoskeletal, Connective Tissue, and Integument Pathology

Musculoskeletal and skin pathology encompass a broad range of congenital anomalies, autoimmune diseases, and neoplastic disorders. This chapter will discuss the characteristics of disease states, their clinical presentations, and, when identifiable, their causes and treatments.

BONE

A. **Congenital anomalies**

1. **Osteogenesis imperfecta** is a term used to describe several clinical phenotypes of hereditary bone fragility.
   a. **Four types** are generally recognized. All are rare.
      (1) Type I shows autosomal dominant inheritance and causes mild-to-moderate long bone disease, blue sclerae, deafness, and little progression after puberty.
      (2) Type II is autosomal recessive and often produces a stillborn infant or death after birth, with generalized crumpled bones.
      (3) Type III is autosomal recessive and produces progressive severe deformity. Patients have white sclerae.
      (4) Type IV is autosomal dominant with variable severity, normal sclerae, and fractures of the long bones and spine.
   b. **Etiology**: The cause in all cases of osteogenesis imperfecta seems to be a **defect in the synthesis of type I collagen**.
   c. **Pathology**
      (1) In bones, woven bone instead of trabecular bone and abnormal arrangements of collagen fibers are seen. Joints show **ligamentous laxity** as a result of abnormal collagen.
      (2) In the eye, some patients have an abnormally thin **sclera with a blue hue**.
      (3) In the ears, there may be fractured ossicles, producing deafness.
      (4) Teeth may be small and discolored (dentinogenesis imperfecta), there may be mitral valve prolapse, and the dermis may be abnormally thin.

Clinical Correlate

Osteogenesis imperfecta is a disease of type I collagen synthesis. Heritability varies among the types. Blue sclerae and lax ligaments are common features.

Note

The defect in osteopetrosis seems to be an inability of osteoclasts to resorb bone.

Clinical Correlate

Achondroplasia is the best known form of dwarfism, characterized by short limbs, large body, frontal bossing, and "saddle nose."

Clinical Note

Gardner's Syndrome is often diagnosed first by the dentist due to multiple radiolucencies in the panograph.

Note

In osteoporosis, the bone is formed normally but in decreased amounts.

3. **Osteopetrosis** is a group of hereditary disorders characterized by **increased density and thickening of bone cortex** with narrowing of medullary cavities. Bones are brittle and fracture easily. Membranous bones are not affected (e.g., cranium). It may be associated with anemia, blindness, deafness, hydrocephalus, and cranial nerve palsies. There are two forms of inheritance.
   a. **Autosomal recessive disease** affects children and produces early death due to anemia as the bones grow and squeeze out the marrow space.
   b. **Autosomal dominant disease** affects adults and does not cause death but may cause increased fractures and encroach upon cranial nerves as they exit from the skull.
4. **Achondroplasia** is an autosomal dominant disease characterized by **abnormal cartilage synthesis** with subsequent decreased epiphyseal bone formation. It spares the cranium and vertebral bones. Clinically, achondroplasia is characterized by **dwarfism** with short extremities and a large body and head.
5. **Osteochondromatosis** is a hereditary disorder characterized by the formation of multiple **exostoses.**
   a. **Clinical features**
      (1) Exostoses may be asymptomatic or produce deformity and compromise the blood supply.
      (2) **Gardner's syndrome** is a rare genetic disorder in which there is an association of exostoses with sebaceous cysts, desmoid tumors, and colonic polyps, which may become carcinomas.
   b. **Pathology.** Exostoses are bony metaphyseal projections capped with cartilage. They are multiple, often symmetric, and originate from epiphyseal cartilage.
6. **Enchondromatosis** (Ollier's disease) is a nonhereditary syndrome characterized by multiple **cartilaginous masses within the medullary cavity of bone,** most commonly in the hands and feet. It often presents with pain and fractures. These masses may undergo malignant transformation; half of all chondrosarcomas arise from enchondromas. **Maffucci's syndrome** is a familial association of enchondromas and hemangiomas of the skin.

8. **Osteoporosis** is a decrease in bone mass, causing fragility of bone. Osteoporosis most commonly occurs in postmenopausal women.
   1. **Pathogenesis**
      a. **Primary causes** include estrogen deficiency, low density of original bone, lack of exercise, and nutritional factors associated with accelerated bone loss.
      b. **Secondary causes** include immobilization, endocrinopathies (e.g., Cushing's, thyrotoxicosis), and malnutrition (e.g., deficiencies of calcium, vitamins C and D, protein).

2. **Clinical features**
   a. Patients may experience **pain and fractures** without obvious trauma.
   b. X-rays show generalized **radiolucency** of bone.
   c. Laboratory tests reveal normal serum calcium, phosphorus, and alkaline phosphatase.
3. **Pathology**. Thinned cortical bone and an enlarged medullary cavity are seen. All bones are affected. Weight-bearing bones (vertebrae, femoral neck) are predisposed to fractures. There is normal bone histology and a normal ratio of mineral/organic bony elements.

C. **Osteomalacia and rickets**

1. **Etiology**. Both diseases are caused by **vitamin D deficiency** from chronic renal insufficiency, intestinal malabsorption, or dietary deficiency.
2. **Clinical features**
   a. **Rickets** occurs in children prior to closure of the epiphyses, leading to bone deformities and pain. Patients show the "rachitic rosary" (deformity of the chest wall as a result of swelling at osteochondral junctions of ribs), bowing of legs, and fractures.
   b. **Osteomalacia** is an impaired mineralization of the osteoid matrix. It causes fractures and bending of bones and widening of osteoid seams.
      (1) Laboratory tests show **low serum calcium and phosphorous** and **high alkaline phosphatase**, which distinguishes this syndrome from osteoporosis.
      (2) X-rays show diffuse radiolucency of bone.

D. **Paget's disease** (osteitis deformans) is due to **excessive bone** resorption with replacement by soft, poorly mineralized matrix in a disorganized array.

1. **Clinical features**
   a. Paget's disease may present with pain, deformity, and fractures. It is usually polyostotic (affecting many bones), involving the skull, pelvis, femur, and vertebrae. When the skull is involved, impingement of cranial nerves often causes deafness. Involvement may cause bone hypervascularity with increased warmth of the overlying skin.
   b. X-ray shows enlarged, radiolucent bones.
   c. Laboratory tests show an **extremely elevated alkaline phosphatase**.
2. **Pathology**. The disease progresses from an osteolytic to an osteoblastic process. Resorbed bone is replaced by a vascular connective tissue, which later becomes mineralized. There is a mosaic rather than trabecular pattern from persistent osteoid seams at the margin of new bone.

IN A NUTSHELL

Osteoporosis may lead to easy fracturing, especially of hips and vertebrae.

NOTE

Rickets and osteomalacia are disorders of osteoid mineralization: osteoid is produced in normal amounts but is not calcified properly.

E. **Fibrous dysplasia** causes focal areas of fibrous replacement of bone. Incidence is higher in teenagers, with men more frequently affected than women.

1. **Clinical features.** Monostotic fibrous dysplasia is often asymptomatic or may lead to pathologic fracture. **Albright's syndrome** is an association of polyostotic fibrous dysplasia, café au lait spots, and sexual precocity in women.
2. **Pathology.** Fibrous dysplasia is usually monostotic, affecting the long bones, ribs, skull, and facial bones. Fibrosis starts within the medullary cavity and remains encased in cortical bone.

F. **Bone abnormalities in hyperparathyroidism** (osteitis fibrosa cystica)

1. **Pathogenesis.** Excess parathyroid hormone activates osteoclasts to resorb bone and causes the kidney to waste calcium.
2. **Clinical features.** Osteitis fibrosa cystica occurs more commonly in primary hyperparathyroidism, causing bone pain and fractures.
3. **Pathology**
   a. **Microscopically,** there is an increased number of osteoclasts with excess bone resorption and fibrous replacement of marrow, causing cystic spaces in trabecular bone and **"brown tumors"** (areas of organized hemorrhage).
   b. **Grossly,** brown tumors may produce cystic enlargements of bones.

G. **Hypertrophic osteoarthropathy**

1. **Clinical features**
   a. Clinically, hypertrophic osteoarthropathy presents with painful swelling of wrists, fingers, ankles, knees, or elbows. The pathogenesis is unknown.
   b. This is a **periosteal inflammation,** and new bone forms at the ends of long bones, metacarpals, and metatarsals.
   c. Arthritis of adjacent joints is commonly seen, often with digital clubbing.
2. **Etiology.** Causes include intrathoracic carcinoma (a paraneoplastic syndrome), sepsis, endocarditis, cyanotic congenital heart disease, and inflammatory bowel disease. The syndrome regresses when the underlying disease is treated.

H. **Fibrous cortical defect** (nonossifying fibroma) is a common developmental abnormality seen in bones of the lower extremities in children. They are non-neoplastic lesions of bone cortex that are composed of fibrous connective tissue.

1. **Clinical features.** Fibrous cortical defect is usually asymptomatic, non-neoplastic, and usually resolves spontaneously.
2. **Pathology.** There are irregular, well demarcated, radiolucent defects in the bony cortex, with an intact subperiosteal shell of bone. In the

Note

Brown tumors are classical signs of hyperparathyroidism.

metaphysis, there are whorls of connective tissue. Occasionally, multinucleated giant cells are seen. This entity must be differentiated from giant cell tumors of bone, which may cross the epiphysis (fibrous cortical defect does not do this). The stromal cells of giant cell tumors are also more atypical, with larger, darker nuclei and less cytoplasm than seen in fibrous cortical defect.

I. **Osteomyelitis**

1. **Pyogenic osteomyelitis**
   a. **Etiology.** Caused by direct inoculation of bone or by seeding of bone after bacteremia. Organisms include ***Staphylococcus aureus,*** Streptococcus, Gonococci, and *Haemophilus influenzae.* Salmonella may be seen in patients with sickle-cell disease. Pseudomonas is common in intravenous drug users and diabetics.
   b. **Clinical features** include fever, localized pain, erythema, and swelling. The x-ray may be normal for up to 2 weeks, then may initially show periosteal elevation.
   c. **Pathology.** Suppuration begins within the metaphyseal medullary cavity and penetrates the cortex. Compression by exudate leads to vascular insufficiency and ischemic necrosis. Specific findings include:
      (1) **Sequestrum,** a necrotic bone fragment
      (2) **Involucrum,** new bone that surrounds the area of inflammation
      (3) **Brodie's abscess,** localized abscess formation in the bone
2. **Tuberculous osteomyelitis** occurs in 1% of cases of TB, causing caseating granulomas in the bones. The term **"Pott's disease"** refers to spinal involvement.

J. **Tumors**

1. **Osteoblastic tumors**
   a. **Osteoma** is a **benign** growth that frequently involves the skull.
      (1) "Hyperostosis frontalis interna" describes an osteoma that extends into the orbit or sinuses.
      (2) Pathology shows dense normal bone.
   b. **Osteoid osteoma** is a benign growth of the diaphysis of long bones, often the tibia or femur.
      (1) **Clinical features** include pain that is worse at night and relieved by aspirin. X-rays show a central radiolucency surrounded by a sclerotic rim.
      (2) **Pathology** shows a 1-cm brown nodule surrounded by dense sclerotic cortical bone. **Microscopically,** the nodule is formed of vascular, woven bone with partially mineralized osteoid.
   c. **Osteoblastoma** is similar to a large osteoid osteoma, but is large, painless, often involves vertebrae, and may be malignant.
   d. **Osteosarcoma** is a **malignant** bone tumor that produces osteoid and bone.

(1) **Incidence.** Men are affected more often than women, and the tumor usually occurs in the second and third decade of life. It is the most common bone tumor in older people and is often associated with Paget's disease. Over one third of patients with retinoblastoma also develop osteosarcoma.

(2) **Pathogenesis** is unclear. There is an increased incidence with irradiation, Paget's disease, and other previous bone pathology.

(3) **Clinical features.** Patients present with localized pain and swelling, weight loss, and anemia. Classic x-ray findings include **Codman's triangle** (periosteal elevation) and bone destruction.

(4) **Pathology. Grossly,** osteosarcoma, particularly in teenagers, often affects the metaphyseal ends of long bones, usually around the knee, producing large necrotic and hemorrhagic mass. **Microscopically,** the tumor may be sclerotic (with mineralized osteoid) or osteolytic (with little osteoid). It also may contain collagen or cartilage. The classic finding is **anaplastic cells with osteoid,** pink, amorphous material that is variably mineralized (Figure 11-1).

(5) **Prognosis is poor.** Patients are treated with amputation and chemotherapy. Metastasis to the lungs is common. Prognosis is improved with aggressive management, such as resecting single pulmonary metastases.

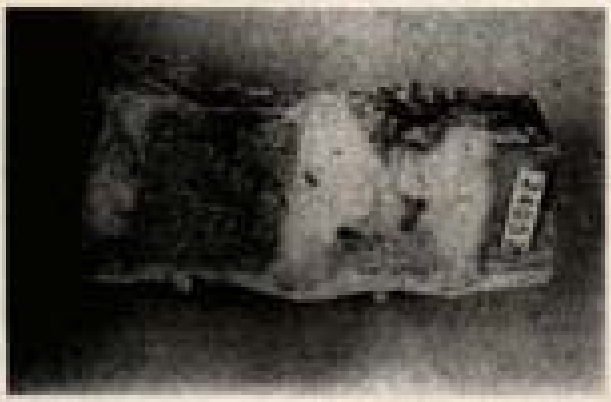


Figure 11-1. Osteogenic sarcoma with vertebral collapse (gross).

2. **Chondromatous tumors**

   a. **Osteochondroma** is an exostosis that forms benign metaphyseal growths. They may be solitary. Lesions are identical to those in multiple form (osteochondromatosis).

b. **Enchondroma** is a solitary cartilaginous growth within the spongiosa of bone. Solitary growths are similar to those in multiple form (Ollier's disease).

c. **Chondromyxoid fibroma** is a benign, rare tumor affecting young men. It forms a firm mass within the metaphyseal marrow cavity of the tibia or femur. The tumor contains fibrous and myxomatous tissue, which must be differentiated from a malignant lesion.

d. **Chondrosarcoma** is a malignant tumor of chondroblasts. The age range is from 30–60 years. Men are more often affected than women.

(1) **Etiology.** The tumor may arise *de novo* or secondary to a pre-existing enchondroma or exostosis.

(2) **Clinical features.** Chondrosarcomas are slower growing than osteosarcomas. They typically present with pain and swelling.

(3) **Pathology.** Tumors typically involve the spine, pelvic bones, and upper extremities. **Microscopically,** they are characterized by atypical chondrocytes and chondroblasts, often with multiple nuclei in a lacuna.

3. **Giant cell tumor** is a malignant neoplasm containing multinucleated giant cells and atypical stromal cells. This is an uncommon tumor, affecting patients from ages 20–50 years.

a. **Clinical features**

(1) Tumors present as a bulky mass with pain and tenderness.

(2) X-rays show an expanding area of radiolucency without a sclerotic rim.

b. **Pathology**

(1) **Grossly,** tumors arise in the epiphyseal region of long bones, forming a club-like deformity at the end of the bone.

(2) **Microscopically,** multiple giant cells, resembling osteoclasts within a matrix of fibroblast-like cells with large, atypical nuclei, occur.

4. **Ewing's sarcoma** is a malignant neoplasm of undifferentiated cells arising within the marrow cavity. It is rare, usually affecting adolescents. Men are affected more often than women.

a. **Etiology.** The tumor arises from mesenchymal cells that have been shown to have some expression of neural antigens.

b. **Clinical features** are pain, tenderness and early widespread dissemination.

c. **Pathology**

(1) **Grossly,** the tumor commonly affects the pelvis and metaphyses of long tubular bones. Cells erode through the cortex and invade surrounding tissues. Half of the cases have "onion skin" or concentric layering of new bone.

(2) **Microscopically,** undifferentiated small cells resembling lymphocytes occur. Surface antigens make the diagnosis.

IN A NUTSHELL

- **Osteochondroma:** *Exostosis from misdirected growth of growth plate*
- **Enchondroma:** *Solitary benign growth of cartilage inside bone*
- **Chondrosarcoma:** *Malignant cartilage-producing tumor*

Note

Systemic lupus erythematosus typically includes joint pain. Because it is a multisystemic immune disorder, it is discussed in the Clinical Immunology section of the Microbiology/Immunology review book.

In a Nutshell

Suppurative arthritis:

- *Manifested by a tender, red, swollen joint (e.g., "a hot knee")*
- *Usually monoarticular, high neutrophil count in joint fluid, and often due to Staph, Strep, and Gonococci*

In a Nutshell

Osteoarthritis:

- *Due to wear and tear on joints*
- *Erosion of articular cartilage leads to bone eburnation and chipping*
- *X-rays show the loss of joint space*
- *Heberden's nodes are found at the DIP joint*

JOINTS

A. **Arthritis**

1. **Suppurative arthritis**
   a. **Pathogenesis.** The primary mechanism of suppurative arthritis is hematogenous seeding of joints during bacteremia, which is more common than direct invasion. Organisms include Gonococcus, Staphylococcus, Streptococcus, *H. influenzae*, and Gram-negative bacilli.
   b. **Clinical features** include tender, swollen, and erythematous joints that require rapid intervention to prevent permanent joint damage.
   c. **Pathology:** This disease is **usually monoarticular,** affecting a large joint. Characteristics of typical suppurative infection are **cloudy synovial fluid** with a **high neutrophil count** that clots readily. If the organism is very virulent or if it is left untreated, the synovium may ulcerate and infection may erode articular cartilage.
2. **Tuberculous arthritis**
   a. **Incidence.** This form occurs more commonly in children.
   b. **Clinical features** include an insidious onset and joint destruction.
   c. **Pathology:** It occurs most often in the spine and hip. The synovial lining is covered with tubercles and granulation tissue. Pannus develops over the articular cartilage and may erode it. Destruction of joint space ensues with fibrosis and calcification, eventually leading to ankylosis.
3. **Osteoarthritis** (degenerative joint disease)
   a. **Incidence.** Osteoarthritis increases with age, affecting women more than men. It affects 80% of people over 70 years old in at least one joint.
   b. **Pathogenesis**
      (1) Aging or **wear and tear** (biomechanical) is the most important mechanism. Also, chondrocyte injury and abnormal collagen activity (biochemical) contribute; usually, both act together.
      (2) Predisposing factors include obesity, previous joint injury, and synovial disease. Most retired football players have at least some osteoarthritis in the knees and ankles.
   c. **Clinical features.** There is an insidious onset with joint stiffness, decreased range of motion, effusions, crepitus, and bony swelling. Symptoms of nerve compression may develop secondary to compression by osteophytes.
   d. **Pathology**
      (1) The most commonly affected joints include vertebrae, hips, knees, and distal interphalangeal (DIP) joints of fingers.
      (2) **Joint mice** are flakes of cartilage in the joint space from erosion.
      (3) **Osteophytes and bone spurs** develop. Denuded, sclerotic, subchondral bone may become exposed in areas (eburnation).

4. **Rheumatoid arthritis** is a systemic chronic inflammatory disease characterized by progressive arthritis. There are many clinical variants.
   a. **Incidence.** Women are affected three times more frequently than men. There is a familial predisposition, and the disease commonly presents from ages 20–60 years.
   b. **Pathogenesis** involves an **autoimmune reaction** with the formation of circulating antibodies **(rheumatoid factor)** against the Fc fragment of autologous IgG, leading to immune complexes.
   c. **Clinical features**
      (1) Symptoms include low-grade fever, malaise, fatigue, and **morning stiffness.**
      (2) Physical examination shows joint swelling, redness, and warmth. In late stages, ankylosis may develop.
      (3) Synovial fluid shows increased cells (usually neutrophils) and poor mucin.
      (4) There is an elevated sedimentation rate and hypergammaglobulinemia. The level of rheumatoid factor may correlate with the severity of the arthritis.
      (5) X-rays show erosions and osteoporosis.
      (6) Systemic features include subcutaneous nodules (20% patients), Sjögren's syndrome (15%), glaucoma, pericarditis, vasculitis, hepatosplenomegaly, and adenopathy.
   d. **Pathology**
      (1) The disease usually starts in the **small joints of the hands and feet** but may involve any joint. There is **usually symmetric involvement.** Patients develop a diffuse proliferative synovitis in which the synovium becomes replaced by **pannus,** a vascularized mass packed with lymphocytes, macrophages, and plasma cells. Pannus erodes articular surfaces, bone, joint capsule, and ligaments. Adhesions and ankylosis may result.
      (2) Rheumatoid nodules are composed of proliferative connective tissue with areas of central necrosis. They may be seen in skin, heart valves, lung, pleura, pericardium, and spleen. Skin nodules are usually on extensor surfaces.
      (3) Arteries may show acute necrotizing vasculitis due to circulating antigen-antibody complexes.

5. **Gout.** In gout, there is **hyperuricemia** associated with recurrent bouts of acute arthritis, resulting from deposition of **monosodium urate** in joint tissues.
   a. **Types**
      (1) In **primary gout** (90% of cases), there is an **inborn error of purine metabolism.** The metabolic defect is usually not known. Specific enzyme defects account for only about 10% of cases (e.g., Lesch-Nyhan syndrome).
      (2) **Secondary gout** is hyperuricemia resulting from a disorder unrelated to purine metabolism (e.g., excessive cell breakdown as in leukemia and polycythemia).

b. **Incidence.** Most cases are in men, but it occasionally affects postmenopausal women. It is familial (primary gout) in about 20% of cases.

c. **Pathogenesis** is an overproduction of uric acid (under 10%) or underexcretion of uric acid (over 90%).

d. **Clinical features.** There is an asymptomatic period of hyperuricemia (> 7 mg/dl) followed by acute episodes of **joint pain and swelling.** After approximately 10 years of recurrent attacks, chronic disabilities ensue (i.e., decreased range of motion, joint deformities). Uric acid kidney stones develop in up to 25% of patients.

e. **Pathology.** Precipitation of urate crystals in joint fluid causes an acute **inflammatory synovitis** with synovial edema and leukocytic infiltrate. It usually affects the joints of the lower extremities, particularly of the **large toe.** Formation of **tophi** (urate deposits surrounded by inflammatory cells, including foreign body giant cells) is pathognomonic. Tophi may form in the helix of ear, bursae, ligaments, and kidney.

In a Nutshell

Gout

- *Gout is the deposition of urate crystals leading to acute, painful attacks of arthritis. The big toe is classically affected.*
- *Gout may result from overproduction or underexcretion of uric acid.*
- *Tophi are pathognomonic.*

B. **Tumors**

1. **Synovioscarcoma**

a. **Incidence.** This is a rare tumor with a peak incidence in early adulthood, affecting boys and girls equally.

b. **Clinical features.** These tumors form slow-growing, painless masses. They are very aggressive with early metastases to the lung and pleura.

2. **Malignant fibrous histiocytoma**

a. **Incidence.** This is a relatively common soft tissue malignancy, affecting adult men more than women.

b. **Pathology.** Tumors arise in soft tissue or bones. They are located in the lower extremities more often than in the upper extremities and in the abdominal cavity. **Microscopically,** tumors are pleomorphic, composed of fibroblasts, histiocytes, and tumor giant cells.

SKIN

A. **Epidermal lesions**

1. **Seborrheic keratoses** are **benign neoplasms** that usually arise in areas exposed to the sun. They are very common in late adulthood.

a. **Clinical features.** Although they are usually left untreated, they may be removed if they become irritated or for cosmetic purposes. Sudden development of multiple lesions may follow an inflammatory dermatitis, hormonal therapy, or may accompany an underlying malignancy.

b. **Pathology**

(1) **Grossly,** lesions are typically located on the face, back, or trunk. They are typically **brown to gray, scaly,** and **greasy.**

(2) **Microscopically**, seborrheic keratosis is a squamoproliferative disorder characterized by hyperkeratosis, papillary epidermal hyperplasia, and occasionally, development of pseudo horn cysts (epidermal pseudocysts filled with keratin).

2. **Keratoacanthoma** is also a benign squamous lesion, arising in sun-exposed areas. It is most common in middle age.
   a. **Clinical features.** Keratoacanthoma is a rapidly growing papule that must be distinguished from squamous cell carcinoma.
   b. **Pathology**
      (1) **Grossly**, lesions are located on the head and arms. They start as a round pink papule that grows within weeks up to 2 cm with a central depression filled with keratin.
      (2) **Microscopically**, the squamous cells are well organized and not anaplastic, although mitoses are present during the rapid growth phase. A key feature of this neoplasm is a lip of normal, nondysplastic epidermis on both sides of the keratin-filled crater. Keratoacanthomas are said to be composed of large squamous cells with a hyaline, "ground-glass" cytoplasm.

3. **Fibroepithelial polyps** are benign. Also known as **skin tags**, these lesions are common in middle age but may also develop during pregnancy. They are also associated with diabetes or intestinal polyposis. They usually occur in intertriginous regions and on the neck. Skin tags are composed of benign squamous epithelium, covering a fibrovascular core.

4. **Basal cell carcinoma** is invasive, but it rarely metastasizes.
   a. **Incidence.** It is most common in middle-aged or elderly individuals and those who have fair complexions. They occur on sun-exposed areas.
   b. **Clinical features.** Basal cell carcinomas are locally aggressive and rarely metastasize. Complete excision is usually curative, but there is approximately a 50% recurrence rate from shave biopsies.
   c. **Pathology**
      (1) **Grossly**, basal cell carcinoma lesions are located on sun-exposed regions or areas containing pilosebaceous follicles. Most lesions are on the face. They form pearly gray papules with heaped up borders and a central depression.
      (2) **Microscopically**, there are nests of tumor cells surrounded by a fibrous stroma. Palisading of tumor cells at the edges of nests is a particularly useful microscopic characteristic.

5. **Actinic keratoses** are premalignant and may develop into squamous cell carcinoma.
   a. **Incidence** is highest in fair-skinned people of middle age. It is associated with chronic sun exposure.
   b. **Pathology**
      (1) **Grossly**, there are rough, crusty, red papules up to 1 cm in diameter.

IN A NUTSHELL

Seborrheic keratoses are gray, scaly greasy lesions with hyperkeratosis, epidermal papillary hyperplasia, and occasional keratin pseudocyst formation. They are benign.

CLINICAL CORRELATE

Skin tags are normal findings on most people; high numbers of them may indicate diabetes.

IN A NUTSHELL

Basal cell carcinoma:

- *Due to sun exposure*
- *Most commonly occur on the face*
- *Rare metastasis*
- *Nests of tumor cells in desmoplastic tissue*
- *Palisading of cells is characteristic*

4. **Squamous cell carcinoma** is a **malignant tumor** that is also found most frequently in **sun-exposed areas.**
   a. **Incidence.** The tumor peaks at 60 years of age with a preponderance among women.
   b. **Etiology.** Chronic sun exposure and fair complexion are the greatest risk factors. Chronic skin ulcers or sinus tracts, long-term exposure to hydrocarbons, burns, and radiation also contribute to risk.
   c. **Clinical features.** When squamous carcinoma occurs on sun-exposed regions, it rarely metastasizes. When it occurs on nonexposed skin, up to 50% metastasize, indicating a fundamentally different biology in two systems.
   d. **Pathology**
      (1) **Grossly**, the appearance is variable, depending on location and invasiveness. Squamous carcinomas may be firm, erythematous, scaly nodules or oozing ulcers with raised borders. On mucosal surfaces, they may be associated with leukoplakia (white plaques), made white by the keratin produced.
      (2) **Microscopic findings** include atypical cells restricted to the epidermis (Bowen's disease or squamous cell carcinoma in situ) and atypical keratinocytes invading the dermis (invasive cancer). Atypical keratinocytes may form squamous pearls, i.e., laminated squamous cells with central keratinization in an "onion-skin" configuration.

In a Nutshell

- *Squamous cell carcinoma arises in sun-exposed areas, skin ulcers, or sinus tracts.*
- *Grossly, squamous cell carcinoma may appear in many forms. Microscopically, "squamous pearls" (formed by atypical keratinocytes) help make the diagnosis.*

B. Dermal lesions

1. **Xanthomas**
   a. **Incidence.** Xanthomas may be idiopathic, or they may be associated with hyperlipidemia or malignancies.
   b. **Pathology.** They are **yellow nodules,** composed of foamy histiocytes with eosinophilic cytoplasm. The cells contain cholesterol, triglycerides, and phospholipids.

In a Nutshell

Xanthomas are collections of lipid-laden histiocytes and are often associated with hyperlipidemia.

2. **Capillary hemangiomas** (strawberry hemangiomas)
   a. **Clinical features.** These lesions usually arise within the first weeks of life and usually resolve spontaneously, starting at 1–3 years of age; most are completely gone by age 5.
   b. **Pathology.** Capillary hemangiomas form a soft, red, lobulated mass, 1–6 cm in diameter, composed of thick-walled capillaries.
3. **Nevus flammeus** (port wine stain) is a common congenital lesion, composed of telangiectatic vessels. Usually located on the neck or face, it appears as a large, flat irregular pink patch that tends to resolve spontaneously.
4. **Kaposi's sarcoma** is a malignant mesenchymal tumor (an angiosarcoma), characterized by an aggressive course in patients with AIDS and by a slower course in elderly men.

In a Nutshell

Kaposi's sarcoma is an angiosarcoma found on skin and mucous membranes. It is associated with AIDS.

C. **Pigmentary disorders**

1. **Freckles** are areas of increased melanin deposition in the basal cell layer of the epidermis.
2. **Vitiligo** is irregular, completely **depigmented patches**.
   a. **Incidence** is common and may affect any race. Risk is increased with a positive family history.
   b. **Etiology** is unknown, but it is possibly autoimmune or related to stress.
   c. **Pathology**. **Microscopically**, the skin is devoid of melanocytes in affected areas.
3. **Melasma** is irregular patches of hyperpigmentation on the face. It most commonly appears during pregnancy and does not completely regress.

D. **Melanocyte tumors**

1. **Nevocellular nevus** is a benign tumor of nevus cells and melanocytes.
   a. **Types of common nevi** include junctional, compound, and intradermal. Although the different types may have distinguishing clinical features, histologic examination is needed for accurate diagnosis.
   b. **Clinical features**
      (1) The relationship between nevi and melanoma is largely unknown except that both are clearly related to sun exposure. Although malignant transformation of nevi is not common, approximately 30% of cases of melanoma are associated with nevi. There is also increased incidence of melanoma associated with giant congenital pigmented nevi.
      (2) In most cases, one can distinguish a benign nevus from melanoma on clinical grounds (i.e., color, contour). A nevus is tan to brown and has sharp, well-circumscribed borders. Color is usually uniform, and the lesions are stable in shape and size.
2. **Lentigo maligna** (Hutchinson's freckle)
   a. This is a premalignant lesion, occurring on sun-exposed surfaces in the elderly.
   b. It is characterized by intraepidermal proliferation of atypical melanocytes. Up to 50% progress to invasive melanoma over the course of several years.
3. **Malignant melanoma**
   a. **Incidence.** Melanoma peaks by ages 40–60.
   b. **Pathology** (Figure 11-2)
      (1) **Lentigo maligna melanoma** arises from lentigo maligna with a peak incidence at age 70. This form of melanoma has the best prognosis.
      (2) **Superficial spreading melanoma** shows extensive horizontal growth with the radiating cells more atypical than those of lentigo maligna. Lesions are most commonly on legs, chest, and back; peak incidence is by age 60.

IN A NUTSHELL

Vitiligo is characterized by irregular patchy depigmentation of unknown origin due to melanocyte deficiency.

NOTE

Melanomas tend to grow horizontally before spreading vertically. Prognosis relates to depth of invasion.

Figure 11-2 Malignant melanoma (microscopic)

(3) **Nodular melanoma** shows extensive dermal invasion and rapid growth. Raised brown-black lesions may be found anywhere on the skin or mucosa. Peak incidence is by age 50 and has the worst prognosis of the melanomas.

c. **Diagnosis.** Staging is by **depth of invasion**, through the layers of the epidermis and dermis. Four-year survival rates range from 10% for the deepest invasion to 100% for the most superficial invasion.

d. **Treatment** is **complete excision**. Systemic disease is treated with chemotherapy or immunotherapy with poor but variable results. Some metastic melanomas resolve spontaneously, and some relapse as internal metastases more than a decade after a seeming "cure."

E. Primary bullous disease

1. **Bullous pemphigoid**
   a. **Incidence.** This disorder is uncommon; however, it occurs more frequently than other primary bullous disease and tends to occur after age 60.
   b. **Clinical features.** Bullous pemphigoid causes large, tense, pruritic bullae, usually on the lower abdomen, groin, inner thighs, and mouth. Most patients have **circulating autoantibodies against the dermoepidermal junction**, the disease follows a chronic relapsing course and is self-limited.

2. **Pemphigus vulgaris**
   a. **Incidence** is most common in the ages 40–60.
   b. **Pathogenesis. Autoantibodies against the intercellular junctions between keratinocytes** cause acantholysis. The loss of intercellular connections causes an altered cell configuration.

c. **Clinical features**

(1) Pemphigus starts with small vesicles, usually on the oral or nasal mucosa, then spreads to other parts of the body. Bullae are delicate and flaccid.

(2) **Nikolsky's sign** is the development of bullae, caused by rubbing the skin with a finger. Pemphigus may result in erosions; secondary infections may lead to 40% mortality. Lesions are treated with corticosteroids.

F. **Infectious diseases**

1. **Impetigo** is a superficial skin infection, usually caused by **Group A β-hemolytic Streptococci** or **Staphylococcus**. It is characterized by eroded pustules, covered by honey-colored crusts. Impetigo may lead to poststreptococcal glomerulonephritis.

2. **Molluscum contagiosum** is a **poxvirus** infection, causing development of multiple, small, firm, umbilicated papules with a characteristic microscopic appearance in which viral clusters cause eosinophilic inclusions in keratinocytes.

3. **Verrucae.** Warts are caused by **papillomaviruses**, which cause epidermal hyperplasia in a characteristic papillary configuration with hyperkeratosis and parakeratosis.

4. **Superficial fungal infections** may be caused by Trichophyton, Microsporum, and Malassezia. Infection is limited to the cornified layer of the epidermis.
   a. **Tinea capitis** ("cradle cap") affects the scalp in children.
   b. **Tinea corporis** infects the trunk and extremities of children. It usually presents as expanding round lesions with erythematous circinate borders.
   c. **Tinea versicolor** causes hypo- or hyperpigmented groups of macules.
   d. **Tinea pedis** causes "athlete's foot."
   e. **Tinea cruris** causes "jock itch."
   f. **Tinea unguium** (onychomycosis) causes thickening and discoloration of the nail bed.

5. **Scalded skin syndrome** is a pediatric condition caused by an exfoliative toxin produced by *S. aureus*. The toxin splits the epidermis at the level of the stratum granulosum, causing a global denudation of the skin.

G. **Hypersensitivity reactions**

1. **Urticaria**, or hives, are usually transient, raised, pruritic, pink wheals characterized by dermal edema.

2. **Eczema** is a class of very common, pruritic skin disorders, characterized by distinctive clinical and pathologic features.
   a. **Clinical forms**
      (1) **Atopic dermatitis** is of variable and often unknown etiology; usually there is a family history of atopy (allergy).

Note

Tinea corporis is also known as "ringworm" and is actually a fungal infection.

(2) **Contact dermatitis** may result from allergic or irritant exposure.
(3) **Lichen simplex chronicus** causes chronic, lichenified plaques, probably caused by rubbing.
(4) **Polymorphous light eruption** is seen after ultraviolet light exposure.
(5) **Drug reactions** resolve when the offending drug is discontinued.
(6) **Exfoliative dermatitis** describes scaling and erythema of the entire skin.

b. **Pathologic types**
(1) **Acute eczema** (i.e., contact dermatitis) describes edematous, oozing, red plaques, often with vesicles and dermal inflammation.
(2) **Subacute eczema** (i.e., childhood atopic dermatitis) is associated with moist, red papules and plaques with epidermal hyperplasia and dermal inflammation.
(3) **Chronic eczema.** Dry, scaly plaques are present for months. Lichenification causes accentuated skin creases and thickened skin.

c. **Treatment.** Moisturizers can be used to control the itching. Oral antihistamines and topical steroids may also be used.

3. **Erythema multiforme**
a. **Pathogenesis.** This may be a hypersensitivity response to drugs (e.g., sulfonamides, penicillins), infections (e.g., herpes, mycoplasma), collagen vascular diseases, or malignancies.
b. **Clinical features.** Erythema multiforme is uncommon. There is often symmetrical involvement of the limbs.
(1) In the minor form, there are few lesions, no systemic symptoms, and the disease is self-limited.
(2) In the major form (**Stevens-Johnson syndrome**), there is fever, respiratory difficulty, widespread skin involvement (including mucous membranes), a high risk of sepsis, and a risk of fatality.
c. **Pathology.** A large erythematous papule that develops central vesiculation; erosion is classic. Lesions are also characterized by edema and inflammatory infiltration.

m. **Psoriasis**

1. **Incidence.** One percent of the population of the United States is affected. The peak incidence is 30 years of age, and the most common form is **psoriasis vulgaris**.

2. **Pathogenesis.** The etiology is unknown, but there is a clear genetic component. Precipitants include hormonal changes, infection, and trauma. Psoriasis may also be associated with arthritis, enteropathy, and myopathy.

3. **Clinical features of psoriasis vulgaris**
a. Lesions are located throughout the body, especially on the nails, knees, elbows, and scalp. They usually do not involve mucous membranes.

IN A NUTSHELL

Erythema multiforme is a hypersensitivity reaction to drugs. Stevens-Johnson syndrome is the severe form.

b. Lesions are well-demarcated coral-colored plaques with **white or silver scale.**

c. The **Auspitz sign** is seen when removal of scale results in pinpoint areas of bleeding. This is characteristic of psoriasis.

4. **Pathologic features of psoriasis vulgaris**

a. Hyperkeratinization with parakeratosis appears in a patchy distribution.

b. Epidermal hyperplasia causes thickening and lengthening of the rete ridges, usually to a uniform depth.

c. Thinning of the surface epidermis, particularly over the dermal papillae, is characteristic.

5. **Treatment** is usually with **topical steroids** and **ultraviolet irradiation.** Severe, systemic disease may be treated with methotrexate.

I. **Inflammatory disorders**

1. **Acne vulgaris** causes comedones, papules, and cysts. It may be related to hormones, drugs, diet, irritants, and genetic factors. An allergy to *Propionibacterium acnes* is clearly involved.

2. **Pityriasis rosea**

a. **Incidence.** This disorder is common, from ages 10–40.

b. **Pathogenesis.** There is a possible viral etiology.

c. **Clinical features.** Pityriasis rosea presents first with a "Herald patch," an approximately 4-cm, red, scaling patch, followed within days by eruption in "turtle neck–short sleeve" distribution. Lesions are small, pink, oval patches along flexural lines (fir tree pattern), appearing in crops. The disease is usually self-limited (1–4 months).

3. **Rosacea**

a. **Incidence.** Rosacea is common from ages 30–50. Women are affected three times more commonly than men, but the syndrome is more severe in men.

b. **Clinical features.** The lesions affect the central face. **Erythema** and **telangiectasias, acneform lesions** (i.e., papules, cysts, pustules), and **rhinophyma** (telangiectasias and hyperplasia of nasal soft tissue) are all seen in various combinations, sometimes causing a severe distortion of the face, particularly the nose.

In a Nutshell

Psoriasis:

- *A silvery, scaly plaque that primarily affects knees, elbows, and the scalp.*
- *Histologically, it is characterized by epidermal hyperplasia and hyperkeratinization.*