USMLE Step 1
Lecture Notes
Pathology

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Authors

Henry Sanchez, M.D.
Professor of Clinical Pathology
University of California, San Francisco
San Francisco, CA

John Barone, M.D.
Anatomic and Clinical Pathologist
Beverly Hills, CA

Contributors

Michael S. Manley, M.D.
Department of Neurosciences
University of California, San Diego
Director, Step 1 Curriculum
Kaplan Medical

Nancy Standler, M.D., Ph.D.
Department of Pathology
W.O. Moss Regional Medical Center
Louisiana State University

Pier Luigi Di Patre, M.D., Ph.D.
Neuropathologist
Institute of Neuropathology
University Hospital of Zürich
Zürich, Switzerland

Director of Medical Curriculum
Mark Tyler-Lloyd, M.D.

Directors of Step 1 Curriculum
Michael S. Manley, M.D.
Leslie D. Manley, Ph.D.

Associate Director of Medical Curriculum
Shefali Vyas, M.D.

Editorial Director
Ruth Baygell

Production Manager
Michael Wolff

Medical Illustrators
Rich LaRocco
Christine Schaar
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These seven volumes of Lecture Notes represent the most-likely-to-be-tested material on the current USMLE Step 1 exam. Please note that these are Lecture Notes, not review books. The Notes were designed to be accompanied by faculty lectures—live, on DVD, or on the web. Reading these Notes without accessing the accompanying lectures is not an effective way to review for the USMLE.

To maximize the effectiveness of these Notes, annotate them as you listen to lectures. To facilitate this process, we’ve created wide, blank margins. While these margins are occasionally punctuated by faculty high-yield “margin notes,” they are, for the most part, left blank for your notations.

Many students find that previewing the Notes prior to the lecture is a very effective way to prepare for class. This allows you to anticipate the areas where you’ll need to pay particular attention. It also affords you the opportunity to map out how the information is going to be presented and what sort of study aids (charts, diagrams, etc.) you might want to add. This strategy works regardless of whether you’re attending a live lecture or watching one on video or the web.

Finally, we want to hear what you think. What do you like about the Notes? What do you think could be improved? Please share your feedback by E-mailing us at medfeedback@kaplan.com.

Thank you for joining Kaplan Medical, and best of luck on your Step 1 exam!

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DEFINITIONS OF PATHOLOGY

1. The study of the essential nature of disease, including symptoms/signs, pathogenes, complications, and morphologic consequences including structural and functional alterations in cells, tissues, and organs.

2. The study of all aspects of the disease process focusing on the pathogenesis leading to classical structural changes (gross and histopathology) as well as molecular alteration.

OVERVIEW OF PATHOLOGY

1. Etiology (cause)
   a. Genetic
   b. Acquired

2. Pathogenesis: temporal sequence and patterns of cellular injury that lead to disease

3. Morphologic changes of the disease process
   a. Gross changes
   b. Microscopic changes

4. Clinical significance
   a. Signs and symptoms of specific diseases
   b. Disease course—complications
   c. Prognosis

METHODS USED IN PATHOLOGY

1. Gross examination of organs
   a. Gross examination of organs on USMLE questions has two major components:
      i. Identifying the organ
      ii. Identifying the pathology
   b. Useful gross features
      i. Size
      ii. Shape
      iii. Consistency
      iv. Color

2. Microscopic examination of tissue
   a. Light microscopy
      i. Hematoxylin and Eosin (H&E)—gold standard stain
Table 1-1. Structures Stained by Hematoxylin and Eosin

<table>
<thead>
<tr>
<th>Hematoxylin</th>
<th>Eosin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stains blue to purple</td>
<td>Stains pink to red</td>
</tr>
<tr>
<td>• Nuclei</td>
<td>• Cytoplasm</td>
</tr>
<tr>
<td>• Nucleoli</td>
<td>• Collagen</td>
</tr>
<tr>
<td>• Bacteria</td>
<td>• Fibrin</td>
</tr>
<tr>
<td>• Calcium</td>
<td>• RBCs</td>
</tr>
<tr>
<td>• Many others</td>
<td>• Thyroid colloid</td>
</tr>
<tr>
<td></td>
<td>• Many others</td>
</tr>
</tbody>
</table>

Common denominator: Hematoxylin binds nucleic acids and calcium salts, while eosin stains the majority of proteins (both extracellular and intracellular).

b. Other histochemical stains (chemical reactions)
   i. Prussian blue—iron
   ii. Congo red—amyloid
   iii. Acid fast (Ziel-Neelson, Fite)—acid-fast bacilli
   iv. Periodic acid-Schiff (PAS)—with high carbohydrate content molecules
   v. Gram stain—bacteria
   vi. Trichrome—cells and connective tissue
   vii. Reticulin—collagen type III molecules

c. Immunohistochemical (antibody) stains
   i. Cytokeratin—epithelial cells
   ii. Vimentin—cells of mesenchymal origin except the three muscle types, stains many sarcomas
   iii. Desmin—smooth, cardiac, and skeletal myosin
   iv. Prostate specific antigen (PSA)
   v. Many others

3. Ancillary techniques
   a. Immunofluorescence microscopy (IFM) is typically used for:
      i. Renal diseases
      ii. Autoimmune diseases
   b. Transmission electron microscopy (TEM) is typically used for:
      i. Renal disease
      ii. Neoplasms
      iii. Infections
      iv. Genetic disorders

4. Molecular techniques
   a. Protein electrophoresis
   b. Southern and Western blots
   c. Polymerase chain reaction (PCR)
   d. Cytogenetic analysis, e.g., karyotyping, in situ hybridization studies
Chapter Summary

* Pathology is the study of disease and concerns itself with the etiology, pathogenesis, morphologic changes, and clinical significance of different diseases.

* Gross examination of organs involves identifying pathologic lesions by evaluating abnormalities of size, shape, consistency, and color.

* Tissue sections stained with hematoxylin (nucleic acids and calcium salts) and eosin (most proteins) are used for routine light microscopic examination.

* Additional techniques that are used to clarify diagnoses in particular settings include histochemical stains, immunohistochemical stains, immunofluorescence microscopy, transmission electron microscopy, and molecular techniques.
Cellular Injury and Adaptation

CAUSES OF CELLULAR INJURY

1. Hypoxia
   a. Most common cause of injury
   b. Definition: lack of oxygen leads to the inability of the cell to synthesize sufficient ATP by aerobic oxidation
   c. Major mechanisms leading to hypoxia
      i. Ischemia: loss of blood supply
         • Most common cause of hypoxia
         • Decreased arterial flow or decreased venous outflow
         • e.g., atherosclerosis, thrombus, thromboembolus
      ii. Cardiopulmonary failure
      iii. Decreased oxygen-carrying capacity of the blood (example: anemia)

2. Infections
   a. Viruses, bacteria, parasites, fungi, and prions
   b. Mechanism of injury
      i. Direct infection of cells
      ii. Production of toxins
      iii. Host inflammatory response

3. Immunologic reactions
   a. Hypersensitivity reactions
   b. Autoimmune diseases

4. Congenital disorders
   a. Inborn errors of metabolism (i.e., inherited disorders [see Chapter 6 for a more detailed discussion of specific genetic disorders])

5. Chemical injury
   a. Drugs
   b. Poisons (cyanide, arsenic, mercury, etc.)
   c. Pollution
   d. Occupational exposure (CCl₄, asbestos, carbon monoxide, etc.)
   e. Social/lifestyle choices (alcohol, cigarette smoking, intravenous drug abuse [IVDA], etc.)

6. Physical forms of injury
   a. Trauma (blunt/penetrating/crush injuries, gunshot wounds, etc.)
   b. Burns
   c. Frostbite

Note
Overview of the Electron Transport Chain

Pathways
NADH → NAD

ETC
Flow of Electricity

O₂ → H₂O
Delivered by Hemoglobin
d. Radiation  
e. Pressure changes  

7. **Nutritional or vitamin imbalance**  
   a. Inadequate calorie/protein intake  
      i. Marasmus (decrease in total caloric intake) and kwashiorkor (decrease in total protein intake)  
      ii. Anorexia nervosa  
   b. Excess caloric intake  
      i. Obesity (second leading cause of premature preventable death in the US)  
      ii. Atherosclerosis  
   c. Vitamin deficiency  
      i. Vitamin A → night blindness, squamous metaplasia, immune deficiency  
      ii. Vitamin C → scurvy  
      iii. Vitamin D → rickets and osteomalacia  
      iv. Vitamin K → bleeding diathesis  
      v. Vitamin B12 → megaloblastic anemia, neuropathy, and spinal cord degeneration  
      vi. Folate → megaloblastic anemia and neural tube defects  
      vii. Niacin → pellagra (diarrhea, dermatitis, and dementia)  
   d. Hypervitaminosis  

**CELLULAR CHANGES DURING INJURY**  

1. General  
   a. Cellular responses to injury  
      i. Adaptation  
      ii. Reversible injury  
      iii. Irreversible injury and cell death (necrosis/apoptosis)  

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**In a Nutshell**  

- **Homeostatic cell**  
- **Metabolic changes**  
  - Ischemia  
  - Toxins, etc.  
- **Adaptation**  
- **Injury**  
- **Reversible changes**  
- **Irreversible changes**  
- **Apoptosis**  
- **Necrosis**  

- **Normal Cell/Tissue**  
  - (homeostasis)  
  - **Stress, increased demand**  
  - **Injurious insult**  
- **Adaptation**  
- **Cell Injury**  
- **Cell Death**  

---  

**Figure 2.1. Cellular Response to Stress and Injurious Stimuli**  

b. Cellular response to injury depends on several important factors  
   i. The *type* of injury  
   ii. The *duration*, including pattern of injury  
   iii. The *severity and intensity* of injury
iv. The type of cell injured
v. The cell’s metabolic state
vi. The cell’s ability to adapt

c. The critical intracellular systems that are susceptible to injury are:
i. DNA
ii. Production of ATP via aerobic respiration
iii. Cell membranes
iv. Protein synthesis

d. Important mechanisms of cell injury
i. Damage to DNA, proteins, lipid membranes, and circulating lipids (LDL) caused by oxygen-derived free radicals
   - Superoxide anion (O$_2$-$^*$)
   - Hydroxyl radical (OH$^-$)
   - Hydrogen peroxide (H$_2$O$_2$)

ii. ATP depletion

iii. Increased cell membrane permeability

iv. Influx of calcium
   - Second messenger
   - Activates a wide spectrum of enzymes
   - Proteases $\rightarrow$ protein breakdown
   - ATPases $\rightarrow$ contributes to ATP depletion
   - Phospholipases $\rightarrow$ cell membrane injury
   - Endonucleases $\rightarrow$ DNA damage

v. Mitochondrial dysfunction
   - Decreased oxidative phosphorylation and ATP production
   - Formation of mitochondrial permeability transition (MPT) channels
   - Release of cytochrome c is a trigger for apoptosis

---

**Note**

**Protective Factors against Free Radicals**

1. Antioxidants
   - Vitamins A, E, and C

2. Superoxide dismutase
   - Superoxide $\rightarrow$ hydrogen peroxide

3. Glutathione peroxidase
   - Hydroxyl ions or hydrogen peroxide $\rightarrow$ water

4. Catalase
   - Hydrogen peroxide $\rightarrow$ oxygen and water

---

**Figure 2-2. Classic Example of Cellular Injury Caused by Hypoxia**
2. Reversible cell injury

**NORMAL**

Normal cell

**REVERSIBLE CELL INJURY**

Injury → Swelling of endoplasmic reticulum mitochondria → Death → Lysosome rupture → Healing

**IRREVERSIBLE INJURY**

Nuclear condensation → Myelin figures → Swelling of endoplasmic reticulum and loss of ribosomes → Membrane blebs → Necrosis → Fragmentation of cell membrane and nucleus → Inflammatory Response

**NECROSIS**

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**Note**

Reversible and irreversible changes represent a spectrum. Keep in mind that any of the reversible changes can become irreversible.

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**Figure 2-3. Cell Injury**

a. Decreased synthesis of ATP by oxidative phosphorylation

b. Decreased function of Na⁺K⁺ ATPase membrane pumps causes:
   i. Influx of Na⁺ and water
   ii. Efflux of K⁺
   iii. Cellular swelling (hydropic swelling)
   iv. Swelling of the endoplasmic reticulum

c. The switch to glycolysis results in:
   i. Depletion of cytoplasmic glycogen
   ii. Increased lactic acid production
   iii. Decreased intracellular pH
d. Decreased protein synthesis
   i. Detachment of ribosomes from the rough endoplasmic reticulum
   e. Plasma-membrane blebs and myelin figures may be seen.

3. Irreversible cell injury
   a. Severe membrane damage
      i. Membrane damage plays a critical role in irreversible injury.
      ii. Membrane injury allows a massive influx of calcium into the cell.
      iii. Efflux of intracellular enzymes and proteins into the circulation
   b. Marked mitochondrial dysfunction
      i. Mitochondrial swelling
      ii. Large densities are seen within the mitochondrial matrix.
      iii. Irreparable damage of the oxidative phosphorylation pathway
      iv. Inability to produce ATP
   c. Rupture of the lysosomes
      i. Release of lysosomal digestive enzymes into the cytosol
      ii. Activation of acid hydrolases followed by autolysis
   d. Nuclear changes (see figure below)
      i. Pyknosis: degeneration and condensation of nuclear chromatin
      ii. Karyorrhexis: nuclear fragmentation
      iii. Karyolysis: dissolution of the nucleus

Clinical Correlate

The loss of membrane integrity (cell death) allows intracellular enzymes to leak out, which can then be measured in the blood. Detection of these proteins in the circulation serves as a clinical marker of cell death and organ injury.

Clinically important examples:

- Myocardial injury: creatine phosphokinase-MB isozyme (CPK-MB), lactate dehydrogenase (LDH), troponin
- Hepatitis: transaminases
- Pancreatitis: amylase and lipase
- Biliary tract obstruction: alkaline phosphatase

Figure 2-4. Nuclear Changes in Irreversible Cell Injury
CELL DEATH

1. Morphologic types of necrosis (cell death in living tissue, often with an inflammatory response)
   a. Coagulative necrosis
      i. Most common form of necrosis, most often due to ischemic injury (infarct)
      ii. Due to the denaturing and coagulation of proteins within the cytoplasm
      iii. Micro: loss of the nucleus but preservation of cellular shape
      iv. Common in most organs, including the heart, liver, and kidney
   b. Liquefaction necrosis
      i. Cellular destruction by hydrolytic enzymes
      ii. Due to autolysis (release of proteolytic enzymes from injured cells) and heterolysis (release of proteolytic enzymes from inflammatory cells)
      iii. Occurs in abscesses, brain infarcts, and pancreatic necrosis
   c. Caseous necrosis
      i. Combination of coagulation and liquefaction necrosis
      ii. Gross: soft, friable, and “cottage cheese–like” appearance
      iii. Characteristic of granulomatous diseases, including tuberculosis
   d. Fat necrosis
      i. Caused by the action of lipases on adipocytes
      ii. Grossly, fat necrosis has a chalky white appearance
   e. Fibrinoid necrosis
      i. Necrotic connective tissue that histologically resembles fibrin
      ii. Micro: has an eosinophilic (pink) homogeneous appearance
      iii. Often due to acute immunologic injury (e.g., hypersensitivity type reactions II and III) and vascular hypertensive damage
   f. Gangrenous necrosis
      i. Gross term used to describe dead tissue
      ii. Common sites: lower limbs, gallbladder, GI tract, and testes
      iii. Dry gangrene: microscopic pattern is coagulative necrosis
      iv. Wet gangrene: microscopic pattern is liquefactive necrosis

2. Apoptosis
   a. Specialized form of programmed cell death without an inflammatory response
   b. Apoptosis is an active process regulated by genes and involves RNA and protein synthesis.
   c. Often affects only single cells or small groups of cells
   d. Morphologic appearance
      i. Cell shrinks in size and has dense eosinophilic cytoplasm.
      ii. Nuclear chromatin condensation followed by fragmentation
      iii. Formation of cytoplasmic membrane blebs
      iv. Breakdown of the cell into fragments (apoptotic bodies)
      v. Phagocytosis of apoptotic bodies by adjacent cells or macrophages
      vi. A lack of an inflammatory response
e. Stimulus for apoptosis
i. Cell injury and DNA damage
ii. Lack of hormones, cytokines, or growth factors
iii. Receptor-ligand signals
   • Fas binding to the Fas ligand
   • Tumor necrosis factor (TNF) binding to TNF receptor 1 (TNFR1)
f. Apoptosis is regulated by genes
i. bcl-2 (inhibits apoptosis)
   • Prevents release of cytochrome c from mitochondria
   • Binds pro-apoptotic protease activating factor (ApaF-1)
ii. p-53 (stimulates apoptosis)
   • Elevated by DNA injury and arrests the cell cycle
   • If DNA repair is impossible, p53 stimulates apoptosis.
g. Execution of apoptosis
i. Mediated by a cascade of caspases
ii. Caspases digest nuclear and cytoskeletal proteins
iii. Caspases also activate endonucleases
h. Physiologic examples of apoptosis
i. Embryogenesis: organogenesis and development
ii. Hormone-dependent apoptosis (menstrual cycle)
iii. Thymus: selective death of lymphocytes
i. Pathologic examples of apoptosis
i. Viral diseases: viral hepatitis (Councilman body)
ii. Graft versus host disease
iii. Cystic fibrosis: duct obstruction and pancreatic atrophy

3. Serum enzyme markers of cell damage
a. Aspartate aminotransferase (AST) – liver injury
b. Alanine aminotransferase (ALT) – liver injury
c. Creatine kinase (CK-MB) – heart injury
d. Amylase and lipase – pancreatic injury; amylase also rises with salivary gland injury

CELLULAR ADAPTIVE RESPONSES TO INJURY

1. General
a. Cellular adaptation is the result of a persistent stress or injury.
b. Adaptive responses are potentially reversible once the stress has been removed.
c. Some forms of adaptation may precede or progress to neoplasia.
2. Atrophy
   a. Definition: decrease in cell/organ size and functional ability
   b. Causes of atrophy
      i. Decreased workload/disuse (immobilization)
      ii. Ischemia (atherosclerosis)
      iii. Lack of hormonal or neural stimulation
      iv. Malnutrition
      v. Aging
   c. Micro: small shrunken cells with lipofuscin granules
   d. EM: decreased intracellular components and autophagosomes

3. Hypertrophy
   a. Definition: an increase in cell size and functional ability due to increased synthesis of intracellular components
   b. Causes of hypertrophy
      i. Increased mechanical demand
         • Physiologic → striated muscle of weight lifters
         • Pathologic → cardiac muscle in hypertension
      ii. Increased endocrine stimulation
         • Puberty (growth hormone, androgens/estrogens, etc.)
         • Gravid uterus (estrogen)
         • Lactating breast (prolactin and estrogen)
   c. Hypertrophy is mediated by
      i. Growth factors, cytokines, and other trophic stimuli
      ii. Increased expression of genes and increased protein synthesis
   d. Hypertrophy and hyperplasia often occur together.
4. Hyperplasia
   a. Definition: an increase in the number of cells in a tissue or organ
   b. Some cell types are unable to exhibit hyperplasia (e.g., nerve, cardiac, skeletal muscle cells).
   c. Physiologic causes of hyperplasia
      i. Compensatory (e.g., after partial hepatectomy)
      ii. Hormonal stimulation (e.g., breast development at puberty)
      iii. Antigenic stimulation (e.g., lymphoid hyperplasia)
   d. Pathologic causes of hyperplasia
      i. Endometrial hyperplasia
      ii. Prostatic hyperplasia of aging
   e. Hyperplasia is mediated by
      i. Growth factors, cytokines, and other trophic stimuli
      ii. Increased expression of growth-promoting genes (proto-oncogenes)
      iii. Increased DNA synthesis and cell division

5. Metaplasia
   a. Definition: a reversible change of one cell type to another, usually in response to irritation
   b. It has been suggested that the replacement cell is better able to tolerate the environmental stresses.
   c. For example, bronchial epithelium undergoes squamous metaplasia in response to the chronic irritation of tobacco smoke.
   d. Proposed mechanism: the reserve cells (or stem cells) of the irritated tissue differentiate into a more protective cell type due to the influence of growth factors, cytokines, and matrix components

6. Dysplasia
   a. Definition: an abnormal proliferation of cells that is characterized by changes in cell size, shape, and loss of cellular organization
   b. Dysplasia is not cancer but may progress to cancer (preneoplastic lesion).
   c. Examples: cervical dysplasia, actinic (solar) keratosis, and oral leukoplakia

OTHER CELLULAR ALTERATIONS DURING INJURY

1. Intracellular accumulations
   a. Lipids
      i. Triglycerides (e.g., fatty change in liver cells)
      ii. Cholesterol (e.g., atherosclerosis, xanthomas)
      iii. Complex lipids (e.g., sphingolipid accumulation)
   b. Proteins
      i. Protein accumulates in proximal renal tubules in proteinuria.
      ii. Russell bodies: intracytoplasmic accumulation of immunoglobulins in plasma cells
   c. Glycogen storage diseases (see Chapter 6)
d. Exogenous pigments
   i. Anthracotic pigmentation of the lung is secondary to the inhalation of carbon
dust
   ii. Tattoos
   iii. Ingestion of lead (e.g., gingival lead line, renal tubular lead deposits)
e. Endogenous pigments
   i. Lipofuscin
      • Wear and tear pigment
      • Perinuclear yellow-brown pigment
      • Indigestible material within lysosomes
      • Common in the liver and heart
   ii. Melanin
      • Black-brown pigment derived from tyrosine
      • Found in melanocytes and substantia nigra
   iii. Hemosiderin
      • Golden yellow-brown granular pigment
      • Found in areas of hemorrhage or bruises
      • Systemic iron overload → hemosiderosis (increase in total body iron stores
without tissue injury) → hemochromatosis (increase in total body iron
stores with tissue injury)
      • Prussian blue stain
   iv. Bilirubin accumulates in newborns in the basal ganglia, causing permanent
damage (kernicterus)
2. Hyaline change
   a. Definition: nonspecific term used to describe any intracellular or extracellular
alteration that has a pink homogenous appearance (proteins) on H&E stains
   b. Examples of intracellular hyaline
      i. Renal proximal tubule protein reabsorption droplets
      ii. Russell bodies
      iii. Alcoholic hyaline
   c. Examples of extracellular hyaline
      i. Hyaline arteriolosclerosis
      ii. Amyloid
      iii. Hyaline membrane disease of the newborn
3. Pathologic forms of calcification
   a. Dystrophic calcification
      i. Definition: precipitation of calcium phosphate in dying or necrotic tissues
      ii. Examples
         • Fat necrosis → saponification
         • Psammoma bodies = laminated calcifications that occur in meningiomas
and papillary carcinomas of the thyroid and ovary
         • Mönckeberg medial calcific sclerosis
         • Atherosclerotic plaques
b. Metastatic calcification
   i. Definition: precipitation of calcium phosphate in normal tissue due to hypercalcemia (supersaturated solution)
   ii. Causes
      • Hyperparathyroidism
      • Parathyroid adenomas
      • Renal failure
      • Paraneoplastic syndrome
      • Vitamin D intoxication
      • Milk-alkali syndrome
      • Sarcoidosis
      • Paget disease
      • Multiple myeloma
      • Metastatic cancer to the bone
   iii. Location of calcifications: interstitial tissues of the stomach, kidneys, lungs, and blood vessels

Chapter Summary

* Cells can be damaged by a variety of mechanisms.
* Hypoxia causes a loss of ATP production secondary to oxygen deficiency and can be caused by ischemia, cardiopulmonary failure, or decreased oxygen-carrying capacity of the blood.
* Infections can injure cells directly, or indirectly, via toxin production or host inflammatory response.
* Hypersensitivity reactions and autoimmune diseases may kill or injure cells.
* Congenital causes of cellular injury include enzyme defects, structural protein defects, chromosomal disorders, and congenital malformations.
* Chemical agents, physical agents, and nutritional imbalances can also injure cells.
* The response of cells to an insult depends on both the state of the cell and the type of insult. The response can range from adaptation to reversible injury to irreversible injury with cell death.
* Intracellular sites and systems particularly vulnerable to injury include DNA, ATP production, cell membranes, and protein synthesis.
* Reversible cell injury is primarily related to decreased ATP synthesis by oxidative phosphorylation, leading to cellular swelling and inadequate protein synthesis.
* Irreversible cell injury often additionally involves severe damage to membranes, mitochondria, lysosomes, and nucleus.
* Death of tissues (necrosis) can produce a variety of histologic patterns, including coagulative necrosis, liquefaction necrosis, caseous necrosis, fibrinoid necrosis, and gangrenous necrosis, often with an inflammatory response.
* Apoptosis is a specialized form of programmed cell death that can be regulated genetically or by cellular or tissue triggers without an inflammatory response.
Inflammation

ACUTE INFLAMMATION

1. General
   a. Acute inflammation is an immediate response to injury, which is part of the innate immunity.
   b. Short duration
   c. Cardinal signs of inflammation
      i. Rubor (redness)
      ii. Calor (heat)
      iii. Tumor (swelling)
      iv. Dolor (pain)
      v. Functio laesa (loss of function)

   Note
   Important components of acute inflammation
   - Hemodynamic changes
   - Neutrophils
   - Chemical mediators

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Figure 3-1. Adaptive Immunity
2. Hemodynamic changes
   a. Initial transient vasoconstriction
   b. Massive vasodilatation mediated by histamine, bradykinin, and prostaglandins
   c. Increased vascular permeability
      i. Chemical mediators of increased permeability
         • Vasoactive amines, histamine, and serotonin
         • Bradykinin, an end-product of the kinin cascade
         • Leukotrienes (e.g., LTC4, LTD4, LTE4)
      ii. Mechanism of increased vascular permeability
         • Endothelial cell and pericyte contraction
         • Direct endothelial cell injury
         • Leukocyte injury of endothelium
   d. Blood flow slows (stasis) due to increased viscosity, allows neutrophils to marginate

**NEUTROPHILS**

1. Important cells in acute inflammation
   a. Neutrophils (life span in tissue 1–2 days)
      i. Synonyms: segmented neutrophils, polymorphonuclear leukocytes (PMN)
      ii. Primary (azurophilic) granules
         • Myeloperoxidase
         • Phospholipase A2
         • Lysozyme (damages bacterial cell walls by catalyzing hydrolysis of 1,4-beta-linkages)
         • Acid hydrolases
         • Elastase
         • Defensins (microbicidal peptides active against many gram-negative and gram-positive bacteria, fungi, and enveloped viruses)
         • Bactericidal permeability increasing protein (BPI)
      iii. Secondary (specific) granules
         • Phospholipase A2
         • Lysozyme
         • Leukocyte alkaline phosphatase (LAP)
         • Collagenase
         • Lactoferrin (chelates iron)
         • Vitamin B12 binding proteins
   b. Macrophages (life span in tissue compartment is 60–120 days)
      i. Acid hydrolases
      ii. Elastase
      iii. Collagenase

2. Neutrophil margination and adhesion
   a. Adhesion is mediated by complementary molecules on the surface of neutrophils and endothelium
      i. Step 1: At sites of inflammation, the endothelial cells have increased expression of E-selectin and P-selectin.
ii. Step 2: Neutrophils weakly bind to the endothelial selectins and roll along the surface.

iii. Step 3: Neutrophils are stimulated by chemokines to express their integrins.

iv. Step 4: Binding of the integrins firmly adheres the neutrophil to the endothelial cell.

Table 3-1. Selectin and Integrin Distribution in the Endothelium and Leukocyte

<table>
<thead>
<tr>
<th></th>
<th>Endothelium</th>
<th>Leukocyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selectins</td>
<td>P-Selectin</td>
<td>Sialyl-Lewis X &amp; PSGL-1</td>
</tr>
<tr>
<td></td>
<td>E-Selectin</td>
<td>Sialyl-Lewis X &amp; PSGL-1</td>
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<tr>
<td></td>
<td>GlyCam-1/CD34</td>
<td>L-Selectin</td>
</tr>
<tr>
<td>Integrins</td>
<td>ICAM-1</td>
<td>LFA-1 &amp; MAC-1</td>
</tr>
<tr>
<td></td>
<td>VCAM-1</td>
<td>VLA-4</td>
</tr>
</tbody>
</table>

![Diagram](image)

Figure 3-2. Adhesion and Migration

b. Modulation of adhesion molecules in inflammation

i. Redistribution to the surface: P-selectin is normally present in the Weibel-Palade bodies of endothelial cells and can be redistributed to the cell surface with exposure to inflammatory mediators such as histamine and thrombin.

ii. Additional synthesis: Cytokines IL-1 and TNF induce production of E-selectin, ICAM-1, and VCAM-1 in endothelial cells.
iii. Increased binding affinity: Chemotactic agents cause a conformational change in the leukocyte integrin 1.β1, which is converted to a high-affinity binding state.

c. Defects in adhesion
   i. Diabetes mellitus
   ii. Corticosteroid use
   iii. Acute alcohol intoxication
   iv. Leukocyte adhesion deficiency
      • Autosomal recessive
      • Recurrent bacterial infections

3. Emigration (diapedesis)
   a. Leukocytes emigrate from the vasculature (postcapillary venule) by extending pseudopods between the endothelial cells.
   b. They then move between the endothelial cells, migrating through the basement membrane toward the inflammatory stimulus.

4. Chemotaxis
   a. Chemotaxis is the attraction of cells toward a chemical mediator that is released in the area of inflammation.
   b. Important chemotactic factors for neutrophils
      i. Bacterial products, such as N-formyl-methionine
      ii. Leukotriene B4 (LTB4)
      iii. Complement system product C5a
      iv. α-Chemokines (IL-8)

5. Phagocytosis and degranulation
   a. Opsonins enhance recognition and phagocytosis of bacteria
   b. Important opsonins
      i. Fc portion of IgG
      ii. Complement system product C3b
      iii. Plasma protein—collectins (bind to bacterial cell walls)
   c. Engulfment
      i. Neutrophil sends out cytoplasmic processes that surround the bacteria.
      ii. The bacteria are internalized within a phagosome.
      iii. The phagosome fuses with lysosomes (degranulation).
   d. Defects in phagocytosis
      i. Chediak-Higashi syndrome
         • Autosomal recessive
         • Neutropenia
         • Neutrophils have giant granules (lysosomes)
         • Defect in chemotaxis and degranulation
6. Intracellular killing
   a. Oxygen-dependent killing
      i. Respiratory burst
         • Requires oxygen and NADPH oxidase
         • Produces superoxide, hydroxyl radicals, and hydrogen peroxide
      ii. Myeloperoxidase
         • Requires hydrogen peroxide and halide (Cl\(^{-}\))
         • Produces HOCl (hypochlorous acid)

   Figure 3-3. Oxygen-Dependent Killing

b. Oxygen-independent killing
   i. Lysozyme
   ii. Lactoferrin
   iii. Acid hydrolases
   iv. Bactericidal permeability increasing protein (BPI)
   v. Defensins

c. Deficiency of oxygen-dependent killing
   i. Chronic granulomatous disease of childhood
      • X-linked or autosomal recessive
      • Deficiency of NADPH oxidase
      • Lack of superoxide and hydrogen peroxide
      • Recurrent bacterial infections with catalase-positive organisms (S. aureus)
      • The nitroblue tetrazolium test will be negative.
   ii. Myeloperoxidase deficiency
      • Autosomal recessive
      • Infections with Candida
CHEMICAL MEDIATORS OF INFLAMMATION

1. Vasoactive amines
   a. Histamine
      i. Produced by basophils, platelets, and mast cells
      ii. Effect: vasodilation and increased vascular permeability
      iii. Triggers for release
         • IgE-mediated mast cell reactions
         • Physical injury
         • Anaphylatoxins (C3a and C5a)
         • Cytokines (IL-1)
   b. Serotonin
      i. Produced by platelets
      ii. Effect: vasodilation and increased vascular permeability

2. The kinin system
   a. Activated Hageman factor (factor XII) converts prekallikrein $\rightarrow$ kallikrein
   b. Kallikrein cleaves high molecular weight kininogen (HMWK) $\rightarrow$ bradykinin
   c. Effects of bradykinin
      i. Increases vascular permeability
      ii. Pain
      iii. Vasodilation
      iv. Bronchoconstriction

CELLULAR

- Newly synthesized
- Preformed mediators in secretory granules

LIVER (major source)

- PLASMA
- Complement activation
- Factor XII (Hageman factor) activation

MEDIATORS
- Prostaglandins
- Leukotrienes
- Platelet-activating factors
- Activated oxygen species
- Nitric oxide
- Cytokines

MEDIATORS
- Histamine
- Serotonin
- Lysosomal enzymes

SOURCE
- Mast cells, basophils, platelets
- Neutrophils, macrophages

MEDIATORS
- Kinin system
- (bradykinin)
- Coagulation/ fibrinolysis system
- Anaphylatoxins
- C3b
- C9b,9 (membrane attack complex)

Figure 3-4. Sources of Chemical Mediators of Inflammation
3. **Arachidonic acid products**
   
a. Cyclooxygenase pathway
   
i. Thromboxane A2
      - Produced by platelets
      - Vasoconstriction and platelet aggregation
   
ii. Prostacyclin (PGI2)
      - Produced by vascular endothelium
      - Vasodilation and inhibits platelet aggregation
   
iii. Prostaglandin E2: pain
   
iv. Prostaglandins PGE2, PGD2, and PGF2: vasodilatation
   
b. Lipooxygenase pathway
   
i. Leukotriene B4 (LTB4): neutrophil chemotaxis
   
ii. Leukotriene C4, D4, E4: vasoconstriction

4. **The complement cascade**
   
a. Important products
   
i. C5b-C9 — membrane attack complex
   
ii. C3a,C5a — anaphylotoxins stimulate the release of histamine
   
iii. C5a — leukocyte chemotactic factor
   
iv. C3b — opsonin for phagocytosis

5. **Cytokines**
   
a. IL-1 and TNF
   
i. Fever and acute phase reactants
   
ii. Enhances adhesion molecules
   
   iii. Stimulates and activates fibroblasts, endothelial cells, and neutrophils
   
   b. IL-8 neutrophil chemoattractant produced by macrophages

---

**In a Nutshell**

*Mediators of Pain*

- Bradykinin
- Prostaglandins (E2)

**In a Nutshell**

*Mediators of Fever*

- Cytokines IL-1, IL-6, and TNF-α
- Prostaglandins

---

**FOUR OUTCOMES OF ACUTE INFLAMMATION**

1. Complete resolution with regeneration
2. Complete resolution with scarring
3. Abscess formation
4. Transition to chronic inflammation

**CHRONIC INFLAMMATION**

1. Causes of chronic inflammation
   
a. Following a bout of acute inflammation
   
b. Persistent infections
   
c. Infections with certain organisms
      
i. Viral infections
      
ii. Mycobacteria
iii. Parasitic infections
iv. Fungal infections
d. Autoimmune diseases
e. Response to foreign material
f. Response to malignant tumors

2. Important cells in chronic inflammation

a. Macrophages
i. Macrophages are derived from blood monocytes.
ii. Tissue-based macrophages (life span in connective tissue compartment is 60–120 days)
   • Connective tissue (histiocyte)
   • Lung (pulmonary alveolar macrophages)
   • Liver (Kupffer cells)
   • Bone (osteoclasts)
   • Brain (microglia)
iii. During inflammation macrophages are mainly recruited from the blood (circulating monocytes).
iv. Chemotactic factors: C5a, MCP-1, MIP-1α, PDGF, TGF-β
v. Secretes a wide variety of active products (monokines)
vi. May be modified into an epithelioid cell in granulomatous processes

b. Lymphocytes
i. B cells and plasma cells
ii. T cells
iii. Lymphocyte chemokine: lymphotaxin

c. Eosinophils
i. Play an important role in parasitic infections and IgE-mediated allergic reactions
ii. Eosinophilic chemokine: eotaxin
iii. Granules contain major basic protein, which is toxic to parasites
d. Basophils
i. Basophils contain similar chemical mediators as mast cells in their granules.
ii. Mast cells are present in high numbers in the lung and skin.
iii. Play an important role in IgE-mediated reactions (allergies and anaphylaxis)
iv. Release histamine

3. Chronic granulomatous inflammation
a. Definition: specialized form of chronic inflammation characterized by small aggregates of modified macrophages (epithelioid cells and multinucleated giant cells) usually populated by CD4+ Th1 lymphocytes
b. Composition of a granuloma
i. Epithelioid cell
   • IFN-γ transforms macrophages → epithelioid cells
   • Enlarged cell with abundant pink cytoplasm
ii. Multinucleated giant cells
   • Formed by the fusion of epithelioid cells
   • Langhans-type giant cell (peripheral arrangement of nuclei)
   • Foreign body type giant cell (haphazard arrangement of nuclei)

iii. Lymphocytes and plasma cells

iv. Central caseous necrosis
   • Present in granulomas due to tuberculosis
   • Is found in other granulomatous diseases as well

---

Figure 3-5. Granuloma Formation

c. Granulomatous diseases
   i. Tuberculosis (caseating granulomas)
   ii. Cat-scratch fever
   iii. Syphilis
   iv. Leprosy
   v. Fungal infections (e.g., coccidiodomycosis)
   vi. Parasitic infections (e.g., schistosomiasis)
   vii. Foreign bodies
   viii. Beryllium
   ix. Sarcoidosis
Tissue Responses to Infectious Agents

1. General
   a. Infectious diseases are very prevalent worldwide and are a major cause of morbidity and mortality.
   b. Infectious agents tend to have tropism for specific tissues and organs.

2. Six major histologic patterns
   a. Exudative inflammation
      i. Acute inflammatory response with neutrophils
         • Bacterial meningitis
         • Bronchopneumonia
         • Abscess
   b. Necrotizing inflammation
      i. Virulent organism producing severe tissue damage and extensive cell death
         • Necrotizing fasciitis
         • Necrotizing pharyngitis
   c. Granulomatous inflammation
      i. Granulomatous response predominates
      ii. Slow-growing organisms
         • Mycobacteria
         • Fungi
         • Parasites
   d. Interstitial inflammation
      i. Diffuse mononuclear interstitial infiltrate
      ii. Common response to viral infectious agents
         • Myocarditis (Coxsackie virus)
         • Viral hepatitis
   e. Cytopathic/cytoproliferative inflammation
      i. Definition: infected/injured cell is altered
      ii. Intranuclear/cytoplasmic inclusions
         • Cytomegalic inclusion disease
         • Rabies—Negri body
      iii. Syncytia formation
         • Respiratory syncytial virus
         • Herpes virus
      iv. Apoptosis: Councilman body in viral hepatitis
   f. No inflammation
      i. Definition: no evidence of an inflammatory response to presence of microbes
      ii. Will occur in severely immunosuppressed individuals due to primary immunodeficiencies or acquired immunodeficient states (e.g., AIDS)
Chapter Summary

- Acute inflammation is an immediate response to injury that can cause redness, heat, swelling, pain, and loss of function.

- Hemodynamic changes in acute inflammation are mediated by vasoactive chemicals and, after a transient initial vasoconstriction, produce massive dilation with increased vascular permeability.

- Neutrophils are important white blood cells in acute inflammation that contain granules with many degradative enzymes.

- Neutrophils leave the bloodstream in a highly regulated process involving margination (moving toward the vessel wall), adhesion (binding to the endothelium), and emigration (moving between endothelial cells to leave the postcapillary venule). Defects in adhesion can contribute to the immunosuppression seen in diabetes mellitus and corticosteroid use.

- Chemotaxis is the attraction of cells toward a chemical mediator, which is released in the area of inflammation.

- The phagocytosis of bacteria by neutrophils is improved if opsonins, such as the Fc portion of immunoglobulin (Ig) G or the complement product C3b, are bound to the surface of the bacteria. Chediak-Higashi syndrome is an example of a genetic disease with defective neutrophil phagocytosis.

- Once a bacterium has been phagocytized, both oxygen-requiring and oxygen-independent enzymes can contribute to the killing of the bacteria. Chronic granulomatous disease of childhood and myeloperoxidase deficiency are genetic immunodeficiencies related to a deficiency of oxygen-dependent killing.

- Chemical mediators of inflammation include vasoactive amines, the kinin system, arachidonic acid products, the complement cascade, coagulation/fibrinolytic cascade, and cytokines.

- Acute inflammation may lead to tissue regeneration, scarring, abscess formation, or chronic inflammation.

- Cells important in chronic inflammation include macrophages, lymphocytes, eosinophils, and basophils.

- Chronic granulomatous inflammation is a specialized form of chronic inflammation with modified macrophages (epithelioid cells and multinucleated giant cells) usually surrounded by a rim of lymphocytes. A wide variety of diseases can cause chronic granulomatous inflammation, most notably tuberculosis, syphilis, leprosy, and fungal infections.

- Patterns of tissue response to infectious agents can include exudative inflammation, necrotizing inflammation, granulomatous inflammation, interstitial inflammation, cytopathic/cytoproliferative inflammation, and no inflammatory response.
Tissue Repair

REGENERATION AND HEALING

1. Tissue repair
   a. Regeneration and healing of damaged cells and tissues starts almost as soon as the inflammatory process begins.
   b. Tissue repair involves five overlapping processes
      i. Hemostasis—coagulation, platelets
      ii. Inflammation—neutrophils, macrophages, lymphocytes, mast cells
      iii. Regeneration—stem cells and differentiated cells
      iv. Fibrosis—macrophages, granulation tissue (fibroblasts, angiogenesis), type III collagen
      v. Remodeling—macrophages, fibroblasts, converting collagen III to I

2. Regeneration
   a. Different tissues have different regenerative capacities.
   b. Labile cells (primarily stem cells)
      i. Regenerate throughout life
      ii. Examples: surface epithelial cells (skin and mucosal lining cells), hematopoietic cells, stem cells, etc.
   c. Stable cells (stem cells and differentiated cells)
      i. Replicate at a low level throughout life
      ii. Have the capacity to divide if stimulated by some initiating event
      iii. Examples: hepatocytes, proximal tubule cells, endothelium, etc.
   d. Permanent cells (few stem cells and/or differentiated cells with the capacity to replicate)
      i. Very low level of replicative capacity
      ii. Examples: neurons and cardiac muscle

3. Fibrosis and remodeling phases
   a. Replacement of a damaged area by a connective tissue scar
   b. Tissue repair is mediated by various growth factors and cytokines primarily from macrophages.
      i. Transforming growth factor (TGF-β)
      ii. Platelet-derived growth factor (PDGF)
      iii. Fibroblast growth factor (FGF)
      iv. Vascular endothelial growth factor (VEGF)
      v. Epidermal growth factor (EDF)
      vi. Tumor necrosis factor (TNF-α) and IL-1
c. Granulation tissue
   i. Synthetically active fibroblasts
   ii. Capillary proliferation

d. Wound contraction is mediated by myofibroblasts

e. Scar formation

4. Primary union (healing by first intention)
   a. Definition: occurs with clean wounds when there has been little tissue damage and
      the wound edges are closely approximated
   b. The classic example is a surgical incision.

5. Secondary union (healing by secondary intention)
   a. Definition: occurs in wounds that have large tissue defects and when the two edges
      of the wound are not in contact
   b. It requires larger amounts of granulation tissue to fill in the defect.
   c. Often accompanied by significant wound contraction
   d. Often results in larger residual scars

6. Repair in specific organs
   a. Liver
      i. Mild injury is repaired by regeneration of hepatocytes, sometimes with restora-
         tion to normal pathology.
      ii. Severe or persistent injury causes formation of regenerative nodules that may
         be surrounded by fibrosis, leading to hepatic cirrhosis.
   b. Brain
      i. Neurons do not regenerate, but microglia remove debris and astrocytes prolif-
         erate, causing gliosis.
   c. Heart
      i. Damaged heart muscle cannot regenerate, so the heart heals by fibrosis.

6. Lung
   a. Type II pneumocytes replace both type I and type II pneumocytes after injury.
   b. Peripheral nerves
      i. Distal part of the axon degenerates
      ii. Proximal part regrows slowly using axonal sprouts to follow Schwann cells to
          the muscle.

ABERRATIONS IN WOUND HEALING

1. Delayed wound healing
   a. Wound healing may be prolonged by foreign bodies, infection, ischemia, diabetes,
      malnutrition, scurvy, etc.

2. Hypertrophic scar
   a. Results in a prominent scar that is localized to the wound
   b. Excess production of granulation tissue and collagen

3. Keloid
   a. Genetic predisposition
   b. More common in African Americans
   c. Tends to affect the earlobes, face, neck, sternum, and forearms
   d. May produce large tumor-like scars, which often extend beyond the injury site
   e. Excess production of collagen that is predominantly type III
CONNECTIVE TISSUE COMPONENTS

1. Collagen (over 29 types)
   a. Type I
      i. Most common
      ii. High tensile strength
      iii. Skin, bone, tendons, and most organs
   b. Type II: cartilage and vitreous humor
   c. Type III: granulation tissue, embryonic tissue, uterus, keloids
   d. Type IV: basement membranes
   e. Hydroxylation of collagen is mediated by vitamin C
   f. Cross-linking of collagen is performed by lysyl oxidase. Copper is a required cofactor.

2. Other extracellular matrix components
   a. Elastic fibers
      i. Elastin proteins are aligned on a fibrillin framework.
      ii. Defects in fibrillin are found in Marfan syndrome.
   b. Adhesion molecules
      i. Fibronectin
      ii. Laminin
   c. Proteoglycans and glycosaminoglycans
      i. Heparan sulfate
      ii. Chondroitin sulfate

3. Basement membranes
   a. The basement membrane has a net negative charge.
   b. Composition of basement membranes
      i. Collagen type IV
      ii. Proteoglycans (heparan sulfate)
      iii. Laminin
      iv. Fibronectin
      v. Entactin

Clinical Correlate

Scurvy: Vitamin C deficiency first affects collagen with highest hydroxyproline content, such as that found in blood vessels. Thus, an early symptom is bleeding gums.

Ehlers-Danlos (ED) Syndrome: Defect in collagen synthesis or structure. Some nine types. ED type IV is a defect in type III collagen.

Osteogenesis Imperfecta: Defect in collagen type I
Chapter Summary

* Tissue repair involves regeneration of the damaged tissue by cells of the same type and healing with replacement by connective tissue.

* Tissue repair involves five overlapping processes including hemostasis, inflammation, regeneration, fibrosis, and remodeling.

* Tissues vary in their regenerative capacities. Labile cell populations that regenerate throughout life include surface epithelial cells, hematopoietic cells, and stem cells. Stable cells that replicate at a low level throughout life, but can divide if stimulated, include hepatocytes, proximal tubule cells, and endothelial cells. Permanent cells that cannot replicate in adult life include neurons and cardiac muscle.

* Healing with replacement of a damaged area by a connective tissue scar is mediated by many growth factors and cytokines, primarily from macrophages. Initially granulation tissue forms, which later undergoes wound contraction mediated by myofibroblasts, eventually resulting in true scar formation.

* Wound healing by first intention (primary union) occurs after clean wounds have been closely approximated. Wound healing by second intention (secondary union) occurs in wounds with larger defects in which the edges cannot be closely approximated.

* Problems that can occur with wound healing include delayed wound healing, hypertrophic scar formation, and keloid formation.

* Different types of collagen are found in different body sites. Type I collagen is the most common form. Type II collagen is found in cartilage. Type III collagen is an immature form found in granulation tissue. Type IV collagen is found in basement membranes. Collagen production requires vitamin C and copper.

* Other extracellular matrix components include elastic fibers, adhesion molecules, and proteoglycans and glycosaminoglycans.

* Basement membranes have a net negative charge and are composed of collagen and other extracellular matrix components.
Circulatory Pathology

EDEMA

1. Definition: presence of excess fluid in the intercellular space
2. Causes of edema include:
   a. Increased hydrostatic pressure
      i. Congestive heart failure (generalized edema)
      ii. Portal hypertension
      iii. Renal retention of salt and water
      iv. Venous thrombosis (local edema)
   b. Hypoalbuminemia and decreased colloid osmotic pressure
      i. Liver disease
      ii. Nephrotic syndrome
      iii. Protein deficiency (e.g., kwashiorkor)
   c. Lymphatic obstruction (lymphedema)
      i. Tumor
      ii. Surgical removal of lymph node drainage
      iii. Parasitic infestation (filaria → elephantiasis)
   d. Increased endothelial permeability
      i. Inflammation
      ii. Type I hypersensitivity reactions
      iii. Drugs (e.g., bleomycin, heroin, etc.)
   e. Increased interstitial sodium
      i. Increased sodium intake
      ii. Primary hyperaldosteronism
      iii. Renal failure
   f. Specialized form of tissue swelling due to increased extracellular glycosaminoglycans
      i. Pretibial myxedema and exophthalmos (Graves disease)
3. Anasarca: severe generalized edema
4. Effusion: fluid within the body cavities
5. Types of edema fluid
   a. Transudate
      i. Edema fluid with low protein content
      ii. Specific gravity <1.020
   b. Exudate
      i. Edema fluid with high protein content and cells

Note
Edema can be localized or generalized, depending on the etiology and severity.
ii. Specific gravity >1.020
iii. Types of exudates
   • Purulent (pus)
   • Fibrinous
   • Eosinophilic
   • Hemorrhagic

   c. Lymphedema related to lymphatic obstruction
      i. Protein-rich fluid produces non-pitting edema
   d. Glycosaminoglycan-rich edema fluid
      i. Increased hyaluronic acid and chondroitin sulfate causes myxedema

6. Active hyperemia versus congestion (passive hyperemia)
   a. Definition: an excessive amount of blood in a tissue or organ secondary to vasodilatation (active) or diminished venous outflow (passive)

<table>
<thead>
<tr>
<th>Table 5-1. Properties of Active Hyperemia and Congestion (Passive Hyperemia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
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<tr>
<td>Mechanism</td>
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<tr>
<td>Examples</td>
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</tr>
</tbody>
</table>

**HEMOSTASIS AND BLEEDING DISORDERS**

1. Hemostasis
   a. Definition: sequence of events leading to the cessation of bleeding by the formation of a stable fibrin-platelet hemostatic plug
   b. Hemostasis involves interactions between the vascular wall, platelets, and the coagulation system.

2. Vascular wall injury
   a. Transient vasoconstriction is mediated by endothelin-1.
   b. Thrombogenic factors
      i. Changes in blood flow cause turbulence and stasis, which favors clot formation.
      ii. Release of tissue factor from injured cells activates factor VII (extrinsic pathway).
      iii. Exposure of thrombogenic subendothelial collagen activates factor XII (intrinsic pathway).
      iv. Release of von Willebrand factor (vWF), which binds to exposed collagen and facilitates platelet adhesion
      v. Decreased endothelial synthesis of antithrombogenic substances (prostacyclin, nitric oxide [NO]), tissue plasminogen activator, and thrombomodulin
3. Platelets
   a. Derived from megakaryocytes in the bone marrow
   b. **Step 1: platelet adhesion**
      i. First, vWF adheres to subendothelial collagen.
      ii. Platelets then adhere to vWF by glycoprotein Ib.
   c. **Step 2: platelet activation**
      i. Platelets undergo a shape change and degranulation occurs.

Table 5-2. Contents of Platelet Alpha Granules and Dense Bodies

<table>
<thead>
<tr>
<th>Alpha Granules</th>
<th>Dense Bodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>· Fibrinogen</td>
<td>· ADP (potent platelet aggregator)</td>
</tr>
<tr>
<td>· Fibronectin</td>
<td>· Calcium</td>
</tr>
<tr>
<td>· Factor V and vWF</td>
<td>· Histamine and serotonin</td>
</tr>
<tr>
<td>· Platelet factor 4</td>
<td>· Epinephrine</td>
</tr>
<tr>
<td>· Platelet-derived growth factor (PDGF)</td>
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</tr>
</tbody>
</table>

   ii. Platelet synthesis of thromboxane A2
   iii. Membrane expression of the phospholipid complex, which is an important substrate for the coagulation cascade

d. **Step 3: platelet aggregation**
   i. Additional platelets are recruited from the bloodstream.
   ii. ADP and thromboxane A2 are potent mediators of aggregation.
   iii. Platelets bind to each other by binding to fibrinogen using Gp IIb-IIIa.

Bridge to Pharmacology

Aspirin irreversibly acetylates cyclooxygenase, preventing platelet production of thromboxane A2.

In a Nutshell

Bernard-Soulier Syndrome
- Autosomal recessive
- Deficiency of platelet Gp Ib
- Defective platelet adhesion

In a Nutshell

Glanzmann Thrombasthenia
- Autosomal recessive
- Deficiency of Gp IIb-IIIa
- Defective platelet aggregation

![Figure 5-1. Platelet Aggregation](image)
Table 5-3. Common Platelet Disorders

<table>
<thead>
<tr>
<th>Thrombocytopenia Disorder</th>
<th>Qualitative Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Decreased production</strong></td>
<td>• von Willebrand disease</td>
</tr>
<tr>
<td>• Aplastic anemia (drugs, virus, etc.)</td>
<td></td>
</tr>
<tr>
<td>• Tumor</td>
<td></td>
</tr>
<tr>
<td><strong>Increased destruction</strong></td>
<td>• Bernard-Soulier syndrome</td>
</tr>
<tr>
<td>• Immune thrombocytopenia (ITP)</td>
<td></td>
</tr>
<tr>
<td>• Thrombotic thrombocytopenic purpura (TTP)</td>
<td></td>
</tr>
<tr>
<td>• Disseminated intravascular coagulation (DIC)</td>
<td></td>
</tr>
<tr>
<td>• Hypersplenism</td>
<td></td>
</tr>
</tbody>
</table>

4. **Immune thrombocytopenia purpura (ITP)**
   a. **Definition:** An immune mediated attack (usually IgG antiplatelet antibodies) against platelets leading to decreased platelets (thrombocytopenia), resulting in petechiae, purpura (bruises), and a bleeding diathesis (e.g., hematomas)
   b. **Etiology**
      i. **Antiplatelet antibodies** against platelet antigens such as Gp IIb-IIIa and Gp Ib-IX (type II hypersensitivity reaction)
      ii. Antibodies are made in the spleen.
      iii. Platelets are destroyed peripherally in the spleen by macrophages, which have Fc receptors that bind IgG-coated platelets.
   c. **Forms of ITP**
      i. **Acute ITP**
         • Seen in children following a viral infection
         • Self-limited disorder
      ii. **Chronic ITP**
         • Usually seen in women in their childbearing years
         • May be the first manifestation of systemic lupus erythematosus (SLE)
         • Petechiae, ecchymoses, menorrhagia, and nosebleeds
   d. **Lab**
      i. Decreased platelet count and prolonged bleeding time
      ii. Normal prothrombin time (PT) and partial thromboplastin time (PTT)
iii. Peripheral blood smear shows thrombocytopenia with enlarged immature platelets (megathrombocytes).
iv. Bone marrow biopsy shows increased numbers of megakaryocytes with immature forms.

c. Treatment
i. Corticosteroids, which decrease antibody production
ii. Immunoglobulin therapy, which floods Fc receptors on splenic macrophages
iii. Spleenectomy, which removes the site of platelet destruction and antibody production

5. Thrombotic thrombocytopenic purpura (TTP)
a. Definition: a rare disorder of hemostasis where there is widespread intravascular formation of fibrin-platelet thrombi due to a deficiency/inhibition of the enzyme ADAMTS13, which is responsible for cleaving large multimers of von Willebrand factor
b. Clinical findings
i. Most often affects adult women
ii. Pentad of characteristic signs
   • Fever
   • Thrombocytopenia
   • Microangiopathic hemolytic anemia (intravascular hemolysis)
   • Neurologic symptoms
   • Renal failure
c. Pathology
i. Widespread formation of platelet thrombi with fibrin (hyaline thrombi) leading to intravascular hemolysis (thrombotic microangiopathy)
d. Lab
i. Decreased platelet count and prolonged bleeding time
ii. Normal PT and PTT
iii. Peripheral blood smear shows thrombocytopenia and schistocytes, and reticulocytosis

6. Hemolytic uremic syndrome (HUS)
a. Definition: a form of thrombotic microangiopathy due to endothelial cell damage
b. Occurs most commonly in children
c. Follows a gastroenteritis with bloody diarrhea

d. Organism: verotoxin-producing *E. coli* 0157:H7

c. Similar clinical pentad

7. **Coagulation**

a. Coagulation factors

i. The majority of the clotting factors are produced by the liver.

ii. The factors are proenzymes that must be converted to the active form.

iii. Some conversions occur on a phospholipid surface.

iv. Some conversions require calcium.
b. The intrinsic coagulation pathway is activated by the contact factors:
   i. Contact with subendothelial collagen
   ii. High molecular weight kininogen (HMWK)
   iii. Kallikrein

c. The extrinsic coagulation pathway is activated by the release of tissue factor.

d. Laboratory tests for coagulation
   i. Prothrombin time (PT)
      • Tests the extrinsic and common coagulation pathways
      • Tests factors VII, X, V, prothrombin, fibrinogen
      • International normalized ratio (INR) standardizes the PT test so that results throughout the world can be compared.
   ii. Partial thromboplastin time (PTT)
      • Tests the intrinsic and common coagulation pathways
      • Tests factors XII, XI, IX, VIII, X, V, prothrombin, fibrinogen
   iii. Thrombin time (TT) tests for adequate fibrinogen levels
   iv. Fibrin degradation products (FDP) tests the fibrinolytic system (increased with DIC)

8. Hemophilia A (classic hemophilia)
   a. Deficiency of factor VIII
   b. X-linked recessive
   c. Clinical features
      i. Predominately affects males
      ii. Symptoms are variable dependent on the degree of deficiency
      iii. Newborns may develop bleeding at the time of circumcision
      iv. Spontaneous hemorrhages into joints (hemarthrosis)
      v. Easy bruising and hematoma formation after minor trauma
      vi. Severe prolonged bleeding after surgery or lacerations
      vii. No petechiae or ecchymoses
   d. Lab
      i. Normal platelet count and bleeding time
      ii. Normal PT and prolonged PTT
   e. Treatment: factor VIII concentrate

9. Hemophilia B (Christmas disease)
   a. Deficiency of factor IX
   b. X-linked recessive
   c. Clinically identical to hemophilia A

10. Acquired coagulopathies
    b. Liver disease: decreased synthesis of virtually all clotting factors

11. Von Willebrand disease
    a. Definition: inherited bleeding disorder characterized by either a deficiency or qualitative defect in von Willebrand factor
    b. vWF is normally produced by endothelial cells and megakaryocytes.
c. Clinical features
   i. Spontaneous bleeding from mucous membranes
   ii. Prolonged bleeding from wounds
   iii. Menorrhagia in young females
   iv. Bleeding into joints is uncommon.

d. Lab
   i. Normal platelet count and a prolonged bleeding time
   ii. Normal PT with often a prolonged PTT
   iii. Abnormal platelet response to ristocetin (adhesion defect) is an important diagnostic test.
   iv. Treatment: treat mild cases (type 1) with desmopressin (an antidiuretic hormone [ADH] analog), which releases vWF from Weibel-Palade bodies of endothelial cells

12. Disseminated intravascular coagulation (DIC)
a. DIC is always secondary to another disorder.
b. Causes
   i. Obstetric complications (placental tissue factor activates clotting)
   ii. Gram-negative sepsis (tumor necrosis factor [TNF] activates clotting)
   iii. Microorganisms (especially meningococcus and rickettsiae)
   iv. AML M3 (cytoplasmic granules in neoplastic promyelocytes activate clotting)
   v. Adenocarcinomas (mucin activates clotting)
c. Pathology
   i. Results in widespread microthrombi
   ii. Consumption of platelets and clotting factors causes hemorrhages.
d. Lab
   i. Platelet count is decreased.
   ii. Prolonged PT/PTT
   iii. Decreased fibrinogen
   iv. Elevated fibrin split products (D-dimers)
e. Treatment: treat the underlying disorder
Figure 5-3. Disseminated Intravascular Coagulation

THROMBOSIS

1. General
   a. Definition: pathologic formation of an intravascular fibrin-platelet thrombus during life
   b. Factors involved in thrombus formation (Virchow's triad)
      i. Endothelial injury
         • Atherosclerosis
         • Vasculitis
         • Many others
      ii. Alterations in laminar blood flow
          • Stasis of blood (e.g., immobilization)
          • Turbulence (e.g., aneurysms)
          • Hyperviscosity of blood (e.g., polycythemia vera)
      iii. Hypercoagulability of blood
          • Clotting disorders (factor V Leiden, deficiency of antithrombin III, protein C, or protein S)
          • Tissue injury (postoperative and trauma)
          • Neoplasia
- Nephrotic syndrome
- Advanced age
- Pregnancy
- Oral contraceptives (estrogen increases synthetic activity of the liver, including clotting factors)

Table 5-4. Comparison of a Thrombus with a Blood Clot

<table>
<thead>
<tr>
<th></th>
<th>Thrombus</th>
<th>Blood Clot</th>
</tr>
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<tbody>
<tr>
<td>Location</td>
<td>Intravascular</td>
<td>Extravascular or intravascular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(postmortem)</td>
</tr>
<tr>
<td>Composition</td>
<td>Platelets</td>
<td>Lacks platelets</td>
</tr>
<tr>
<td></td>
<td>Fibrin</td>
<td>Fibrin</td>
</tr>
<tr>
<td></td>
<td>RBCs and WBCs</td>
<td>RBCs and WBCs</td>
</tr>
<tr>
<td>Lines of Zahn</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Shape</td>
<td>Has shape</td>
<td>Lacks shape</td>
</tr>
</tbody>
</table>

c. Common locations of thrombus formation
   i. Coronary and cerebral arteries
   ii. Heart chambers atrial fibrillation or post-MI (mural thrombus)
   iii. Aortic aneurysms
   iv. Heart valves (vegetations)
   v. Deep leg veins (DVTs)

d. Outcomes of thrombosis include:
   i. Vascular occlusion and infarction
   ii. Embolism
   iii. Thrombolysis
   iv. Organization and recanalization

EMBOLISM

1. Definition: any intravascular mass that has been carried down the bloodstream from its site of origin, resulting in the occlusion of a vessel

2. Composition of emboli
   a. Thromboemboli—most common (98%) type of emboli
   b. Atheromatous emboli—severe atherosclerosis
   c. Fat emboli—bone fractures and soft-tissue trauma
   d. Bone marrow emboli—bone fractures and cardiopulmonary resuscitation (CPR)
   e. Gas emboli
      i. Decompression sickness ("the bends" and Caisson disease)
      ii. Rapid ascent results in nitrogen gas bubbles in the blood vessels.
   f. Amniotic fluid emboli
      i. Complication of labor
      ii. Fetal squamous cells are seen in the maternal pulmonary vessels
      iii. May result in DIC
3. Pulmonary emboli (PE)
   a. Epidemiology
      i. Often clinically silent
      ii. Most commonly missed diagnosis in hospitalized patients
      iii. Found in almost half of all hospital autopsies
   b. Pathology
      i. Most (95%) pulmonary emboli arise from deep leg vein thrombosis (DVT) in the leg
      ii. Pelvic venous plexuses of the prostate and uterus
      iii. Right side of the heart
   c. Diagnosis
      i. V/Q lung scan V/Q mismatch
      ii. Doppler ultrasound of the leg veins to detect a DVT
      iii. Plasma D-dimer ELISA test is elevated
   d. Potential outcomes of PEs
      i. No sequelae (75%)
         • Asymptomatic or transient dyspnea/tachypnea
         • No infarction (dual blood supply)
         • Complete resolution
      ii. Infarction (15%)
         • More common in patients with cardiopulmonary compromise
         • Shortness of breath (SOB), hemoptysis, pleuritic chest pain, pleural effusion
         • Gross: hemorrhagic wedge-shaped infarct
         • Regeneration or scar formation
      iii. Sudden death (5%)
         • Large emboli may lodge in the bifurcation (saddle embolus) or large pulmonary artery branches and cause sudden death.
         • Obstruction of >50% of the pulmonary circulation
   iv. Chronic secondary pulmonary hypertension (3%)
      • Caused by recurrent PEs
      • Increased pulmonary resistance
      • Lead to secondary pulmonary hypertension

4. Systemic arterial emboli
   a. Most arise in the heart.
   b. Most arterial emboli cause infarction.
   c. Common sites of infarction include the lower extremities, brain, intestine, kidney, and spleen.
   d. Paradoxical emboli
      i. Definition: any venous embolus that gains access to the systemic circulation by crossing over from the right to the left side of the heart through a septal defect

Bridge to Anatomy
The dual blood supply to the lungs is from the pulmonary artery and the bronchial arteries.

Clinical Correlate
The classic presentation of massive PE is an intensive care unit (ICU), postoperative, or bedridden patient who gets out of bed and collapses.
INFARCTION

1. Infarction
   a. Definition: localized area of necrosis secondary to ischemia
   b. Pathogenesis
      i. Most infarcts (99%) result from thrombotic or embolic occlusion of an artery or vein.
      ii. Vasospasm
      iii. Torsion of arteries and veins (e.g., volvulus, ovarian, and testicular torsion)
   c. Factors that predict the development of an infarct include
      i. Vulnerability of the tissue to hypoxia
      ii. Degree of occlusion
      iii. Rate of occlusion
      iv. Presence of a dual blood supply or collateral circulation
      v. Oxygen-carrying capacity of the blood (anemia, carbon monoxide poisoning, etc.)
   d. Common sites of infarction
      i. Heart
      ii. Brain
      iii. Lungs
      iv. Intestines
      v. Kidneys

2. Gross pathology of infarction
   a. Often has a wedge shape
   b. Apex of the wedge tends to point to the occlusion.
   c. Anemic infarcts (pale or white color)
      i. Occur in solid organs with a single blood supply such as the spleen, kidney, and heart
   d. Hemorrhagic infarcts (red color)
      i. Occur in organs with a dual blood supply or collateral circulation, such as the lung and intestines
      ii. Also occur with venous occlusion (e.g., testicular torsion)

3. Microscopic pathology of infarction
   a. Coagulative necrosis—most organs
   b. Liquifactive necrosis—brain
   c. General sequence of tissue changes after infarction:

   ischemia → coagulative necrosis → inflammation → granulation tissue → fibrous scar
SHOCK

1. General
   a. Definition: shock is characterized by vascular collapse and widespread hypoperfusion of cells and tissue due to reduced blood volume, cardiac output, or vascular tone
   b. Cellular injury is initially reversible.
   c. If the hypoxia persists, the cellular injury becomes irreversible, leading to the death of cells and the patient.

2. Major causes of shock
   a. Cardiogenic shock (pump failure)
      i. Myocardial infarction
      ii. Cardiac arrhythmias
      iii. Pulmonary embolism
      iv. Cardiac tamponade
   b. Hypovolemic shock (reduced blood volume)
      i. Hemorrhage
      ii. Fluid loss secondary to severe burns
      iii. Severe dehydration
   c. Septic shock (bacterial infection)
      i. Gram-negative septicemia
      ii. Release of endotoxins (bacterial wall lipopolysaccharides) into the circulation
      iii. High levels of endotoxin results in
         - Production of cytokines TNF, IL-1, IL-6, and IL-8
         - Vasodilatation and hypotension
         - Acute respiratory distress syndrome (ARDS)
         - DIC
         - Multiple organ dysfunction syndrome
      iv. Mortality rate: 50%
   d. Neurogenic shock (generalized vasodilatation)
      i. Anesthesia
      ii. Brain or spinal cord injury
   c. Anaphylactic shock (generalized vasodilatation)—type I hypersensitivity reaction

3. Stages of shock
   a. Stage I: compensation, in which perfusion to vital organs is maintained by reflex mechanisms
      i. Increased sympathetic tone
      ii. Release of catecholamines
      iii. Activation of the renin-angiotensin system
   b. Stage II: decompensation
      i. Progressive decrease in tissue perfusion
      ii. Potentially reversible tissue injury occurs
      iii. Development of a metabolic (lactic) acidosis, electrolyte imbalances, and renal insufficiency
c. Stage III: irreversible
   i. Irreversible tissue injury and organ failure
   ii. Ultimately resulting in death

---

**Figure 5-4. Activation of the Baroreceptor Reflex in Shock**

4. Pathology
   a. Kidneys
      i. Acute tubular necrosis (acute renal failure)
      ii. Oliguria and electrolyte imbalances occur.
   b. Lungs undergo diffuse alveolar damage ("shock lung")
   c. Intestines
      i. Superficial mucosal ischemic necrosis and hemorrhages
      ii. Prolonged injury may lead to sepsis with bowel flora.
   d. Liver undergoes centrlobular necrosis ("shock liver").
   e. Adrenals undergo the Waterhouse-Frischerichsen syndrome.
      i. Commonly associated with meningococcal septic shock
      ii. Bilateral hemorrhagic infarction
      iii. Acute adrenal insufficiency
Chapter Summary

- Edema is the presence of excess fluid in the intercellular space. Causes of edema include increased hydrostatic pressure, increased interstitial sodium, hypoalbuminemia and decreased colloid pressure, lymphatic obstruction, and increased endothelial permeability. Anasarca is the term used for severe generalized edema.

- Transudates have low protein content and specific gravity, while exudates have high protein content and specific gravity.

- Hyperemia is an excessive amount of blood in a tissue or organ and can be due either to vasodilation (active hyperemia) or diminished venous outflow (passive hyperemia or congestion).

- Hemostasis is the sequence of events leading to cessation of bleeding by the formation of a stable fibrin-platelet hemostatic plug. Vascular wall injury triggers transient vasoconstriction, facilitation of platelet adhesion, and activation of both the extrinsic and intrinsic clotting pathways. Formation of a platelet thrombus occurs when platelets adhere to von Willebrand factor attached to subendothelial collagen, undergo shape change and degranulation, and then aggregate with additional platelets.

- Causes of thrombocytopenia due to decreased platelet production include aplastic anemia and tumor. Causes of thrombocytopenia due to increased platelet destruction include immune thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), and hypersplenism. Causes of qualitative platelet defects include von Willebrand disease, Bernard-Soulier syndrome, Glanzmann thrombasthenia, aspirin, and uremia.

- In immune thrombocytopenic purpura (ITP), antiplatelet antibodies destroy platelets, primarily in the spleen. In thrombotic thrombocytopenic purpura (TTP), there is widespread formation of platelet thrombi with fibrin but without activation of the coagulation system. Hemolytic uremic syndrome (HUS) can clinically resemble TTP and is triggered by E. coli strain 0157:H7.

(Continued)
Chapter Summary (continued)

* The intrinsic coagulation pathway is activated by contact factors and is clinically tested with the partial thromboplastin time (PTT). The extrinsic coagulation pathway is activated by the release of tissue factor, and is tested with the prothrombin time (PT), which also tests the common coagulation pathway.

* Hemophilia A is an X-linked recessive deficiency of factor VIII, which is clinically characterized by hemorrhrosis, easy bruising, and severe prolonged bleeding after surgery or lacerations. Clinically, hemophilia B closely resembles hemophilia A but is due to deficiency of factor IX. Acquired coagulopathies can be due to vitamin K deficiency and liver disease. Von Willebrand disease is an inherited bleeding disorder characterized by a deficiency or qualitative defect in von Willebrand factor, which facilitates formation of platelet clots.

* Disseminated intravascular coagulation (DIC) can be triggered by a variety of severe medical conditions and results in formation of many microthrombi that consume platelets and clotting factors, leading, in turn, to a superimposed bleeding tendency.

* Factors involved in thrombus formation include endothelial injury, alterations in laminar blood flow, and hypercoagulability of blood. Thrombi can lead to a spectrum of outcomes, including vascular occlusion and infarction, embolism, thrombolysis, and organization and recanalization.

* The term embolism is used for any intravascular mass (solid, liquid, or gas) that has been carried downstream from its site of origin, resulting in occlusion of a vessel. Ninety-eight percent of emboli are thromboemboli, but many other materials have also formed emboli. Pulmonary emboli are a common form of emboli that are often clinically silent but can cause infarction or sudden death. Most pulmonary emboli arise from deep vein thromboses. Systemic arterial emboli usually arise in the heart and may cause infarction in a variety of sites, depending upon where they lodge.

* Infarction is a localized area of necrosis secondary to ischemia. Ninety-nine percent of infarcts result from thrombotic occlusion of an artery or vein. Anemic infarcts occur in organs with a single blood supply, whereas hemorrhagic infarcts occur in organs with a dual blood supply or secondary to venous occlusion. The general sequence of tissue changes after infarction is: ischemia leads to coagulative necrosis, which leads to inflammation, which leads to granulation tissue, which leads to fibrous scar.

* Shock is characterized by vascular collapse and widespread hypoperfusion of cells and tissues due to reduced blood volume, cardiac output, or vascular tone. Major forms of shock include cardiogenic shock, hypovolemic shock, septic shock, and neurogenic shock. Shock has been clinically divided into compensated shock (stage I), decompensated shock (stage II), and irreversible injury (stage III). Different organs show distinctive microscopic patterns in shock.
DISORDERS INVOLVING AN EXTRA AUTOSOME

1. Down syndrome (trisomy 21)

![Down Syndrome Diagram]

Figure 6-1. Down Syndrome

a. Karyotype: 47 XX or XY +21
b. Most common of the chromosomal disorders (incidence: 1 in 700 births)
c. Risk increases with maternal age
d. Pathogenesis
   i. Meiotic nondisjunction (95%)
   ii. Robertsonian translocation (4%)
   iii. Mosaicism due to mitotic nondisjunction during embryogenesis (1%)
e. Clinical findings
   i. Severe mental retardation (most common cause of genetic mental retardation)
   ii. Mongoloid facial features (flat face, low-bridged nose, and epicanthal folds)
   iii. Brushfield spots—speckled appearance of the iris
   iv. Muscular hypotonia
   v. Broad short neck
   vi. Palmar (simian) crease
   vii. Congenital heart defects
      * Endocardial cushion defect leads to the formation of an atrioventricular canal (a common connection between all four chambers of the heart)

Note

Robertsonian Translocation
Defined as a translocation involving two acrocentric chromosomes with the break points occurring close to the centromeres. This results in an extremely large chromosome and a tiny one, which is typically lost.
viii. Duodenal atresia ("double-bubble" sign)
ix. Hirschsprung disease
x. Increased risk (15–20×) of acute lymphoblastic leukemia (ALL)
xi. Alzheimer disease (by age 40 virtually all will develop Alzheimer disease)
f. Lab: Down syndrome can be screened by assaying maternal serum levels of α-fetoprotein, chorionic gonadotropin, and unconjugated estriol.

2. Edwards syndrome (trisomy 18)

![Figure 6-2. Edwards Syndrome](image)

- Karyotype: 47 XX or XY +18
- Risk increases with maternal age
- Caused by nondisjunction
- Clinical findings
  - Mental retardation
  - Low-set ears and micrognathia
  - Congenital heart defects
  - Overlapping flexed fingers
  - Rocker-bottom feet
- Very poor prognosis due to severe congenital malformations
3. Patau syndrome (trisomy 13)

![Diagram of Patau Syndrome]

Figure 6-3. Patau Syndrome

- a. Karyotype: 47 XX or XY +13
- b. Risk increases with maternal age
- c. Caused by nondisjunction
- d. Clinical findings
  - i. Mental retardation
  - ii. Cleft lip and/or palate
  - iii. Cardiac defects
  - iv. Renal abnormalities
  - v. Microcephaly
  - vi. Polydactyly
- e. Very poor prognosis due to severe congenital malformations

DISORDERS INVOLVING CHROMOSOMAL DELETIONS

1. Cri du chat syndrome
   - a. Karyotype: 46 XX or XY, 5p–
   - b. Pathogenesis: deletion of the short arm of chromosome 5
   - c. Clinical findings
     - i. Characteristic high-pitched catlike cry
     - ii. Mental retardation
     - iii. Congenital heart disease
     - iv. Microcephaly

2. Microdeletions
   - a. Of 13q14—the retinoblastoma gene
   - b. The WAGR (Wilms tumor, Aniridia, Genitourinary anomalies, and mental Retardation) complex is associated with microdeletion of 11p13
DISORDERS INVOLVING SEX CHROMOSOMES

1. Klinefelter syndrome
   a. Karyotype: 47 XXY
   b. Caused by meiotic nondisjunction
   c. Common cause of male hypogonadism
   d. Lab
      i. Elevated FSH and LH
      ii. Low levels of testosterone
   e. Clinical findings
      i. Testicular atrophy
      ii. Infertility due to azoospermia
      iii. Eunuchoid body habitus
      iv. High-pitched voice
      v. Female distribution of hair
      vi. Gynecomastia

2. Turner syndrome
   a. Karyotype: 45 XO
   b. Common cause of female hypogonadism
   c. The second X chromosome is necessary for oogenesis and normal development of the ovary.
   d. No Barr body present
   e. Clinical features
      i. Failure to develop secondary sex characteristics
      ii. Short stature with widely spaced nipples
      iii. Gonadal dysgenesis: atrophic “streaked” ovaries
      iv. Primary amenorrhea
      v. Infertility
      vi. Cystic hygroma and webbing of the neck
      vii. Hypothyroidism
      viii. Congenital heart disease
         • Preductal coarctation of the aorta
         • Bicuspid aortic valve
      ix. Hydrops fetalis
      x. Females with 45,X;46,XY mosaicism are at risk for gonadoblastoma.
HERMAPHRODITISM

1. Determination of sex
   a. Karyotypic (genetic) sex: presence of a Y chromosome results in testicular development
   b. Gonadal sex: presence of ovarian or testicular tissue
   c. Ductal sex: presence of Müllerian (female – Fallopian tube, uterus, cervix, and upper portion of vagina) or Wolffian (male – epididymis, vas deferens, seminal vesicles, and ejaculatory ducts) duct adult derivatives
   d. Phenotypic (genital) sex: external appearance of the genitalia

2. True hermaphrodite
   a. Definition: presence of both ovarian and testicular tissue within an individual
   b. Genetic sex: 46 XX, 46 XY, 45 X/XY (mosaics)
   c. Gonadal sex
      i. Ovary on one side and testes on the other
      ii. Ovotestes: a gonad with both testicular and ovarian tissue
3. **Female pseudohermaphroditism**
   a. Genetic sex: normal female (46 XX)
   b. Gonadal and ductal sex: normal female internal organs
   c. Phenotypic sex: ambiguous or virilized external genitalia
   d. Exposure of a female fetus to androgens *in utero*
      i. Congenital adrenal hyperplasia
      ii. Androgen-producing tumors (ovarian Sertoli-Leydig cell tumor)
      iii. Exogenous androgens

4. **Male pseudohermaphroditism**
   a. Genetic sex: normal male (46 XY)
   b. Gonadal and ductal sex: testes present
   c. Phenotypic sex: ambiguous or female genitalia
   d. *Testicular feminization* (complete androgen insensitivity syndrome)
      i. Most common cause of male pseudohermaphroditism
      ii. Defect: mutation of the androgen receptor (Xq11-12)

**MENDELIAN DISORDERS**

1. **General**
   a. Definition: mendelian disorders are characterized by *single gene mutations*
   b. Common types of mutations
      i. *Point mutation*: single nucleotide base substitution
         • *Synonymous mutation* (silent mutation): a base substitution resulting in a codon that codes for the same amino acid
         • *Missense mutation*: a base substitution resulting in a new codon and a change in amino acids
         • *Nonsense mutation*: a base substitution producing a stop codon and therefore producing a truncated protein
      ii. *Frameshift*: insertion or deletion of bases leading to a shift in the reading frame of the DNA
   c. Location of mutations
      i. Mutations involving coding regions of DNA may result in
         • Abnormal amino acid sequences
         • Decreased production of the protein
         • Truncated or abnormally folded protein
         • Altered or lost function of the protein
      ii. Mutations of promoter or enhancer regions: interfere with transcription factors, resulting in decreased transcription of the gene
   d. Patterns of inheritance
      i. Autosomal dominant
      ii. Autosomal recessive
iii. X-linked recessive
iv. X-linked dominant
v. Triplet repeat mutations
vi. Genetic imprinting
vii. Mitochondrial
viii. Multifactorial

Table 6.1. General Characteristics of Autosomal Dominant and Recessive Diseases

<table>
<thead>
<tr>
<th></th>
<th>Autosomal Recessive</th>
<th>Autosomal Dominant</th>
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<tr>
<td>Onset</td>
<td>Early uniform onset (infancy/childhood)</td>
<td>Variable onset (may be delayed into adulthood)</td>
</tr>
<tr>
<td>Penetration</td>
<td>Complete penetrance</td>
<td>Incomplete penetrance with variable expression</td>
</tr>
<tr>
<td>Mutation</td>
<td>Usually an enzyme protein</td>
<td>Usually a structural protein or receptor</td>
</tr>
<tr>
<td>Requires</td>
<td>Mutation of both alleles</td>
<td>Mutation of one allele</td>
</tr>
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</table>

AUTOSOMAL RECESSIVE DISORDERS

1. Cystic fibrosis (mucoviscidosis)
   a. Most common lethal genetic disorder in Caucasians
   b. Defect: mutation of the chloride channel protein, cystic fibrosis transmembrane conductance regulator (CFTR)
   c. Genetics
      i. CFTR gene is located on chromosome 7
      ii. Most common mutation is a deletion of the amino acid phenylalanine at position 508 (ΔF508)
   d. Pathogenesis: defective chloride channel protein leads to abnormally thick viscous mucus, which obstructs the ducts of exocrine organs
   e. Distribution of disease (eccrine sweat glands and exocrine glands)
      i. Lungs
         · Recurrent pulmonary infections with P. aeruginosa and S. aureus
         · Chronic bronchitis
         · Bronchiectasis
      ii. Pancreas
         · Plugging of pancreatic ducts results in atrophy and fibrosis
         · Pancreatic insufficiency
         · Fat malabsorption
         · Malodorous steatorrhea
         · Deficiency of fat-soluble vitamins
   iii. Male reproductive system: absence or obstruction of the vas deferens and epididymis often leads to male infertility

Bridge to Biochemistry

The majority of cystic fibrosis cases result from deletion of phenylalanine at position 508 (ΔF508), which interferes with proper protein folding and the post-translational processing of oligosaccharide side chains. The abnormal chloride channel protein is degraded by the cytosolic proteasome complex rather than translocated to the cell membrane.
iv. Liver: plugging of the biliary canaliculi may result in biliary cirrhosis
v. GI tract: small intestinal obstruction (meconium ileus)
vi. Salivary glands: appear not to be significantly affected in CF except for more mucus in the ducts

f. Diagnosis
i. Sweat test (elevated NaCl)
ii. DNA probes

![Figure 6-5. The Use of Allele-Specific Oligonucleotide (ASO) Probes for Cystic Fibrosis]

- Black dot = Sample reacts with probe
- White circle = Sample does not react with probe

Bridge to Biochemistry

Phenylalanine hydroxylase converts phenylalanine into tyrosine.

2. Phenylketonuria (PKU)
   a. Enzyme defect: deficiency of phenylalanine hydroxylase, resulting in toxic levels of phenylalanine
   b. Presentation
      i. Normal at birth but develop profound mental retardation by 6 months of age
      ii. Lack of tyrosine: light-colored skin and hair
      iii. May have a mousy or musty odor to the sweat and urine (secondary to metabolite [phenylacetate] accumulation)
   c. Diagnostic screened at birth
   d. Treatment: dietary restriction of phenylalanine; avoid aspartame
   e. Variant: benign hyperphenylalaninemia
      i. Partial enzyme deficiency
      ii. Mildly increased levels of phenylalanine are insufficient to cause mental retardation.
3. Alkaptonuria (ochronosis)
   a. Enzyme defect: deficiency of homogentisic acid oxidase resulting in the accumulation of homogentisic acid
   b. Homogentisic acid has an affinity for connective tissues (especially cartilage), resulting in a black discoloration (as a consequence of oxidation of homogentisic acid)
   c. Clinical features
      i. Urine is pale yellow, but turns black upon standing
      ii. Black cartilage
      iii. Discoloration of the nose and ears
      iv. Early onset of degenerative arthritis
4. Albinism
   a. Definition: deficiency of melanin pigmentation in the skin, hair follicles, and eyes (oculocutaneous albinism)
   b. Enzyme defect: tyrosinase deficiency
   c. Increased risk of basal cell and squamous cell carcinomas
5. Glycogen storage diseases
   a. Definition: a group of rare diseases that have in common a deficiency in an enzyme necessary for the metabolism of glycogen, which results in the accumulation of glycogen in the liver, heart, and skeletal muscle
   b. Type I (von Gierke disease)
      i. Enzyme defect: deficiency of glucose-6-phosphatase
      ii. Hepatomegaly and hypoglycemia
   c. Type II (Pompe disease)
      i. Enzyme defect: deficiency of lysosomal α-1,4-glucosidase (acid maltase)
      ii. Hepatomegaly
      iii. Skeletal muscle hypotonia
      iv. Cardiomegaly
      v. Death from cardiac failure by age 2 years
   d. Type V (McArdle syndrome)
      i. Enzyme defect: deficiency of muscle glycogen phosphorylase
      ii. Exercise-induced muscle cramps
6. Tay-Sachs disease
   a. Enzyme defect: deficiency of hexosaminidase A
   b. Leads to the accumulation of GM2 ganglioside in the lysosomes of the CNS and retina
   c. Genetic defect: mutation of HEXA gene on chromosome 15

Note
Lysosomal Storage Diseases
Defined as a deficiency of a lysosomal enzyme (acid hydrolase), which leads to the accumulation of a complex substrate within the lysosome leading to enlarged cells that become dysfunctional
- Tay-Sachs
- Niemann-Pick
- Gaucher
- Mucopolysaccharidoses
- Fabry
- Metachromatic leukodystrophy
Table 6-2. Lysosomal Storage Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Enzyme Deficiency</th>
<th>Accumulating Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tay-Sachs disease</td>
<td>Hexosaminidase A</td>
<td>GM₂ ganglioside</td>
</tr>
<tr>
<td>Niemann-Pick disease</td>
<td>Sphingomyelinase</td>
<td>Sphingomyelin</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>Glucocerebrosidase</td>
<td>Glucocerebroside</td>
</tr>
<tr>
<td>Fabry disease</td>
<td>α-Galactosidase A</td>
<td>Ceramide trihexoside</td>
</tr>
<tr>
<td>Metachromatic</td>
<td>Aryl sulfatase A</td>
<td>Sulfatide</td>
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<tr>
<td>leukodystrophy</td>
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<tr>
<td>Hurler syndrome</td>
<td>α-L-iduronidase</td>
<td>Dermatan sulfate</td>
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<td></td>
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<td>Heparan sulfate</td>
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<tr>
<td>Hunter syndrome</td>
<td>L-iduronosulfate sulfatase</td>
<td>Dermatan sulfate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heparan sulfate</td>
</tr>
</tbody>
</table>

d. Common in Ashkenazi Jews (1 in 30 carrier rate)
e. Distribution of disease
   i. Retina: cherry-red spot (accentuation of the macula)
   ii. CNS: dilated neurons with cytoplasmic vacuoles
f. Presentation
   i. Normal at birth with onset of symptoms by 6 months
   ii. Progressive mental deterioration and motor incoordination
   iii. Death by age 2–3 years
g. EM: distended lysosomes with whirled membranes
h. Diagnosis: enzyme assays and DNA probes

7. Niemann-Pick disease
a. Enzyme defect: deficiency of sphingomyelinase
b. Leading to the accumulation of sphingomyelin within the lysosomes of the CNS and reticuloendothelial system (monocytes and macrophages located in reticular connective tissue)
c. Common in Ashkenazi Jews
d. Distribution of disease
   i. Retina: cherry-red spot
   ii. CNS: distended neurons with a foamy cytoplasmic vacuolization
   iii. Reticuloendothelial system
      • Hepatosplenomegaly
      • Lymphadenopathy
      • Bone marrow involvement
e. Presentation
   i. Normal at birth with onset of symptoms by 6 months
   ii. Massive splenomegaly and lymphadenopathy
   iii. Progressive mental and motor manifestations
   iv. Death by age 2 years
f. EM: distended lysosomes containing lamellated figures ("zebra bodies")
g. Diagnosis: biochemical assay of sphingomyelinase activity and DNA probes

8. **Gaucher disease**
   a. Most common lysosomal storage disorder
   b. Enzyme defect: deficiency of glucocerebrosidase
   c. Leading to the accumulation of glucocerebrosidase predominately in the lysosomes of the reticuloendothelial system (monocytes and macrophages located in reticular connective tissue)
   d. Clinical presentation
      i. Type I represents 99% of cases and presents in adulthood
      ii. Hepatosplenomegaly
      iii. Hypersplenism → thrombocytopenia/pancytopenia
      iv. Lymphadenopathy
      v. Bone marrow involvement—may lead to bone pain, deformities, and fractures
      vi. CNS manifestations occur in types II and III
   e. Micro: Gaucher cells: enlarged macrophages with a fibrillar (tissue-paper–like) cytoplasm
   f. Diagnosis: biochemical enzyme assay of glucocerebrosidase activity

9. **Mucopolysaccharidosis (MPS)**
   a. Definition: group of lysosomal storage disorders characterized by deficiencies in the lysosomal enzymes required for the degradation of mucopolysaccharides (glycosaminoglycans)
   b. Clinical features
      i. Mental retardation
      ii. Cloudy cornea
      iii. Hepatosplenomegaly
      iv. Skeletal deformities and coarse facial features
      v. Joint abnormalities
      vi. Cardiac lesions
   c. MPS I (Hurler syndrome)
      i. Deficiency of α-L-iduronidase
      ii. Severe form
   d. MPS II (Hunter syndrome)
      i. X-linked recessive inheritance
      ii. Deficiency of L-iduronosulfate sulfatase
      iii. Milder form

**AUTOSOMAL DOMINANT DISORDERS**

1. **Familial hypercholesterolemia**
   a. Most common inherited disorder (1 in 500)
   b. Defect: mutation in low density lipoprotein (LDL) receptor gene on chromosome 19
   c. Five major classes of mutations
      i. Class I: no LDL receptor synthesis
      ii. Class II: defect in transportation out of the endoplasmic reticulum
Bridge to Biochemistry

HMG-CoA reductase is the rate-limiting enzyme in the synthesis of cholesterol. Normally, cholesterol represses the expression of the HMG-CoA reductase gene (negative feedback).

iii. Class III: defect in LDL receptor binding
iv. Class IV: defect in ability to internalize bound LDL
v. Class V: defect in the recycling of the LDL receptor
d. The mutation in the LDL receptor causes:
   i. Increased levels of circulating cholesterol
   ii. Loss of feedback inhibition of HMG-Coenzyme A (HMG-CoA) reductase
   iii. Increased phagocytosis of LDL by macrophages
e. Presentation
   i. Elevated serum cholesterol
      • Heterozygotes have elevations of 2 to 3 times the normal level
      • Homozygotes have elevations of 5 to 6 times the normal level
   ii. Skin xanthomas (collections of lipid-laden macrophages)
   iii. Xanthelasmas around the eyes
   iv. Premature atherosclerosis (homozygotes often develop MIs in late teens and twenties)

2. Marfan syndrome
   a. Genetic defect
      i. Mutation of the fibrillin gene (FBN1) on chromosome 15q21
      ii. Fibrillin is a glycoprotein that functions as a scaffold for the alignment of elastic fibers.
   b. Distribution of disease
      i. Skeletal system
         • Tall, thin build with long extremities
         • Hyperextensible joints
         • Pectus excavatum (inwardly depressed sternum)
         • Pectus carinatum (pigeon breast)
      ii. Eyes (ectopia lentis): bilateral subluxation of the lens
      iii. Cardiovascular system
         • Cystic medial degeneration of the media of elastic arteries with a loss of elastic fibers and smooth muscle cells → dissecting aortic aneurysm
         • Aortic dissection is a major cause of death.
         • Dilatation of the aortic ring → aortic valve insufficiency
         • Mitral valve prolapse

3. Ehlers-Danlos syndrome (EDS)
   a. Definition: group of inherited connective tissue diseases that have in common a defect in collagen structure or synthesis
   b. Clinical features
      i. Distribution of disease: skin, joints, and ligaments
      ii. Hyperextensible skin, which is easily traumatized
      iii. Hyperextensible joints
   c. Ten different variants with different modes of inheritance
      i. EDS Type 3—AD unknown defect; most common type
      ii. EDS Type 4—AD defect in the type III collagen gene

Note

Disorders of collagen biosynthesis include scurvy, osteogenesis imperfecta, Ehlers-Danlos syndrome, Alport syndrome, and Menkes disease.
iii. EDS Type 6—AD defect in the lysyl hydroxylase gene (enzyme responsible for hydroxylation of lysine residues)
iv. EDS Type 9—XLR defect in copper metabolism
   - Mutation of copper-binding protein on X chromosome
   - Low levels of ceruloplasmin and serum copper
   - Decreased activity of lysyl oxidase
   - Lysyl oxidase is copper dependent and is necessary for cross-linking of collagen fibers
d. Complications
   i. Poor wound healing
   ii. Joint dislocations
   iii. Diaphragmatic hernias (EDS Type 1)
   iv. Retinal detachment and kyphoscoliosis (EDS Type 6)
   v. Arterial or colonic rupture (EDS Type 4)

4. Neurofibromatosis
   a. Type 1 (von Recklinghausen disease)
      i. Accounts for 90% of cases of neurofibromatosis
      ii. Frequency: 1 in 3,000
      iii. Genetics
         - Tumor suppressor gene: NF-1
         - Chromosome 17 (17q11.2)
         - Normal gene product (neurofibromin) inhibits p21 ras oncoprotein
      iv. Multiple neurofibromas
         - Benign tumor of peripheral nerves
         - Often numerous and may be disfiguring
         - Plexiform neurofibromas are diagnostic
         - Rare (3%) malignant transformation
    v. Pigmented skin lesions ("cafe-au-lait spots")
       - Light brown macules usually located over nerves
       - Patients with NF-1 tend to have six or more
    vi. Pigmented iris hamartomas (Lisch nodules)
    vii. Increased risk of meningiomas and pheochromocytoma (dark/dusky-colored tumor)
   b. Type 2 (bilateral acoustic neurofibromatosis)
      i. Accounts for 10% of cases of neurofibromatosis
      ii. Frequency: 1 in 45,000
      iii. Genetics
          - Tumor suppressor gene: NF-2 (22q12.2)
          - Chromosome 22
          - Normal gene product (merlin) is a critical regulator of contact-dependent inhibition of proliferation
      iv. Bilateral acoustic neuromas
      v. Neurofibromas and cafe-au-lait spots
      vi. Increased risk of meningioma and ependymomas

Clinical Correlate
Menkes disease is an X-linked recessive condition that is caused by mutations in the gene encoding a Cu²⁺ efflux protein. Cells from an affected individual accumulate high concentrations of Cu²⁺ that cannot be released.
5. von Hippel-Lindau disease
   a. Genetics
      i. Tumor suppressor gene: VHL
      ii. Chromosome 3p (3p26-p25)
      iii. Normal gene product's main action is to tag proteins (e.g., hypoxia inducible factor 1α—a transcription factor that induces the expression of angiogenesis factors) with ubiquitin for degradation.
   b. Clinical presentation
      i. Retinal hemangioblastoma (von Hippel tumor)
      ii. Hemangioblastoma of cerebellum, brain stem, and spinal cord (Lindau tumor)
      iii. Cysts of the liver, pancreas, and kidneys
      iv. Multiple bilateral renal cell carcinomas

X-LINKED RECESSIVE CONDITIONS

1. **Definition**: males with mutant recessive gene on X chromosome have the condition
   a. Daughters of affected males are obligate carriers, who in many situations are asymptomatic.
   b. Sons of affected males do not carry the mutation.
   c. Daughters of carrier females are normal or carriers.
   d. Sons of carrier females may be affected or normal (because males are hemizygous for the X chromosome).

2. **Lesch-Nyhan syndrome**
   a. Deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGPRT)
   b. Impaired salvaging of the purines hypoxanthine and guanine
   c. Mental retardation, hyperuricemia, and self-mutilation

3. **Testicular feminization**
   a. Androgen insensitivity
   b. Failure of normal masculinization of external genitalia of XY males

4. **Chronic granulomatous disease**
   a. Defective NADPH oxidase enzyme complex of phagocytes
   b. Phagocytes cannot produce superoxide bursts to kill bacteria
   c. Recurrent infections, hypergammaglobulinemia, hepatosplenomegaly, and lymphadenopathy

5. **Bruton agammaglobulinemia**
   a. Defective Bruton tyrosine kinase (Btk) at band Xq21.3
   b. No immunoglobulin production
   c. Recurrent bacterial infections

X-LINKED DOMINANT CONDITIONS

1. **Definition**: similar to X-linked recessive, but both males and females show disease

2. **Alport syndrome**
   a. Hereditary glomerulonephritis with nerve deafness
TRIPLET REPEAT MUTATIONS

1. Fragile X syndrome
   a. Genetics
      i. Triplet nucleotide repeat mutations: nucleotide sequence CGG repeats typically hundreds to thousands of times
      ii. Mutation occurs in the FMR-1 gene (familial mental retardation-1 gene) on X chromosome (Xq27.3)
      iii. X-linked dominant disease
   b. Clinical presentation
      i. Mental retardation in affected males and 50% of female carriers
      ii. Elongated face with a large jaw
      iii. Large everted ears
      iv. Macro-orchidism
   c. Diagnosis: DNA probe analysis

2. Huntington disease
   a. Genetics: triplet repeat mutation (CAG) of the Huntington gene produces an abnormal protein (Huntingtin), which is neurotoxic
   b. Atrophy of caudate nucleus
   c. Clinical presentation
      i. Early onset (age range: 20–50 years) of progressive dementia
      ii. Choreiform movements

GENOMIC IMPRINTING

1. Definition: differential expression of genes based on chromosomal inheritance from maternal versus paternal origin

2. Prader-Willi syndrome
   a. Microdeletion on paternal chromosome 15 {del(15)(q11;q13)}
   b. Clinical presentation
      i. Mental retardation
      ii. Obesity
      iii. Hypogonadism
      iv. Hypotonia

3. Angelman syndrome ("happy puppet" syndrome)
   a. Microdeletion on maternal chromosome 15 {del(15)(q11q13)}
   b. Clinical presentation
      i. Mental retardation
      ii. Seizures
      iii. Ataxia
      iv. Inappropriate laughter

Note
Most common genetic causes of mental retardation:
- Down syndrome
- Fragile X syndrome

Note
Triplet repeat expansion can occur in a coding region (Huntington and spinobulbar muscular atrophy) or in an untranslated region of the gene (fragile X and myotonic dystrophy).
4. May play a role in Huntington disease, neurofibromatosis, and myotonic dystrophy

![Genetic Diagram]

*The inheritance of a deletion on chromosome 15 from a male produces Prader-Willi syndrome, whereas inheritance of the same deletion from a female produces Angelman syndrome.*

**Figure 6-6. Genomic Imprinting**

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**MITOCHONDRIAL DNA DISORDERS**

1. **Definition:** mitochondrial DNA codes for mitochondrial oxidative phosphorylation enzymes; inheritance is only from mother to child, because only the ovum contributes mitochondria to the zygote

2. *Leber hereditary optic neuropathy*
   a. Loss of retinal cells leads to central vision loss

3. **Myoclonic epilepsy**
   a. Pattern of seizures with abrupt jerks

---

**MULTIFACTORIAL INHERITANCE**

1. **Definition:** disease caused by a combination of multiple minor gene mutations and environmental factors

2. Examples include open neural tube defects and type 2 diabetes mellitus
Chapter Summary

* Disorders involving an extra autosomal chromosome include Down syndrome, Edwards syndrome, and Patau syndrome. Down syndrome (trisomy 21) is the most common of the chromosomal disorders and is characterized by severe mental retardation, mongoloid facial features, hypotonia, and palmar creases. Serious complications of Down syndrome include congenital heart disease (endocardial cushion defects), duodenal atresia, Hirschsprung disease, acute lymphoblastic leukemia, and early onset of Alzheimer disease. Edwards syndrome (trisomy 18) is characterized by mental retardation, low-set ears, micrognathia, congenital heart defects, overlapping flexed fingers, and rocker-bottom feet. Patau syndrome (trisomy 13) is characterized by mental retardation, cleft lip and/or palate, cardiac defects, renal abnormalities, microcephaly, and polydactyly.

* Chromosomal deletions can also cause genetic disease. Cri du chat syndrome (5p-) is a chromosomal deletion syndrome characterized by a high-pitched, catlike cry; mental retardation; congenital heart disease, and microcephaly. Microdeletions are associated with retinoblastoma and Wilm's tumor.

* Klinefelter syndrome and Turner syndrome are important disorders of sex chromosomes. Klinefelter syndrome (47,XXY) is a common cause of male hypogonadism and is characterized by testicular atrophy, infertility due to azoospermia, eunuchoid body habitus, high-pitched voice, female distribution of hair, and gynecomastia. Turner syndrome (45,XO) is a common cause of female hypogonadism and is characterized by absent Barr bodies, failure to develop secondary sex characteristics, short stature, atrophic “streak” ovaries, primary amenorrhea, infertility, cystic hygroma and webbing of the neck, hypothyroidism, congenital heart disease (pseudocoloration of the aorta, bicuspid aortic valve), and hydrops fetalis.

* True hermaphrodites have both ovarian and testicular tissue and are exceptionally rare. Female pseudohermaphrodites are genetically normal females with normal female internal organs but ambiguous or virilized external genitalia, usually as a result of exposure to endogenous or exogenous androgens. Male pseudohermaphrodites are genetically normal males with testes and ambiguous or female external genitalia; the most common cause is testicular feminization, due to a genetically defective androgen receptor.

* Mendelian disorders are characterized by single gene mutations, which may be either point mutations or frameshift mutations. These mutations may produce autosomal dominant, autosomal recessive, or X-linked diseases.

* Cystic fibrosis is a common autosomal recessive disorder due to a defect in the chloride channel protein, the cystic fibrosis transmembrane conductance regulator (CFTR), and can be diagnosed when elevated NaCl is identified in sweat. Cystic fibrosis now has mean survival of 30 years and is characterized clinically by recurrent severe pulmonary infections and pancreatic insufficiency.

* Phenylketonuria (PKU) is an autosomal recessive disease due to deficiency of phenylalanine hydroxylase, which can cause severe mental retardation if not identified by biochemical screening at birth.

* Alkaptonuria is an autosomal recessive disease due to deficiency of homogentisic acid, which is characterized clinically by degenerative arthritis, black discoloration of cartilage (including that in the nose and ears), and urine that turns black on standing.

* Albinism is an autosomal deficiency of melanin pigmentation in the skin, hair follicles, and eyes that occurs secondary to tyrosinase deficiency and is associated with an increased risk of basal cell and squamous cell skin cancers.

(Continued)
Chapter Summary (continued)

- Glycogen storage diseases are rare diseases due to abnormalities of glycogen metabolism that result in accumulation of glycogen in liver, heart, and skeletal muscle. Important subtypes include von Gierke disease, Pompe disease, and McArdle syndrome.

- Tay-Sachs disease is an autosomal recessive disease seen in Ashkenazi Jews, which is due to deficiency of hexosaminidase A, leading to GM₂ ganglioside deposition with progressive mental deterioration, culminating in death by age 2–3.

- Niemann-Pick disease is an autosomal recessive deficiency of sphingomyelinase, leading to accumulation of sphingomyelin with hepatosplenomegaly, mental deterioration, and death by age 2.

- Gaucher disease is an autosomal recessive deficiency of glucocerebrosidase, leading to accumulation of glucocerebroside, with hepatosplenic enlargement and bone marrow involvement. Most cases present in adulthood; cases presenting at younger ages may have CNS manifestations.

- The mucopolysaccharidoses (MPS) are lysosomal storage disorders characterized by deficiencies in the lysosomal enzymes required for the degradation of mucopolysaccharides (glycosaminoglycans). Mental retardation, hepatosplenomegaly, and skeletal deformities occur in this group; Hunter syndrome (MPS II) is less severe than Hurler syndrome (MPS I).

- Familial hypercholesterolemia is a common autosomal dominant disorder with atherosclerotic manifestations (worst in homozygotes) due to genetic defects of several forms involving the low density lipoprotein (LDL) receptor gene.

- Marfan syndrome is an autosomal dominant disorder due to mutation of the fibrillin gene (FBN1) characterized by skeletal abnormalities (tall build with hyperextensible joints and chest abnormalities), subluxation of the lens, and cardiovascular system problems (cystic medial necrosis, dissecting aortic aneurysm, valvular insufficiency).

- Ehlers-Danlos syndrome is a group of inherited connective tissue diseases that have in common a defect in collagen structure or synthesis and are characterized clinically by hyperextensible skin and joints with complications including poor wound healing, joint dislocations, daphraegmatic hernias, retinal detachment, kyphoscoliosis, and arterial or colonic rupture.

- Von Recklinghausen disease (neurofibromatosis type 1) is an autosomal dominant defect in the tumor suppressor gene NF-1, which is characterized clinically by multiple neurofibromas, café-au-lait spots of the skin, Lisch nodules of the iris, and an increased risk of meningiomas and pheochromocytomas. Bilateral acoustic neurofibromatosis (neurofibromatosis type 2) is less common than von Recklinghausen disease and due to a defect in tumor suppressor gene NF-2. It is characterized clinically by bilateral acoustic neuromas, neurofibromas, café-au-lait spots, and an increased risk of meningiomas and ependymomas.

- Von Hippel-Lindau disease is due to an abnormality of a tumor suppressor gene of chromosome 3p and is characterized clinically by hemangioblastomas in the central nervous system and retina, renal cell carcinoma, and cysts of internal organs.

- Fragile X syndrome is an important cause of familial mental retardation and is due to a triple nucleotide repeat mutation in the FMR-1 gene on the X chromosome. It is characterized clinically by mental retardation (affected males more severe than female carriers), elongated face, large ears, and macro-orchidism.

(Continued)
Chapter Summary (continued)

* Huntington disease is due to a triple repeat mutation of the Huntington gene, which clinically produces atrophy of the caudate nucleus with choreiform movements and progressive dementia.

* Genomic imprinting refers to differential expression of genes based on chromosomal inheritance from maternal versus paternal origin. The classic examples are the mental retardation syndromes Prader-Willi syndrome (paternal deletion of chromosome 15 with obesity and hypogonadism) and Angelman syndrome (maternal deletion of chromosome 15 producing ataxia and inappropriate laughter characterized as “happy puppet”).

* Most X-linked disorders are recessive, with males expressing the disease and producing daughter carriers; examples include Lesch-Nyhan syndrome (hyperuricemia, mental retardation, and self-mutilation due to impaired purine salvage), testicular feminization (androgen insensitivity leads to failure of normal masculinization), chronic granulomatous disease (impaired killing of bacteria by neutrophils leads to repeated infections), and Bruton agammaglobulinemia (lack of immunoglobulin production causes recurrent bacterial infections).

* Rare X-linked disorders are dominant, causing disease in both daughters and sons. Alport disease (hereditary glomerulonephritis with nerve deafness) is an example.

* Mitochondrial DNA disorders are transmitted from the mother, but not the father, to the offspring. These include Leber hereditary optic neuropathy and myoclonic epilepsy.

* Multifactorial inheritance occurs when disease is caused by multiple gene mutations and environmental factors; examples include open neural tube defects and type 2 diabetes mellitus.
HYPERSENSITIVITY REACTIONS

1. Type I (Immediate) hypersensitivity (anaphylactic type)
   a. Definition: hypersensitivity reactions are characterized by IgE-related release of
chemical mediators from mast cells and basophils. The release is triggered by
exposure to an antigen.
   b. Requires prior sensitization to the antigen
   c. Requires cross-linking of IgE Fc receptors on the surface of mast cells and baso-
phils
   d. Release of chemical mediators
      i. Histamine and heparin
      ii. Eosinophil chemotactic factor
      iii. Leukotriene B4 and neutrophil chemotactic factor
      iv. Prostaglandin D4, platelet-activating factor (PAF), and leukotrienes C4 and D4
   e. Influx of eosinophils amplify and perpetuate the reaction
   f. Effects may be localized or systemic
      i. Systemic: anaphylaxis (e.g., bee stings and drugs)
      ii. Localized: food allergies, atopy, and asthma

2. Type II hypersensitivity (antibody-mediated)
   a. Definition: hypersensitivity reaction characterized by production of an IgG or IgM
antibody directed against a specific target cell or tissue
   b. Complement-dependent cytotoxicity
      i. Fixation of complement results in osmotic lysis or opsonization of antibody-
coated cells.
      ii. Examples: autoimmune hemolytic anemia, transfusion reactions, erythroblast-
sis fetalis
   c. Antibody-dependent cell-mediated cytotoxicity (ADCC)
      i. Cytotoxic killing of an antibody-coated cell
      ii. Example: pernicious anemia
   d. Antireceptor antibodies
      i. Antibodies activate or interfere with receptors
      ii. Examples: Graves disease, myasthenia gravis

3. Type III hypersensitivity (immune complex disease)
   a. Definition: hypersensitivity reaction characterized by the formation of in situ or
circulating antibody-antigen immune complexes, which deposit in tissue resulting
in inflammation and tissue injury
b. Examples
   i. Serum sickness
   ii. Systemic lupus erythematosus (SLE)
   iii. Glomerulonephritis
4. **Type IV hypersensitivity (cell-mediated type)**
   a. Definition: hypersensitivity reaction mediated by sensitized T lymphocytes
   b. Delayed type hypersensitivity
      i. CD4+ Th1-cell lymphocytes mediate granuloma formation
      ii. PPD skin test and tuberculosis
   c. Cytotoxic T-cell–mediated
      i. CD8+ T-cell lymphocytes destroy antigen-containing cells.
      ii. Viral infections, immune reaction to tumors, contact dermatitis, and graft rejection

**Figure 7-1. Type III Hypersensitivity**
AUTOIMMUNE DISEASES

1. Systemic lupus erythematosus (SLE)
   a. Definition: chronic systemic autoimmune disease characterized by loss of self-tolerance and production of autoantibodies
   b. Epidemiology
      i. Females >> Males (M:F = 1:9)
      ii. Peak incidence: age 20–45 years
      iii. African American > Caucasian
   c. Autoantibodies
      i. Antinuclear antibody (ANA) (>95%)
      ii. Anti-dsDNA (40–60%)
      iii. Anti-Sm (20–30%)
      iv. Antihistone antibodies
   d. Mechanism of injury: type II and III hypersensitivity reactions
   e. Distribution of disease
      i. Hematologic (type II hypersensitivity reaction)
         • Hemolytic anemia
         • Thrombocytopenia
         • Neutropenia
         • Lymphopenia
      ii. Arthritis: polyarthritis and synovitis without joint deformity (type III hypersensitivity reaction)
      iii. Skin (type III hypersensitivity reaction)
         • Malar “butterfly” rash
         • Maculopapular rash
         • Ulcerations and bullae formation
      iv. WHO classification of kidney manifestations (type III hypersensitivity reaction)
         • Class I: normal
         • Class II: mesangial lupus nephritis
         • Class III: focal proliferative glomerulonephritis
         • Class IV: diffuse proliferative glomerulonephritis (most common and severe)
         • Class V: membranous glomerulonephritis
   v. Heart: Libman-Sacks endocarditis (nonbacterial verrucous endocarditis) (type III hypersensitivity reaction)
   vi. Serosal surfaces: pericarditis, pleuritis, and pleural effusions (type III hypersensitivity reaction)
   vii. CNS: focal neurologic symptoms, seizures, and psychosis (type III hypersensitivity reaction)
   f. Treatment: steroids and immunosuppressive agents
   g. Prognosis
      i. Chronic, unpredictable course with remissions and relapses
      ii. Ten-year survival: 85%
      iii. Death is frequently due to renal failure and infections

Note
Multiple autoantibodies may be produced and are commonly directed against nuclear antigens (DNA, histones, nonhistone nuclear RNA proteins) and blood cells.
2. Sjögren syndrome (sicca syndrome)
   a. Definition: an autoimmune disease characterized by destruction of the lacrimal and salivary glands, resulting in the inability to produce saliva and tears
   b. Clinical features
      i. Females > males; age range: 30 to 50 years
      ii. Keratoconjunctivitis sicca (dry eyes) and corneal ulcers
      iii. Xerostomia (dry mouth)
      iv. Mikulicz syndrome: enlargement of the salivary and lacrimal glands
   c. Often associated with rheumatoid arthritis and other autoimmune diseases
   d. Anti-ribonucleoprotein antibodies
      i. SS-A (Ro)
      ii. SS-B (La)
   e. Complication: increased risk of developing non-Hodgkin lymphoma

3. Scleroderma (progressive systemic sclerosis)
   a. Definition: autoimmune disease characterized by fibroblast stimulation and deposition of collagen in the skin and internal organs
   b. Females > males; age range: 20 to 55 years
   c. Pathogenesis: activation of fibroblasts by cytokines interleukin 1 (IL-1), platelet-derived growth factor (PDGF), and/or fibroblast growth factor (FGF) leads to fibrosis
   d. Diffuse scleroderma
      i. Anti-DNA topoisomerase I antibodies (Scl-70) (70%)
      ii. Widespread skin involvement
      iii. Early involvement of the visceral organs
         a. Esophagus—dysphagia
         b. GI tract—malabsorption
         c. Pulmonary fibrosis—dyspnea on exertion
         d. Cardiac fibrosis—arrhythmias
         e. Kidney fibrosis—renal insufficiency
   e. Localized scleroderma (CREST syndrome)
      i. Anti-centromere antibodies
      ii. Skin involvement of the face and hands
      iii. Late involvement of visceral organs
      iv. Relatively benign clinical course

In a Nutshell

CREST Syndrome
- Calcinosis
- Raynaud phenomenon
- Esophageal dysmotility
- Sclerodactyly
- Telangiectasia

4. Dermatomyositis and polymyositis
   a. Closely related conditions with immune-mediated muscle damage
   b. Dermatomyositis has skin involvement and is due to antibody-mediated damage.
   c. Polymyositis does not have skin involvement and is due to T cell-mediated damage.
   d. Most often occurs in 40 to 60-year-old women who have muscle pain and atrophy, particularly involving shoulders
   e. Dermatomyositis is characterized by purple-red (heliotrope) rash on eyelids.
   f. Both have increased serum creatine kinase and sometimes positive ANA.

5. Mixed connective tissue diseases
   a. Overlap condition with features of systemic lupus erythematosus, systemic sclerosis, and polymyositis
   b. Antiribonucleoprotein antibodies nearly always positive
PRIMARY IMMUNE DEFICIENCY SYNDROMES

1. X-linked agammaglobulinemia of Bruton
   a. Definition: inherited immunodeficiency characterized by a developmental failure to produce mature B cells and plasma cells, resulting in agammaglobulinemia
   b. Genetics: mutation of B-cell Bruton tyrosine kinase (Btk)
   c. Clinical findings
      i. Male infants
      ii. Recurrent infections beginning at 6 months of life due to the loss of passive maternal immunity
      iii. Common infections: pharyngitis, otitis media, bronchitis, and pneumonia

2. Common variable immunodeficiency
   a. Definition: group of disorders characterized by a B-cell maturation defect and hypogammaglobulinemia
   b. Clinical findings
      i. Both sexes are affected
      ii. Onset is in childhood
      iii. Recurrent bacterial infections
      iv. Increased susceptibility to Giardia lamblia
   c. Complications
      i. Increased frequency of developing autoimmune diseases
      ii. Increased risk of non-Hodgkin lymphoma and gastric cancer

3. DiGeorge syndrome
   a. Definition: embryologic failure to develop the 3rd and 4th pharyngeal pouches, resulting in the absence of the parathyroid glands and thymus
   b. Clinical findings
      i. Hypocalcemia and tetany
      ii. T-cell deficiency
      iii. Recurrent infections with viral and fungal organisms

4. Severe combined immunodeficiency (SCID)
   a. Definition: combined deficiency of cell-mediated and humoral immunity often caused by a stem-cell defect
   b. Modes of inheritance
      i. X-linked (mutation of the chemokine receptor)
      ii. Autosomal recessive (deficiency of adenosine deaminase)
   c. Clinical features
      i. Recurrent infections with bacteria, fungi, viruses, and protozoa
      ii. Susceptible to Candida, cytomegalovirus (CMV), and Pneumocystis carinii infection
      iii. Have adverse reactions to live virus immunizations
   d. Treatment
      i. Stem cell transplant
   e. Prognosis: without treatment most infants die of infection within a year

Note

Adenosine → Inosine

Adenosine deaminase

Deoxyadenosine → deoxyinosine

Adenosine Deaminase Deficiency
Adenosine deaminase is an important enzyme in purine metabolism; deficiency of a deoxynucleoside deaminase results in accumulation of deoxyadenosine within lymphoid stem cells.
5. Wiskott-Aldrich syndrome
   a. Genetics
      i. X-linked recessive inheritance
      ii. Mutation in the gene for Wiskott-Aldrich syndrome protein (WASP)
   b. Clinical triad
      i. Recurrent infections
      ii. Severe thrombocytopenia
      iii. Eczema (chronic spongiform dermatitis)
   c. Treatment: bone marrow transplant
   d. Complications
      i. Increased risk of non-Hodgkin lymphoma
      ii. Death due to infection or hemorrhage

6. Complement system disorders
   a. Factors in both the classical and alternate pathways
      i. C3 deficiency causes both recurrent bacterial infections and immune complex disease.
      ii. C5, C6, C7, and C8 deficiencies cause recurrent meningococcal and gonococcal infections.
   b. Factors in classical pathway only
      i. C1q, C1r, C1s, C2, and C4 deficiencies cause marked increases in immune complex diseases, including infections with pyogenic bacteria.
   c. Factors in alternate pathway only
      i. Factor B and properdin deficiencies cause increased neisserial infections.
   d. Deficiencies in complement regulatory proteins
      i. C1-INH deficiency (hereditary angioedema)
      ii. Causes edema at mucosal surfaces
      iii. C2 and C4 levels are low
SECONDARY IMMUNE DEFICIENCY SYNDROMES

1. Systemic diseases
   a. Diabetes mellitus
   b. Collagen vascular disease (e.g., SLE)
   c. Chronic alcoholism
2. Renal transplantation
   a. Patients are immunocompromised due to the immunosuppressive drugs required to prevent rejection of the transplanted organ
   b. Hyperacute rejection
      i. Mediated by preformed antibodies
      ii. Occurs immediately after transplantation
      iii. Micro: neutrophilic vasculitis with thrombosis
   c. Acute rejection
      i. Occurs weeks or up to 6 months after organ transplantation
      ii. Abrupt onset of oliguria and azotemia
      iii. Micro: neutrophilic vasculitis and interstitial lymphocytes
      iv. Treated with increased doses of immunosuppressive drugs
   d. Chronic rejection
      i. Occurs greater than 6 months or years after organ transplantation
      ii. Gradual onset of oliguria, hypertension (HTN), and azotemia
      iii. Micro: intimal fibrosis of vessels and interstitial lymphocytes
      iv. Poor response to treatment

Note
Cardiac Transplantation
The major complication in long-term cardiac transplant patients is accelerated graft arteriosclerosis.
3. Acquired immunodeficiency syndrome (AIDS)
   a. Definition: HIV positive and CD4 count <200 cells/µL or HIV positive and an AIDS-defining disease
   b. Epidemiology
      i. Males > females
      ii. Occurs in all ages and ethnic groups
      iii. All areas of the country are affected.
   c. Transmission of HIV
      i. Sexual contact (most common mode of transmission)
         • Homosexuals
         • Increasing rate of heterosexual transmission
         • Cofactors: herpes and syphilis
      ii. Parenteral transmission
         • Intravenous drug use
         • Hemophiliacs
         • Blood transfusions
         • Accidental needle sticks in hospital workers
      iii. Vertical transmission
   d. Human immunodeficiency virus (HIV)
      i. Enveloped RNA retrovirus
      ii. Reverse transcriptase
      iii. HIV infects CD4-positive cells
         • CD4+ T-cell lymphocytes
         • All macrophages
         • Lymph node follicular dendritic cells
         • Langerhans cells

Clinical Correlate

There is no evidence that AIDS is transmitted by casual contact.
Figure 7-3. Mechanisms of HIV Infection

iv. Binding of CD4 by gp120
v. Entry into cell by fusion requires gp41 and coreceptors
   - CCR5 (β-chemokine receptor 5)
   - CXCR4 (α-chemokine receptor)
e. Diagnosis
   i. HIV antibody ELISA test
   ii. Western blot confirmation
f. Monitoring
   i. CD4 count
   ii. HIV-1 RNA viral load by PCR

Table 7-1. Important CD4 Count Levels

<table>
<thead>
<tr>
<th>CD4 Count (cells/μL)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>700–1,500</td>
<td>Normal</td>
</tr>
<tr>
<td>200–500</td>
<td>Oral thrush, Kaposi sarcoma, tuberculosis, zoster</td>
</tr>
<tr>
<td>100–200</td>
<td><em>Pneumocystis carinii</em> pneumonia, dementia</td>
</tr>
<tr>
<td>&lt;100</td>
<td><em>Toxoplasmosis</em>, <em>cryptococcus</em>, cryptosporidiosis</td>
</tr>
<tr>
<td>&lt;50</td>
<td><em>Cytomegalovirus</em>, <em>Mycobacterium-avium</em> complex, progressive multifocal leukoencephalopathy</td>
</tr>
</tbody>
</table>
g. Treatment
   i. Combination antiretroviral treatment
   ii. Reverse transcriptase inhibitors
   iii. Protease inhibitors
   iv. Prophylaxis for opportunistic infections based on CD4 count
h. Acute phase
   i. Initial infection
   ii. Viremia with a reduction in CD4 count
   iii. Mononucleosis-like viral symptoms and lymphadenopathy
   iv. Seroconversion
i. Latent phase
   i. Asymptomatic or persistent generalized lymphadenopathy
   ii. Continued viral replication in reservoir sites
   iii. Low level of virus in the blood
   iv. Minor opportunistic infections
      * Oral thrush (candidiasis)
      * Varicella zoster
   v. Average duration of latent phase: 10 years
j. Progression to AIDS
   i. Reduction of CD4 count to <200 cells/μL
   ii. Reemergence of viremia
   iii. AIDS-defining diseases occur
   iv. Death

Table 7-2. Opportunistic Infection and Common Sites of Infection in AIDS Patients

<table>
<thead>
<tr>
<th>Opportunistic Infection</th>
<th>Common Sites of Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pneumocystis carinii</em></td>
<td>Lung (pneumonia), bone marrow</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Lung, disseminated</td>
</tr>
<tr>
<td><em>Mycobacterium avium-intracellulare</em></td>
<td>Lung, GI tract, disseminated</td>
</tr>
<tr>
<td>Cocciidioidomycosis</td>
<td>Lung, disseminated</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>Lung, disseminated</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Lung, retina, adrenals, and GI tract</td>
</tr>
<tr>
<td><em>Giardia lamblia</em></td>
<td>GI tract</td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td>GI tract</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Esophagus and CNS (encephalitis)</td>
</tr>
<tr>
<td><em>Candida</em></td>
<td>Oral pharynx and esophagus</td>
</tr>
<tr>
<td><em>Aspergillus</em></td>
<td>CNS, lungs, blood vessels</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>CNS</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>CNS (meningitis)</td>
</tr>
<tr>
<td>JC virus</td>
<td>CNS (progressive multifocal leukoencephalopathy)</td>
</tr>
</tbody>
</table>
k. Hairy leukoplakia: Epstein-Barr virus (EBV)–associated due to infection of squamous cells
l. Kaposi sarcoma
   i. Common in homosexual males
   ii. Associated with human herpes virus 8 (HHV8), which has cellular tropism for endothelial cells, B cells, T cells, and monocytes
   iii. Common sites: skin, GI tract, lymph nodes, and lungs
m. Non-Hodgkin lymphoma
   i. Tend to be high-grade B-cell lymphomas
   ii. Extranodal CNS lymphomas are common.

n. Cervical cancer
o. HIV wasting syndrome
p. AIDS nephropathy
q. AIDS dementia complex

Chapter Summary

* Type I hypersensitivity (anaphylactic type) reactions are characterized by IgE-related release of chemical mediators from mast cells and basophils following exposure to an antigen. Examples of type I hypersensitivity reactions include systemic anaphylaxis following bee stings and drugs. Localized forms of anaphylactic reaction include food allergies, atopy, and asthma.

* Type II hypersensitivity (cytotoxic type) reactions are characterized by production of an IgG or IgM antibody directed against a specific target cell or tissue. Examples include the complement-dependent cytotoxicity of autoimmune hemolytic anemia, the antibody-dependent cell-mediated cytotoxicity of pernicious anemia, and the antireceptor antibodies of Graves disease.

* Type III hypersensitivity (immune complex disease) reactions are characterized by the formation of in situ or circulating antibody-antigen complexes that deposit in tissue, resulting in inflammation and tissue injury. Examples include serum sickness, systemic lupus erythematosus, and glomerulonephritis.

* Type IV hypersensitivity (cell-mediated type) reactions are mediated by sensitized T lymphocytes. Examples include the delayed hypersensitivity of PPD skin tests and tuberculosis and the cytotoxic T-cell-mediated destruction of antigen-containing cells in viral infections, immune reaction to tumors, contact dermatitis, and graft rejection.

* Systemic lupus erythematosus is a chronic systemic autoimmune disease characterized by a loss of self-tolerance and production of autoantibodies. Clinical manifestations include hemolytic anemia and other autoimmune hematologic manifestations, arthritis, skin rashes, and involvement of the renal, cardiovascular, and neurologic systems.

* Sjögren syndrome (sicca syndrome) is an autoimmune disease characterized by destruction of the lacrimal and salivary glands resulting in the inability to produce saliva and tears. Sjögren syndrome is associated with the antinuclear protein antibodies SS-A and SS-B, and also with other autoimmune diseases such as systemic lupus erythematosus.

* Scleroderma (progressive systemic sclerosis) is an autoimmune disease characterized by fibroblast stimulation and deposition of collagen in the skin and internal organs. Scleroderma can have anti-DNA topoisomerase I antibodies (Scl-70), widespread skin involvement, and early involvement of the esophagus, GI tract, lung, heart, and kidney. Localized forms have a more benign course.

(Continued)
Chapter Summary (continued)

* X-linked agammaglobulinemia of Bruton is an inherited immunodeficiency characterized by a developmental failure to produce mature B cells and plasma cells, resulting in agammaglobulinemia with recurrent bacterial infections.

* Common variable immunodeficiency is a group of disorders characterized by a B-cell maturation defect and hypogammaglobulinemia expressed as increased susceptibility to bacterial infections, *Giardia lamblia*, autoimmune diseases, lymphoma, and gastric cancer.

* DiGeorge syndrome is an embryologic failure to develop the third and fourth pharyngeal pouches, resulting in the absence of the parathyroid glands and thymus, leading to hypocalcemia with tetany, T-cell deficiency, and recurrent infections with viral and fungal organisms.

* Severe combined immunodeficiency (SCID) is a combined deficiency of cell-mediated and humoral immunity often caused by a stem cell defect that, without treatment, causes death by infection within 1 year. Affected infants are susceptible to recurrent infections by bacteria, fungi, viruses, and protozoa.

* Wiskott-Aldrich syndrome is an X-linked condition characterized by recurrent infections, severe thrombocytopenia, and eczema.

* Secondary immune deficiency syndromes can be caused by systemic diseases such as diabetes mellitus, collagen vascular disease (i.e., SLE), and chronic alcoholism.

* Rejection following renal transplantation can occur in three patterns: hyperacute rejection due to preformed antibodies that trigger vascular thrombosis, acute rejection characterized by neutrophilic vasculitis, and chronic rejection characterized by intimal fibrosis of vessels.

* Acquired immunodeficiency syndrome (AIDS) is said to be present when a patient is HIV positive with CD4 count less than 200 or HIV positive with an AIDS-defining disease. HIV can be spread by sexual contact, parenteral transmission, or vertical transmission. The virus is an RNA retrovirus with reverse transcriptase and a predilection for infecting CD4+ cells. Diagnosis is by HIV antibody ELISA test followed by Western blot confirmation. A variety of drugs are now available for treatment.

* HIV infection produces a mononucleosis-like acute phase, an asymptomatic latent phase, and then progression to AIDS. Clinical AIDS is characterized by susceptibility to a wide variety of opportunistic infections. AIDS patients are also prone to develop hairy leukoplakia, Kaposi sarcoma, high-grade B-cell lymphomas, cervical cancer, a wasting syndrome, nephropathy, and dementia.
Amyloidosis

DEFINITION
A group of diseases characterized by the deposition of an extracellular protein that has specific properties

COMMON FEATURES OF AMYLOID
1. Individual subunits form β-pleated sheets
2. Micro
   a. Amorphous eosinophilic extracellular deposits of amyloid are seen on the H&E stain.
   b. The deposits stain red with the Congo red stain.
   c. Apple green birefringence of the amyloid is seen on the Congo red stain under polarized light.

COMPOSITION OF AMYLOID
1. A fibrillar protein that varies with each disease
2. Amyloid P (AP) component
3. Glycosaminoglycans (heparan sulfate)

SYSTEMIC TYPES OF AMYLOID
1. Primary amyloidosis
   a. Type of amyloid: Amyloid light chain (AL)
   b. Fibrillar protein: kappa or lambda light chains
   c. Plasma cell disorders (multiple myeloma, B-cell lymphomas, etc.)
2. Reactive systemic amyloidosis (secondary amyloidosis)
   a. Type of amyloid: Amyloid-associated (AA)
   b. Fibrillar protein: serum amyloid A (SAA)
   c. SAA is an acute phase reactant produced by the liver
   d. SAA is elevated with ongoing chronic inflammation and neoplasia
   e. Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), TB, bronchiectasis, osteomyelitis, Crohn disease, cancer, etc.
3. Familial Mediterranean fever
   a. Type of amyloid: AA
   b. Fibrillar protein: serum amyloid A (SAA)
Clinical Correlate
Carpal tunnel syndrome is caused by compromise of the median nerve within the tunnel formed by the carpal bones and flexor retinaculum.

c. Autosomal recessive disease
d. Recurrent inflammation, fever, and neutrophil dysfunction

4. Hemodialysis-associated amyloidosis
a. Type of amyloid: Aβ2M
b. Fibrillar protein = β2-microglobulin
c. May cause carpal tunnel syndrome and joint disease

LOCALIZED TYPES OFAMYLOID
1. Senile cerebral amyloidosis (Alzheimer disease)
a. Type of amyloid: Aβ
b. Fibrillar protein: β-amyloid precursor protein (βAPP)
c. Found in Alzheimer plaques and in cerebral vessels
d. The gene for βAPP is located on chromosome 21.

2. Senile cardiac/systemic amyloidosis
a. Type of amyloid: ATTR
b. Fibrillar protein: transthyretin
c. Men >70 years old
d. May cause heart failure as a result of restrictive/infiltrative cardiomyopathy

3. Endocrine type
a. Medullary carcinoma of the thyroid (procalcitonin)
b. Adult-onset diabetes (amylin)
c. Pancreatic islet cell tumors (amylin)

CLINICAL FEATURES
1. Distribution of disease in systemic forms
   a. Kidney
      i. Most commonly involved organ
      ii. Nephrotic syndrome
      iii. Progressive renal failure
   b. Heart
      i. Restrictive cardiomyopathy
      ii. Low voltage EKG
      iii. Cardiac arrhythmias and CHF
   c. Hepatosplenomegaly
d. Gastrointestinal tract
   i. Tongue enlargement (macroglossia, primarily in AL type)
   ii. Malabsorption

2. Diagnosis:
   a. Biopsy of the rectal mucosa, gingiva, or the abdominal fat pad
   b. Congo red stain shows apple green birefringence under polarized light.

3. Prognosis: the prognosis of systemic amyloidosis is poor.
Chapter Summary

* Amyloidosis is a group of diseases characterized by the deposition of an extracellular protein that tends to form β-pleated sheets and stain red with apple green birefringence with Congo red stain.

* Amyloid is composed of a fibrillar protein, amyloid P component, and glycosaminoglycans. The specific composition of the protein varies with each disease producing amyloidosis.

* In primary amyloidosis, which can complicate plasma cell disorders, the amyloid protein is AL, and the fibrillar protein is kappa or lambda light chains.

* Reactive systemic amyloidosis (secondary amyloidosis) can complicate neoplasia and ongoing inflammation due to many chronic diseases (macrophages) including rheumatoid arthritis, systemic lupus erythematosus, tuberculosis, osteomyelitis, and Crohn disease. The amyloid protein in reactive systemic amyloidosis is AA, and the fibrillar protein is serum amyloid A (SAA), which is an acute phase reactant produced by the liver.

* Familial Mediterranean fever is an autosomal recessive inflammatory disease with amyloid protein AA and fibrillar protein SAA.

* Hemodialysis-associated amyloidosis is associated with amyloid protein Aβ2M and fibrillar protein β2-microglobulin.

* Localized forms of amyloidosis are seen in senile cerebral amyloidosis (amyloid protein Aβ and fibrillar protein β-amyloid precursor protein); senile cardiac/systemic amyloidosis (amyloid protein ATTR and fibrillar protein transthyretin); and in some endocrine diseases, including medullary carcinoma of the thyroid (procalcitonin), adult-onset diabetes (amylin), and pancreatic islet cell tumors (amylin).

* Systemic amyloidosis has a poor prognosis and tends to involve the kidney, heart, liver, spleen, and GI tract.
Principles of Neoplasia

DEFINITION
An abnormal cell or tissue that grows more rapidly than normal cells or tissue, by acquiring multiple genetic changes over time and continuing to grow after the stimuli that initiated the new growth is removed.

EPIDEMIOLOGY
1. General facts
   a. Cancer is the second leading cause of death in the United States.
      i. Estimated number of new cancers in 2008: 1,437,180
      ii. Estimated number of deaths from cancer in 2008: 565,650

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause of Death</th>
<th>Number of Deaths</th>
<th>Percentage of Total Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Heart diseases</td>
<td>652,091</td>
<td>26.6</td>
</tr>
<tr>
<td>2</td>
<td>Cancer</td>
<td>559,312</td>
<td>22.8</td>
</tr>
<tr>
<td>3</td>
<td>Cerebrovascular diseases</td>
<td>143,579</td>
<td>5.9</td>
</tr>
<tr>
<td>4</td>
<td>Chronic lower respiratory diseases (COPD)</td>
<td>130,933</td>
<td>5.3</td>
</tr>
<tr>
<td>5</td>
<td>Accidents (unintentional injuries)</td>
<td>117,809</td>
<td>4.8</td>
</tr>
<tr>
<td>6</td>
<td>Diabetes mellitus</td>
<td>75,119</td>
<td>3.1</td>
</tr>
<tr>
<td>7</td>
<td>Pneumonia and influenza</td>
<td>71,599</td>
<td>2.9</td>
</tr>
<tr>
<td>8</td>
<td>Alzheimer disease</td>
<td>63,001</td>
<td>2.6</td>
</tr>
<tr>
<td>9</td>
<td>Nephritis, nephrotic syndrome, and nephrosis</td>
<td>43,901</td>
<td>1.8</td>
</tr>
<tr>
<td>10</td>
<td>Septicemia</td>
<td>34,136</td>
<td>1.4</td>
</tr>
<tr>
<td>11</td>
<td>Suicide</td>
<td>32,637</td>
<td>1.3</td>
</tr>
<tr>
<td>12</td>
<td>Cirrhosis and chronic liver disease</td>
<td>27,530</td>
<td>1.1</td>
</tr>
<tr>
<td>13</td>
<td>Hypertension and hypertensive renal disease</td>
<td>24,902</td>
<td>1.0</td>
</tr>
<tr>
<td>14</td>
<td>Homicide (assault)</td>
<td>19,544</td>
<td>0.8</td>
</tr>
<tr>
<td>15</td>
<td>Parkinson disease</td>
<td>18,124</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**Total of 2,448,017 deaths.
Table 9-2. Leading Causes of Death in Children Ages 1–14 in the United States, 2001*

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause of Death</th>
<th>Percentage of Total Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Accidents</td>
<td>37.3</td>
</tr>
<tr>
<td>2</td>
<td>Cancer</td>
<td>11.7</td>
</tr>
<tr>
<td>3</td>
<td>Congenital anomalies</td>
<td>7.6</td>
</tr>
<tr>
<td>4</td>
<td>Homicide</td>
<td>6.0</td>
</tr>
<tr>
<td>5</td>
<td>Heart disease</td>
<td>4.1</td>
</tr>
<tr>
<td>6</td>
<td>Suicide</td>
<td>2.3</td>
</tr>
<tr>
<td>7</td>
<td>Pneumonia and influenza</td>
<td>1.7</td>
</tr>
<tr>
<td>8</td>
<td>Septicemia</td>
<td>1.5</td>
</tr>
<tr>
<td>9</td>
<td>In situ/Benign/Unknown neoplasms</td>
<td>1.3</td>
</tr>
<tr>
<td>10</td>
<td>Chronic lower respiratory disease</td>
<td>1.2</td>
</tr>
</tbody>
</table>


Table 9-3. Estimated New Cancer Cases by Site and Sex,* Year 2008, in the United States†

<table>
<thead>
<tr>
<th>Males</th>
<th>Percentage</th>
<th>Females</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td></td>
<td>Site</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>25</td>
<td>Breast</td>
<td>26</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>15</td>
<td>Lung and bronchus</td>
<td>14</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>10</td>
<td>Colon and rectum</td>
<td>10</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7</td>
<td>Uterine corpus</td>
<td>6</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>5</td>
<td>Non-Hodgkin lymphoma</td>
<td>4</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>5</td>
<td>Melanoma of the skin</td>
<td>4</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>4</td>
<td>Thyroid</td>
<td>4</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3</td>
<td>Ovary</td>
<td>3</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>3</td>
<td>Kidney &amp; renal pelvis</td>
<td>3</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3</td>
<td>Leukemia</td>
<td>3</td>
</tr>
</tbody>
</table>

*Excludes basal and squamous cell skin cancers and in situ carcinomas, except urinary bladder

Table 9-4. Estimated New Cancer Mortality by Site and Sex, Year 2008, in the United States*

<table>
<thead>
<tr>
<th>Site</th>
<th>Males Percentage</th>
<th>Site</th>
<th>Females Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung and bronchus</td>
<td>31</td>
<td>Lung and bronchus</td>
<td>26</td>
</tr>
<tr>
<td>Prostate</td>
<td>10</td>
<td>Breast</td>
<td>15</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>8</td>
<td>Colon and rectum</td>
<td>9</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6</td>
<td>Ovary</td>
<td>6</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4</td>
<td>Pancreas</td>
<td>6</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4</td>
<td>Leukemia</td>
<td>3</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>4</td>
<td>Non-Hodgkin lymphoma</td>
<td>3</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3</td>
<td>Uterine corpus</td>
<td>3</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3</td>
<td>Brain &amp; other nervous system</td>
<td>2</td>
</tr>
</tbody>
</table>


2. Predisposition to cancer
   a. Geographic and racial factors
      i. Stomach cancer—Japan >> United States
      ii. Breast cancer—United States >> Japan
      iii. Liver hepatoma—Asia >> United States
      iv. Prostate cancer—African American > Caucasian
   b. Occupational exposures
   c. Age
   d. Heredity predisposition
      i. Familial retinoblastoma
      ii. Multiple endocrine neoplasia
      iii. Familial polyposis coli
   e. Acquired preneoplastic disorders
      i. Cervical dysplasia
      ii. Endometrial hyperplasia
      iii. Cirrhosis
      iv. Ulcerative colitis
      v. Chronic atrophic gastritis

CARCINOGENIC AGENTS

1. Chemical carcinogens
   a. Carcinogenesis is a multistep process involving a sequence of initiation (mutation) followed by promotion (proliferation).
   b. Initiators
      i. Direct-acting chemical carcinogens: These are mutagens that cause cancer directly by modifying DNA.
ii. Indirect-acting chemical carcinogens (procarcinogens): These require metabolic conversion to form active carcinogens.

c. Promoters
   i. Cause cellular proliferation of mutated (initiated) cells
   ii. Proliferation of a mutated cell may lead to accumulation of additional mutations

d. Clinically important chemical carcinogens
   i. Nitrosamines: gastric cancer
   ii. Cigarette smoke: multiple malignancies
   iii. Polycyclic aromatic hydrocarbons: bronchogenic carcinoma
   iv. Asbestos: bronchogenic carcinoma, mesothelioma
   v. Chromium and nickel: bronchogenic carcinoma
   vi. Arsenic: squamous cell carcinomas of skin and lung, angiosarcoma of liver
   vii. Vinyl chloride: angiosarcoma of liver
   viii. Aromatic amines and azo dyes: hepatocellular carcinoma
   ix. Alkalating agents: leukemia, lymphoma, other cancers
   x. Benzene: leukemia
   xi. Naphthylamine: bladder cancer

e. Potential carcinogens are screened by the Ames test
   i. Detects any mutagenic effects of potential carcinogens on bacterial cells in culture
   ii. Mutagenicity in vitro correlates well with carcinogenicity in vivo.

2. Radiation
   a. Ultraviolet radiation
      i. UVB sunlight is the most carcinogenic.
      ii. Produces pyrimidine dimers in DNA leading to transcriptional errors and mutations of oncogenes and tumor suppressor genes
      iii. Increased risk of skin cancer
      iv. Xeroderma pigmentosum: autosomal recessive inherited defect in DNA repair
   b. Ionizing radiation
      i. X-rays and gamma rays, alpha and beta particles, protons, neutrons
      ii. Cells in mitosis or the G2 phase of the cell cycle are most sensitive to radiation.
      iii. Radiation causes cross-linking and chain breaks in nucleic acids.
      iv. Atomic bomb: leukemias, thyroid cancer, other cancers
      v. Uranium miners: lung cancer

3. Oncogenic viruses
   b. DNA oncogenic viruses
      i. Hepatitis B virus causes hepatocellular carcinoma.
      ii. Epstein-Barr virus (EBV)
         • Burkitt lymphoma
         • B-cell lymphomas in immunosuppressed patients
         • Nasopharyngeal carcinoma

Bridge to Biochemistry

Diseases associated with DNA repair include xeroderma pigmentosum and hereditary nonpolyposis colorectal cancer.
iii. Human papilloma virus (HPV) causes
   - Benign squamous papillomas (warts-condyloma acuminatum)
   - Cervical, vulvar, vaginal, penile, and anal carcinoma
iv. Kaposi-sarcoma-associated herpesvirus (HHV8) causes Kaposi sarcoma

4. Loss of immune regulation
   a. Immunosurveillance normally destroys neoplastic cells via recognition of “non-self” antigens.
   b. Both humoral and cell-mediated immune responses play a role.
   c. Patients with immune system dysfunction have increased number of neoplasms, especially malignant lymphomas.

CARCINOGENESIS

1. General
   a. Carcinogenesis is a multistep process.
   b. Development of all human cancers requires the accumulation of multiple genetic changes.
      i. Inherited germ-line mutations
      ii. Acquired mutations
   c. A tumor is derived from a monoclonal expansion of a mutated cell.
   d. Most important mutations involve
      i. Growth promoting genes (protooncogenes)
      ii. Growth inhibiting tumor suppressor genes
      iii. The genes regulating apoptosis and senescence

2. Activation of growth promoting oncogenes
   a. Protooncogenes are normal cellular genes involved with growth and cellular differentiation.
   b. Oncogenes are derived from protooncogenes by either
      i. A change in the gene sequence, resulting in a new gene product (oncoprotein)
      ii. Loss of gene regulation resulting in overexpression of the normal gene product
   c. Mechanisms of oncogene activation
      i. Point mutations
      ii. Chromosomal translocations
      iii. Gene amplification
      iv. Insertional mutagenesis
   d. Activated oncogenes lack regulatory control and are overexpressed, resulting in unregulated cellular proliferation.
Table 9-5. Clinically Important Oncogenes

<table>
<thead>
<tr>
<th>Oncogene</th>
<th>Tumor</th>
<th>Gene Product</th>
<th>Mechanism of Activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>hst-1 &amp; int-2</td>
<td>Cancer of the stomach, breast, bladder, and melanoma</td>
<td><strong>Growth factors</strong>&lt;br&gt;Fibroblast growth factor</td>
<td>Overexpression</td>
</tr>
<tr>
<td>sis</td>
<td>Astrocytoma</td>
<td><strong>Platelet-derived growth factor</strong></td>
<td>Overexpression</td>
</tr>
<tr>
<td>erb-B1</td>
<td>SCC of lung</td>
<td><strong>Growth factor receptors</strong>&lt;br&gt;Epidermal growth factor receptor</td>
<td>Overexpression</td>
</tr>
<tr>
<td>erb-B2</td>
<td>Breast, ovary, lung</td>
<td>Epidermal growth factor receptor</td>
<td>Amplification</td>
</tr>
<tr>
<td>erb-B3</td>
<td>Breast</td>
<td>Epidermal growth factor receptor</td>
<td>Overexpression</td>
</tr>
<tr>
<td>ret</td>
<td>MEN II &amp; III, familial thyroid (medullary) cancer</td>
<td><strong>Glial neurotrophic factor receptor</strong></td>
<td>Point mutation</td>
</tr>
<tr>
<td>abl</td>
<td>CML, ALL</td>
<td><strong>Signal transduction proteins</strong>&lt;br&gt;bcr-abl fusion protein with tyrosine kinase activity</td>
<td>Translocation t(9;22)</td>
</tr>
<tr>
<td>K-ras</td>
<td>Lung, pancreas, and colon</td>
<td><strong>GTP binding protein</strong></td>
<td>Point mutation</td>
</tr>
<tr>
<td>c-myc</td>
<td>Burkitt lymphoma</td>
<td><strong>Nuclear regulatory protein</strong></td>
<td>Translocation t(8;14)</td>
</tr>
<tr>
<td>L-myc</td>
<td>Small cell lung carcinoma</td>
<td><strong>Nuclear regulatory protein</strong></td>
<td>Amplification</td>
</tr>
<tr>
<td>N-myc</td>
<td>Neuroblastoma</td>
<td><strong>Nuclear regulatory protein</strong></td>
<td>Amplification</td>
</tr>
<tr>
<td>bcl-1</td>
<td>Mantle cell lymphoma</td>
<td><strong>Cell cycle regulatory proteins</strong>&lt;br&gt;Cyclin D protein</td>
<td>Translocation t(11;14)</td>
</tr>
<tr>
<td>CDK4</td>
<td>Melanoma, GBM</td>
<td><strong>Cyclin dependent kinase</strong></td>
<td>Amplification</td>
</tr>
</tbody>
</table>

3. **Inactivation of tumor suppressor genes**
   a. Definition: tumor suppressor genes encode proteins that regulate and suppress cell proliferation by inhibiting progression of the cell through the cell cycle
   b. Mechanisms of action of tumor suppressor genes
      i. p53 prevents a cell with damaged DNA from entering S-phase.
      ii. Rb prevents the cell from entering S-phase until the appropriate growth signals are present.
   c. Knudson's "two hit hypothesis" states that both tumor suppressor genes must be inactivated for oncogenesis.
   d. Mode of action of inherited germ-line mutations
      i. First hit: inherited germ-line mutation
      ii. Second hit: acquired somatic mutation
   e. Examples of inherited germ-line mutations
      i. Familial retinoblastoma
         • Germ-line mutation of Rb on chromosome 13
         • High rate of retinoblastoma and osteosarcoma
      ii. Li-Fraumeni syndrome
         • Germ-line mutation of p53 on chromosome 17
         • High rate of many types of tumors
Table 9-6. Clinically Important Tumor Suppressor Genes

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>3p25</td>
<td>VHL</td>
<td>von Hippel-Lindau disease, renal cell carcinoma</td>
</tr>
<tr>
<td>11p13</td>
<td>WT-1</td>
<td>Wilm tumor</td>
</tr>
<tr>
<td>11p15</td>
<td>WT-2</td>
<td>Wilm tumor</td>
</tr>
<tr>
<td>13q14</td>
<td>Rb</td>
<td>Retinoblastoma, osteosarcoma</td>
</tr>
<tr>
<td>17p13.1</td>
<td>p53</td>
<td>Lung, breast, colon, etc.</td>
</tr>
<tr>
<td>17q12-21</td>
<td>BRCA-1</td>
<td>Hereditary breast and ovary cancer</td>
</tr>
<tr>
<td>13q12-13</td>
<td>BRCA-2</td>
<td>Hereditary breast cancer</td>
</tr>
<tr>
<td>5q21</td>
<td>APC</td>
<td>Adenomatous polyps and colon cancer</td>
</tr>
<tr>
<td>18q21</td>
<td>DCC</td>
<td>Colon cancer</td>
</tr>
<tr>
<td>17q11.2</td>
<td>NF-1</td>
<td>Neurofibromas</td>
</tr>
<tr>
<td>22q12</td>
<td>NF-2</td>
<td>Acoustic neuromas, meningiomas</td>
</tr>
</tbody>
</table>

4. Regulation of apoptosis
   a. bcl-2
      i. Prevents apoptosis
      ii. Overexpressed in follicular lymphomas t(14:18)
         • Chromosome 14—immunoglobulin heavy chain gene
         • Chromosome 18—bcl-2
   b. Genes promoting apoptosis
      i. bax, bad, bcl-xS, bid
      ii. p53 → Promotes apoptosis in mutated cells by stimulating bax synthesis
   c. c-myc
      i. Promotes cellular proliferation
      ii. When associated with p53 leads to apoptosis
      iii. When associated with bcl-2 inhibits apoptosis
# DIAGNOSIS OF CANCER

Table 9-7. General Features of Benign versus Malignant Neoplasms

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gross</strong></td>
<td>• Larger in size</td>
</tr>
<tr>
<td>• Small size</td>
<td>• Rapid growth</td>
</tr>
<tr>
<td>• Slow growing</td>
<td>• Necrosis and hemorrhage are commonly seen</td>
</tr>
<tr>
<td>• Encapsulated or well-demarcated borders</td>
<td>• Poorly demarcated</td>
</tr>
<tr>
<td><strong>Micro</strong></td>
<td>• Vary from well to poorly (anaplastic) differentiated</td>
</tr>
<tr>
<td>• Expansile growth with well-circumscribed</td>
<td>• Tumor cells vary in size and shape (pleomorphism)</td>
</tr>
<tr>
<td>borders</td>
<td>• Increased nuclear to cytoplasmic ratios</td>
</tr>
<tr>
<td>• Tend to be well differentiated</td>
<td>• Nuclear hyperchromasia and prominent nucleoli</td>
</tr>
<tr>
<td>• Resemble the normal tissue counterpart</td>
<td>• High mitotic activity with abnormal mitotic figures</td>
</tr>
<tr>
<td>from which they arise</td>
<td>• <em>Invasive growth pattern</em></td>
</tr>
<tr>
<td>• Noninvasive and never metastasize</td>
<td>• Has potential to metastasize</td>
</tr>
</tbody>
</table>

1. **Histologic diagnosis of cancer**
   a. Microscopic examination of tissue or cells is required to make the diagnosis of cancer.
      i. Complete excision
      ii. Biopsy
      iii. Fine needle aspiration
      iv. Cytologic smears (Pap smear)
   b. Immunohistochemistry
      i. May be helpful in confirming the tissue of origin of metastatic or poorly differentiated tumors
         ii. Uses monoclonal antibodies that are specific for a cellular component
            • All of the serum tumor markers (listed below)
            • Thyroglobulin: thyroid cancers
            • S100: melanoma and neural tumors
            • Actin: smooth and skeletal muscle
            • CD markers: lymphomas/leukemias
            • Estrogen receptors: breast cancer
            • Intermediate filaments (see Table 9-8)
Table 9-8. Expression of Intermediate Filaments by Normal and Malignant Cells

<table>
<thead>
<tr>
<th>Intermediate Filament</th>
<th>Normal Tissue Expression</th>
<th>Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratin</td>
<td>All epithelial cells</td>
<td>Carcinomas</td>
</tr>
<tr>
<td>Vimentin</td>
<td>Mesenchymal cells</td>
<td>Sarcomas</td>
</tr>
<tr>
<td>Desmin</td>
<td>Muscle cells</td>
<td>Uterine leiomyoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Neurofilament</td>
<td>CNS and PNS neurons</td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td></td>
<td>Neural crest derivatives</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>Glial fibrillary acidic protein (GFAP)</td>
<td>Glial cells</td>
<td>Astrocytomas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ependymomas</td>
</tr>
</tbody>
</table>

**Note**

Most neoplasms (90%) arise from epithelium, with the remainder from mesenchymal cells.

c. Ancillary tests for the diagnosis of cancer include:
   i. Electron microscopy
   ii. Flow cytometry
   iii. Cytogenetics
   iv. PCR/DNA probes

2. **Serum tumor markers**
   a. Tumor markers are usually normal cellular components that are increased in neoplasms but may also be elevated in non-neoplastic conditions.
   b. Serum tumor markers are used for:
      i. Screening (e.g., prostate specific antigen [PSA]) for cancer
      ii. Monitoring treatment efficacy
      iii. Detecting recurrence of cancers
   c. Clinically useful markers
      i. Alpha-fetoprotein (AFP): hepatoma, nonseminomatous testicular germ-cell tumors
      ii. Beta human chorionic gonadotropin (hCG): trophoblastic tumors, choriocarcinoma
      iii. Calcitonin: medullary carcinoma of the thyroid
      iv. Carcinoembryonic antigen (CEA): carcinomas of the lung, pancreas, stomach, breast, and colon
      v. CA-125: malignant ovarian epithelial tumors
      vi. CA19-9: malignant pancreatic adenocarcinoma
      vii. Placental alkaline phosphatase: seminoma
      viii. PSA: prostate cancer

3. **Grading and staging**
   a. Tumor grade
      i. Histologic estimate of the malignancy of a tumor
   ii. Criteria
      - Degree of differentiation from low grade (well-differentiated) to high grade (poorly differentiated/anaplastic)
      - Number of mitosis
b. Tumor stage
   i. Clinical estimate of the extent of tumor spread
   ii. TNM staging system criteria
      • T: size of the primary tumor
      • N: extent of regional lymph node spread
      • M: presence of metastatic disease
   iii. In general, staging is a better predictor of prognosis than tumor grade.

4. Tumor progression
   a. Definition: tendency of a tumor to become more malignant over time
   b. Natural selection: evolution of a more malignant clone over time due to a selective growth advantage
   c. Genetic instability: malignant cells are more prone to mutate and accumulate additional genetic defects

5. Metastasis
   a. Initial routes of metastasis
   i. Lymphatic spread is the most common route of spread for epithelial carcinomas.
   ii. Hematogenous spread is typically seen with:
      • Most sarcomas (e.g., osteogenic sarcoma)
      • Renal cell carcinoma
      • Hepatocellular carcinoma
      • Follicular carcinoma of the thyroid
      • Choriocarcinoma
   iii. Seeding of body cavities and surfaces occurs in ovarian carcinoma.
   iv. Transplantation via mechanical manipulation (e.g., surgical incision, needle tracts) may occur but is relatively rare.

Chapter Summary

* Cancer is the second leading cause of death in the United States in both adults and children. In men, the sites with the highest new cancer rates are (in order of decreasing frequency): prostate, lung and bronchus, and colon and rectum. These same sites have the highest mortality rate, although lung and bronchus cancers more commonly cause death than prostate cancer. In women, the sites with the highest new cancer rate are (in order of decreasing frequency): breast, lung and bronchus, and colon and rectum. These same sites have the highest mortality rate, although lung and bronchus cancers more commonly cause death than breast cancer.

* The incidence of different cancers can vary with geographic site, racial factors, occupational exposures, age, hereditary predisposition, and acquired preneoplastic disorders.

* A variety of chemical carcinogens have been identified that can act as initiators or promoters of specific cancers. Ultraviolet light and ionizing radiation are also carcinogenic. A relatively small number of cancers have been linked to infection with specific viruses. Patients with immune system dysfunction also have an increased number of neoplasms.

(Continued)
Chapter Summary (continued)

* Carcinogenesis is a multistep process requiring the accumulation of multiple genetic changes as the result of either inherited germ-line mutations or acquired mutations, leading to the monoclonal expansion of a mutated cell.

* Cancer growth can involve either activation of growth promoting oncogenes or inactivation of tumor suppressor genes.

* Activated oncogenes lack regulatory control and are overexpressed, resulting in unregulated cellular proliferation. Examples of clinically important oncogenes include erb, ras, and myc.

* Tumor suppressor genes encode proteins that regulate and suppress cell proliferation by inhibiting progression of the cell through the cell cycle. Inactivation of these genes leads to uncontrolled cellular proliferation with tumor formation. Examples of clinically important tumor suppressor genes include VHL, p53, Rb, APC, DCC, and NF-1.

* Cancers can also develop if apoptosis (programmed cell death) is prevented by mutations in genes such as bcl-2, bax, bad, and bcl-xS.

* When compared with similar benign lesions, malignant neoplasms tend to be more rapidly growing due to a greater portion of cells that are in mitosis; tend to have areas of necrosis and hemorrhage; tend to have invasive growth pattern; tend to have the potential to metastasize; tend to have high mitotic activity with abnormal mitotic figures; and tend to have pleomorphic cells with increased nuclear to cytoplasmic ratio, nuclear hyperchromasia, and prominent nucleoli.

* A diagnosis of cancer requires the examination of cells and/or tissue that may be obtained by complete excision or biopsy of the lesion, fine needle aspiration, or cytologic smears. Immunohistochemistry can be helpful in confirming the tissue of origin of metastatic or poorly differentiated tumors.

* Serum tumor markers are usually normal cellular components that are increased in neoplasms but may also be elevated in non-neoplastic conditions. They can be used for screening, monitoring of treatment efficacy, and detecting recurrence. Examples include AFP, hCG, CEA, CA-125, and PSA.

* Tumor grade is a histologic estimate of the malignancy of a tumor. Tumor stage is a clinical estimate of the extent of tumor spread.

* Many tumors tend to become more malignant over time as a result of natural selection of more malignant clones and genetic instability of malignant cells.

* Lymphatic spread is the most common route of spread for epithelial carcinomas. Hematogenous spread is most likely to be seen with sarcomas, renal-cell carcinoma, hepatocellular carcinoma, follicular carcinoma of the thyroid, and choriocarcinoma. Tumors are also less commonly spread by seeding of body cavities and surfaces and via mechanical manipulations such as surgical incisions and needle tracts.
Environment- and Lifestyle-Related Pathology

POISONING AND TOXINS

1. Carbon monoxide
   a. Sources: auto emissions, home heaters, byproduct of fires, cigarette smoking
   b. Pathogenesis
      i. Odorless, colorless gas
      ii. High affinity for hemoglobin (200x the affinity for hemoglobin compared with oxygen)
      iii. Forms carboxyhemoglobin, which shifts the oxygen dissociation curve to the left, leading to decreased delivery of oxygen to tissues
      iv. Causes systemic hypoxia
   c. Symptoms depend on the carboxyhemoglobin concentration
      i. 10% → asymptomatic
      ii. 30% → headache and shortness of breath on exertion
      iii. 50% → loss of consciousness, convulsions, and coma
      iv. 60% → death
   d. Bright “cherry-red” color of the skin, mucosal membranes, and the blood
   e. Treatment
      i. Remove patient from the source of exposure
      ii. 100% oxygen
      iii. Hyperbaric oxygen

2. Mushroom poisoning
   a. Amanita muscaria—recovery with supportive therapy; rarely lethal
   b. Amanita phalloides
      i. Toxin (amanitin) inhibits RNA polymerase
      ii. Abdominal pain, vomiting, and diarrhea
      iii. Fulminant hepatitis with extensive liver necrosis
      iv. Coma and death

3. Arsenic poisoning
   a. Can be detected in hair and nails long after exposure due to the binding to disulfide groups in proteins
   b. Acute poisoning
      i. Hemorrhagic gastroenteritis
      ii. CNS toxicity → coma and seizures
      iii. “Garlic-scented” breath
c. Chronic poisoning
   i. Malaise and abdominal pain
   ii. Peripheral neuropathy and muscular weakness
   iii. Skin changes (hyperpigmentation and dermatitis)
   iv. Mees lines: transverse bands on the fingernails

d. Complications: squamous cell carcinoma of the skin and lung, angiosarcoma of the liver

4. Lead poisoning (plumbism)
   a. Epidemiology
      i. Most common type of chronic metal poisoning in the United States
      ii. Primarily affects children
   b. Sources: lead paint, lead plumbing, lead pots, and leaded gasoline
   c. CNS toxicity
      i. Lethargy and somnolence
      ii. Cognitive impairment and behavioral problems
      iii. Mental retardation
      iv. Cerebral edema → encephalopathy
   d. Wrist and foot drop occur in adults due to peripheral motor nerve demyelination
   e. Abdominal pain (lead colic)
   f. Renal tubular acidosis and renal failure
   g. Microcytic anemia with basophilic stippling
   h. Deposition of lead at the gingivodental line ("lead line")
   i. X-ray: long bones have lead lines (increased bone density) at the epiphyseal growth plates
   j. Diagnosis
      i. Blood lead levels
      ii. Increased free erythrocyte protoporphyrin
   k. Treatment: stop the exposure; chelating drugs

5. Mercury poisoning
   a. Neurotoxicity
      i. Intention tremors
      ii. Dementia and delirium ("mad as a hatter")
   b. Nephrotoxicity (acute tubular necrosis)
   c. Treatment: stop the exposure; chelating drugs

6. Cyanide poisoning
   a. Clinical finding: "bitter almond-scented" breath
   b. Mechanism: cyanide blocks cellular respiration by binding to mitochondrial cytochrome oxidase (cytochrome aa₃)
   c. Systemic asphyxiant
Table 10-1. Industrial Toxins

<table>
<thead>
<tr>
<th>Industrial Toxin</th>
<th>Occupation</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soot (polycyclic aromatic hydrocarbons)</td>
<td>English chimney sweeps</td>
<td>Scrotal cancer</td>
</tr>
<tr>
<td>Vinyl chloride</td>
<td>Plastic industry</td>
<td>Angiosarcoma of the liver</td>
</tr>
<tr>
<td>Uranium and radon gas</td>
<td>Miners</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>β-Naphthylamine</td>
<td>Dye makers and rubber workers</td>
<td>Bladder cancer</td>
</tr>
<tr>
<td>Benzo[a]pyrene</td>
<td>Steel mills and cigarette smoke</td>
<td>Lung and bladder cancer</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>Dry cleaners</td>
<td>Liver and kidney toxicity</td>
</tr>
<tr>
<td>Organophosphates</td>
<td>Farmers</td>
<td>Irreversible cholinesterase inhibitors</td>
</tr>
</tbody>
</table>

**LIFESTYLE CHOICES**

1. Smoking
   a. Epidemiology
      i. Number one cause of preventable premature death in the United States
      ii. Percentage of the U.S. population that smokes: ~25%
      iii. Males > females
      iv. There is a high rate of smoking in female teenagers.
   b. Types of smoke
      i. Mainstream smoke (smoke inhaled by the smoker)
      ii. Sidestream smoke (passive smoke inhalation)
   c. Smoke contains over 4,000 components and over 40 known carcinogens
      i. Carbon monoxide
      ii. Arsenic
      iii. Formaldehyde
      iv. Hydrogen cyanide
      v. Nicotine (addictive component)
   d. Cancers
      i. Lung (number one cause of cancer death in the United States)
      ii. Oral cavity, pharynx, and larynx
      iii. Esophagus and stomach
      iv. Cervical cancer
      v. Pancreas
      vi. Kidney, ureter, and bladder
      vii. Leukemia (benzene)

   **Clinical Correlate**

   Top 3 Causes of Death in Smokers
   - Heart disease
   - Lung cancer
   - COPD
Clinical Correlate

The dose of exposure is measured in terms of "pack years."

Smoking cessation for 15 years reduces the overall risk of dying—almost to the level of nonsmokers. It's never too late to quit.

e. Cardiovascular disease
   i. Major risk factor for atherosclerosis
   ii. Coronary artery disease
   iii. Myocardial infarctions
   iv. May induce coronary vasospasm
   v. Peripheral vascular disease
   vi. Aortic aneurysms
   vii. Buerger disease
   viii. Stroke

f. Respiratory diseases
   i. Chronic bronchitis
   ii. Emphysema
   iii. Asthma
   iv. Increased pulmonary infections

g. Effect on women
   i. Often develop early menopause
   ii. Increased rate of postmenopausal osteoporosis

h. Effect on pregnant women
   i. Increased risk of spontaneous abortions and stillbirths
   ii. Intrauterine growth retardation

i. Effect on children
   i. Increased risk of sudden infant death syndrome (SIDS)
   ii. Increased number of otitis media and upper respiratory infections (URIs)
   iii. Increased incidence of asthma

2. Ethyl alcohol (ethanol)
   a. Acute alcohol intoxication
      i. CNS depressant
      ii. Inebriation, coma, respiratory arrest

b. Chronic alcoholism
   i. Liver → fatty change, alcoholic hepatitis, and micronodular cirrhosis
   ii. GI → acute gastritis and the Mallory-Weiss syndrome
   iii. Pancreas → acute and chronic pancreatitis
   iv. Blood → megaloblastic anemia
   v. Newborns → fetal alcohol syndrome
   vi. Heart → dilated cardiomyopathy
   vii. CNS → Wernicke syndrome (ataxia, nystagmus, ophthalmoplegia) and Korsakoff syndrome (confabulation, psychosis)
   viii. Cancers
      • Hepatocellular carcinoma due to cirrhosis
      • Oropharynx, larynx, and esophagus due to smoking and drinking alcohol

3. Methyl alcohol (methanol, wood alcohol)
   a. Metabolized to formaldehyde (by alcohol dehydrogenase) and formic acid
   b. Present in solvents, paint remover, and other household chemicals
c. Retina → necrosis of retinal ganglion cells results in blindness

d. CNS → inebriation, coma, and death

e. Treatment: ethyl alcohol

DRUGS OF ABUSE

1. Heroin
a. Overdoses → cardiopulmonary arrest and sudden death
b. Infections
   i. Skin abscesses and cellulitis
   ii. Bacterial endocarditis (S. aureus)
   iii. Increased risk of contracting HIV and hepatitis viruses
c. Pulmonary pathology
   i. Foreign body granuloma in the lungs
   ii. Pulmonary abscesses
   iii. Pulmonary edema
d. Focal segmental glomerulosclerosis

e. Secondary amyloidosis
f. Treatment: for reversal use naloxone (an opiate antagonist)

2. Cocaine (directly prevents the reuptake of dopamine, serotonin, and norepinephrine into presynaptic neurons)
a. Euphoria
b. Seizures
c. Cardiac arrhythmias and sudden death
d. Hypertension and stroke
e. Chronic use may result in:
   i. Perforation of the nasal septum
   ii. Dilated cardiomyopathy

3. Marijuana
a. A commonly used illicit drug
b. Acute intoxication
   i. Usually euphoria, but sometimes dysphoria
   ii. Diminished coordination, altered time sense, perceptual changes
   iii. Injected conjunctivae
c. Severe acute intoxication
   i. Feelings of panic, paranoia, frank hallucinations, depersonalization, recurrence of psychosis in schizophrenic patients
d. Severe chronic use
   i. Possible predisposition for airway disease, unknown consequences on cognitive functioning

4. Hallucinogens
a. Lysergic acid diethylamide (LSD)
   i. Increased heart rate and blood pressure
   ii. Acute panic reaction, visual hallucinations

Clinical Correlate
The telltale sign of IVDA are "track marks" in the antecubital fossa, which are produced from the healing of skin abscesses and/or phlebosclerosis.
iii. Behavior-related trauma, possible impulsive or irrational behavior
b. Mescaline (in peyote)—similar to LSD, may also cause nausea/vomiting
c. MDMA (ecstasy)
i. Hypertension, tachycardia, diaphoresis, dehydration
ii. Hyperthermia, rhabdomyolysis, myoglobinuric renal failure
iii. DIC
iv. May lead to depletion of brain serotonin
5. Benzodiazepines
a. Acute toxicity: drowsiness, impaired judgment, impaired motor skills, slurred speech
b. More serious toxicity: hypothermia, hypotension, respiratory depression
c. Dependency risk; cycle of withdrawal and symptom recurrence
6. Amphetamines
a. Acute toxicity: disorientation, agitation, hypertension, chest pain, palpitations, dry mouth, nausea and vomiting, diaphoresis, mydriasis
b. Chronic effects: anorexia, pulmonary edema, stroke, eroded teeth, cellulitis, psychotic reactions

PHYSICAL INJURIES

1. Mechanical injuries
a. Contusions are due to blunt force injury to deeper tissues with resulting hemorrhage.
b. Abrasions are due to superficial damage to the skin.
c. Lacerations are jagged wounds through the full thickness of the skin.
2. Burns
a. First degree—partial thickness burns that heal without scarring
b. Second degree burns—damage the whole epidermis, cause blistering, and usually heal without scarring
c. Third degree burns—full thickness burns that can cause extensive necrosis of epidermis and adnexal structures. Vulnerable to infection. Healing occurs with scarring.
3. Electrical injury
a. Tissue damage under the skin surface is often far worse than superficial damage.
b. Both AC and DC currents cause damage.
4. Drowning
a. Important cause of death in children
b. Aspiration of fresh or salt water damages type II pneumocytes and causes diffuse alveolar damage.
5. Radiation injury
a. Ionizing radiation (x-rays; gamma rays) can damage DNA and other cellular components, with the most sensitive tissues including those with the highest mitotic activity: lymphoid tissue, bone marrow, gastrointestinal mucosa, and germinal tissue.
b. Nonionizing radiation (ultraviolet light B) damages pairs of adjacent pyrimidines in DNA and can cause sunburn, actinic keratoses, and skin cancers (basal cell carcinoma, squamous cell carcinoma, and melanoma).
Chapter Summary

* Acute aspirin toxicity can cause coma and death secondary to respiratory alkalosis and metabolic acidosis; chronic aspirin toxicity impairs platelet function and can cause gastritis.

* Unopposed estrogens are associated with an increased risk of endometrial and breast cancer. Oral contraceptives are associated with an increased risk of deep vein thrombosis in smokers.

* Carbon monoxide poisoning causes systemic hypoxia that may lead to death. Mushroom poisoning can cause fulminant hepatitis. Acute arsenic poisoning can cause hemolytic anemia and coma; chronic arsenic poisoning causes abdominal pain and neurovascular problems. Lead poisoning can cause mental impairment, peripheral nerve damage, abdominal pain, renal failure, and anemia. Mercury caries the brain and kidney. Cyanide is a systemic esphyxiant.

* A variety of organic and inorganic industrial toxins have been associated with specific cancers.

* Smoking is the number one cause of preventable premature death in the United States. It is associated with cancers in many sites, cardiovascular disease, respiratory disease, early menopause, osteoporosis, and prenatal problems. Infants and children exposed to smoking have an increased incidence of sudden infant death syndrome, upper respiratory infections, otitis media, and asthma.

* Acute alcohol intoxication causes central nervous system depression which, if severe enough, can lead to coma and respiratory arrest. Chronic alcoholism can cause cirrhosis, gastritis, pancreatitis, anemia, fetal alcohol syndrome, cerebellar atrophy, Wernicke and Korsakoff syndromes, and cancers of the liver due to alcoholic cirrhosis, and cancers of the oropharynx, larynx, and esophagus (alcohol acts synergistically with carcinogens in cigarette smoke). Methyl alcohol poisoning can cause blindness, coma, and death.

* Heroin abuse can cause sudden death, skin abscesses, endocarditis, increased risk of contacting HIV and viral hepatitis, pulmonary complications local segmental alveolitis, and secondary amyloidosis. Cocaine abuse can produce seizures, cardiac arrhythmias that may lead to sudden death, hypertension, stroke, cardiomyopathy, and perforated nasal septum. Marijuana is the most commonly used illicit drug. It can produce mild to profound intoxication and may be associated with long-term effects from chronic use. Other commonly abused drugs include hallucinogens (LSD, mescaline, MDMA), benzodiazepines, and amphetamines.

* Other causes of injury include physical trauma, thermal injury (burns), electrical injury, drowning, and radiation injury.
DISORDERS OF PIGMENTATION

1. Vitiligo
   a. Definition: irregular, completely depigmented patches
   b. Common; may affect any race; familial predisposition
   c. Unknown etiology; possibly autoimmune
   d. Micro: affected areas are devoid of melanocytes
2. Melasma
   a. Definition: irregular blotchy patches of hyperpigmentation on the face
   b. Associated with oral contraceptive use and pregnancy ("mask of pregnancy")
   c. May regress after pregnancy
3. Freckles (ephelides)
   a. Definition: light brown macules on face, shoulders, and chest
   b. Common in fair-skinned children
   c. Darken and fade with the seasons due to sunlight exposure
   d. Micro
      i. Increased melanin deposition in the basal cell layer of the epidermis
      ii. Normal number of melanocytes
4. Benign lentigo
   a. Definition: benign, localized proliferation of melanocytes
   b. Small, oval, light brown macules
   c. Micro: linear melanocytic hyperplasia

MELANOCYTIC TUMORS
1. Congenital nevi (birthmarks)
   a. Present at birth
   b. Giant congenital nevi have increased risk of developing melanoma.
2. Nevocellular nevus (mole)
   a. Definition: benign tumor of melanocytes (melanocytic nevus cells)
   b. Clearly related to sun exposure
   c. Types of nevi: junctional, compound, and intradermal
   d. Gross
      i. Uniform tan to brown color
      ii. Sharp, well circumscribed borders
      iii. Tend to be stable in shape and size
   e. Malignant transformation is uncommon
3. Dysplastic nevi (BK moles)
   a. Definition: nevi are larger and irregular and may have pigment variation
   b. Micro: the nevus exhibits cytological and architectural atypia
   c. Dysplastic nevus syndrome
      i. Autosomal dominant (CMM1 gene on chromosome 1)
      ii. Often have multiple dysplastic nevi
      iii. Increased risk of melanoma
4. Malignant melanoma
   a. Definition: malignancy of melanocytes
   b. Incidence
      i. Increasing at a rapid rate
      ii. Melanoma peaks in ages 40–70
   c. Risk factors
i. Chronic sun exposure, sunburns
ii. Fair-skinned individuals
iii. Dysplastic nevus syndrome
iv. Familial melanoma is associated with loss of function mutation of the p16 tumor suppressor gene on chromosome 9.
d. Gross
   i. Asymmetric, irregular borders, variegated color, large diameter, enlarging, macule, papule, or nodule
   ii. Males: upper back; females: back and legs
e. Lentigo maligna melanoma
   i. Usually located on the face or neck of older individuals
   ii. Best prognosis
f. Superficial spreading melanoma
   i. Most common type of melanoma
   ii. Has a primarily horizontal growth pattern
g. Acral-lentiginous melanoma
   i. Most common melanoma in dark-skinned individuals
   ii. Affects palms, soles, and subungual area
h. Nodular melanoma
   i. Nodular tumor with a vertical growth pattern
   ii. Worst prognosis of the melanomas
   i. Prognosis
      i. Staging is by depth of invasion (vertical growth)
         • Breslow’s thickness
         • Clark’s levels
j. Treatment
   i. Wide surgical excision
   ii. Systemic disease is treated with chemotherapy or immunotherapy
   iii. May resolve spontaneously

EPIDERMAL AND DERMAL LESIONS

1. Acanthosis nigricans
   a. Definition: thickened, hyperpigmented skin in axillae and groin often associated with obesity and hyperinsulinism
   b. Associated rarely with internal malignancy (stomach and other gastrointestinal malignancies)

2. Seborrheic keratoses
   a. Definition: benign squamous proliferative neoplasm
   b. Very common in middle-aged and elderly individuals
   c. Distribution: trunk, head, neck, and extremities
d. Gross
   i. Tan to brown coin-shaped plaques with a granular surface
   ii. “Stuck on” appearance
e. Micro
   i. Basaloid epidermal hyperplasia
   ii. “Horn cysts” (keratin-filled epidermal pseudocysts)
f. Treatment
   i. Usually left untreated
   ii. May be removed if they become irritated or for cosmetic purposes
g. Sign of Leser-Trelat (paraneoplastic syndrome): sudden development of multiple lesions may accompany an underlying malignancy

3. Psoriasis
   a. Definition: autoimmune disorder accompanied by increased proliferation and turnover of epidermal keratinocytes
   b. Epidemiology
      i. Affects 1% of the U.S. population
      ii. Most common form is psoriasis vulgaris
      iii. Unknown etiology
      iv. Clear genetic component
   c. Gross
      i. Common sites: knees, elbows, and scalp
      ii. Gross: the classic skin lesion is a well-demarcated erythematous plaque with a silvery scale
      iii. Auspitz sign: removal of scale results in pinpoint bleeding
      iv. Nail beds show pitting and discoloration
   d. Pathogenesis: increased epidermal turnover
   e. Micro
      i. Epidermal hyperplasia (acanthosis)
      ii. Patchy hyperkeratinization with parakeratosis
      iii. Uniform elongation and thickening of the rete ridges
      iv. Thinning of the epidermis over the dermal papillae
      v. Munro microabscesses
   f. Treatment
      i. Topical steroids and ultraviolet irradiation
      ii. Severe systemic disease may be treated with methotrexate.

4. Pemphigus
   a. Definition: rare, potentially fatal autoimmune disorder that is characterized by intraepidermal blister formation. Pemphigus vulgaris is the most common form
   b. Pathogenesis: production of autoantibodies directed against a part of the keratinocyte desmosome called desmoglein 3 results in loss of intercellular adhesion (acantholysis) and blister formation
   c. Clinical findings: easily ruptured, flaccid blisters are seen classically
   d. Immunofluorescence shows a net-like pattern of IgG staining between the epidermal keratinocytes that create bullae.
   e. Micro
      i. Intraepidermal acantholysis is a hallmark feature.
      ii. The acantholysis leaves behind a basal layer of keratinocytes, which has a tombstone-like arrangement.
5. **Bullous pemphigoid**
   a. **Definition:** relatively common autoimmune disorder of older individuals that is characterized by subepidermal blister formation
   b. **Pathogenesis:** production of autoantibodies directed against a part of the keratinocyte hemidesmosome called *bullous pemphigoid antigens 1 and 2* results in separation of the epidermis from the dermis and blister formation
   c. **Clinical findings:** tense bullae that do not rupture easily
   d. **Immunofluorescence shows linear deposits of IgG at the epidermal-dermal junction.**

6. **Dermatitis herpetiformis**
   a. **Definition:** rare immune disorder that is often associated with celiac sprue and is characterized by subepidermal blister formation
   b. **Pathogenesis:** production of IgA antibodies directed against gliadin and other antigens that deposit in the tips of the dermal papillae and result in subepidermal blister formation
   c. **Clinical findings:** itchy, grouped vesicles and occasional bullae on the extensor surfaces
   d. **Immunofluorescence shows granular IgA deposits at the tips of the dermal papillae.**
   e. **Micro**
      i. Microabscesses are seen at the tips of the dermal papillae.
      ii. Eventually subepidermal separation results in blister formation.
   f. **Treatment:** often responds to a gluten-free diet

*Figure 11-2. Intraepidermal and Subepidermal Blisters*
7. Ichthyosis vulgaris
   a. Definition: common inherited (autosomal dominant) skin disorder that is characterized by a thickened stratum corneum with absent stratum granulosum
   b. Clinical findings: patients have hyperkeratotic, dry skin that particularly involves palms, soles, and extensor areas

8. Xerosis
   a. Definition: a common cause of pruritus and dry skin in the elderly that is due to decreased skin lipids

9. Eczema
   a. Definition: a group of related inflammatory skin diseases characterized by pruritus
      i. Acute eczema causes a vesicular, erythematous rash
      ii. Chronic eczema develops following chronic scratching, and is characterized by dry, thickened hyperkeratotic skin.
      iii. Atopic dermatitis is due to an IgE-mediated hypersensitivity reaction and causes dry skin and eczema.
      iv. Contact dermatitis
         • Allergic type (poison ivy, nickel in jewelry)
         • Photodermatitis type (such as photosensitivity reaction after tetracycline)

10. Polymorphous light eruption
    a. Definition: most common form of photodermatosis and causes erythematous macules, papules, plaques, or vesicles on exposure to sunlight

11. Chronic cutaneous lupus erythematosus
    a. Definition: causes epidermal atrophy with deposition of DNA-anti DNA immune complexes in the basement membrane of the epidermis
    b. Clinical findings: causes an erythematous maculopapular eruption that typically involves the nose and cheeks ("butterfly" rash).

12. Erythema multiforme
    a. Definition: a hypersensitivity skin reaction to infections (Mycoplasma pneumoniae, herpes simplex) or drugs (sulfonamides, penicillin, barbiturates, phenytoin)
      i. Erythema multiforme is characterized by vesicles, bullae, and "targetoid" erythematous lesions.
      ii. Most severe form is Stevens-Johnson syndrome, which has extensive involvement of skin and mucous membranes.

13. Pityriasis rosea
    a. Definition: causes a pruritic rash that starts with an oval-shaped "herald patch" and progresses to a papular eruption of the trunk that characteristically follows lines of cleavage to produce a "Christmas tree" distribution

14. Granuloma annulare
    a. Definition: a chronic inflammatory disorder that may be associated with diabetes mellitus
    b. Clinical findings: causes formation of erythematous papules, which evolve into plaques and involve the back of the hands and feet

15. Erythema nodosum
    a. Definition: causes raised, erythematous, painful nodules of subcutaneous adipose tissue, typically on the anterior shins
b. Can be associated with granulomatous diseases and streptococcal infection

16. **Epidermal inclusion cyst**
   a. Definition: a common benign skin cyst lined with stratified squamous epithelium and filled with keratin debris

**MALIGNANT TUMORS**

1. **Squamous cell carcinoma (SCC)**
   a. Incidence: the tumor peaks at 60 years of age
   b. Risk factors
      i. Chronic sun exposure (ultraviolet UVB)
      ii. Fair complexion
      iii. Chronic skin ulcer or sinus tracts
      iv. Long-term exposure to hydrocarbons, arsenic, burns, radiation
      v. Immunosuppression
      vi. Xeroderma pigmentosum
   c. Precursors of squamous cell carcinoma
      i. Actinic keratosis
         • Sun-induced dysplasia of the keratinocytes
         • Gross: rough, red papules on the face, arms, and hands
      ii. Bowen disease: squamous cell carcinoma in situ
   d. Gross
      i. Occurs on sun-exposed areas (face and hands)
      ii. Tan nodular mass, which commonly ulcerates
   e. Micro
      i. Nets of atypical keratinocytes invade the dermis
      ii. Formation of keratin pearls
      iii. Intercellular bridges (desmosomes) between tumor cells
   f. Prognosis
      i. Rarely metastasizes
      ii. Complete excision is usually curative.
   g. Variant: keratoacanthoma (well differentiated SCC)
      i. Rapidly growing, dome-shaped nodules with a central keratin-filled crater
      ii. Often self-limited and regresses spontaneously

2. **Basal cell carcinoma**
   a. Most common tumor in adults in the Western world
   b. Most common in middle-aged or elderly individuals arising from the basal cells of hair follicles
   c. Risk factors
      i. Chronic sun exposure
      ii. Fair complexion
      iii. Immunosuppression
      iv. Xeroderma pigmentosum
d. Gross
   i. Occurs on sun-exposed, hair-bearing areas (face)
   ii. Pearly papules
   iii. Nodules with heaped-up, translucent borders
   iv. Telangiectasia
   v. Ulceration (rodent ulcer)
e. Micro: invasive nests of basloid cells with a *palisading growth pattern*
f. Prognosis
   i. Grows slowly but may be locally aggressive
   ii. Rarely metastasizes
g. Treatment
   i. Shave biopsies have a 50% recurrence rate
   ii. Complete excision is usually curative.

3. Histiocytosis X (*Langerhans cell histiocytosis*)
   a. Definition: proliferation of Langerhans cells (histiocytes), which are normally found within the epidermis
   b. Three clinical variants
      i. Unifocal (eosinophilic granuloma)
      ii. Multifocal (Hand-Schüller-Christian disease)
      iii. Acute disseminated (Letterer-Siwe syndrome)
   c. Langerhans cells are CD 1a positive
Chapter Summary

* Disorders of skin pigmentation include vitiligo (irregular depigmented patches due to lack of melanocytes of possibly autoimmune etiology), melasma ("mask of pregnancy"), ephelides (freckles), and benign lentigines (like freckles but not under control of sun exposure).

* Melanocytic tumors include congenital nev (birth marks, giant ones have increased risk of melanoma), nevocellular nevus (common moles with proliferating nevus cells; subclassified as junctional, compound, and intradermal), dysplastic nevus (larger, more irregular, and with more pigment variation than common moles, cytological and architectural atypia, may be part of autosomal dominant nevus syndrome with increased risk of melanoma if multiple), and malignant melanoma.

* Malignant melanoma (risk factors: sun exposure, fair skin, dysplastic nevus syndrome) has a rapidly increasing incidence (peak middle age and older) and prognosis ranging from excellent (thin lesions that can be completely excised to poor (metastatic lesions, often arising in primary sites with tumor thickness greater than 1 mm). In general melanomas cause asymptomatic, irregular, large-diameter macules, papules, or nodules, with variegated color, found most often on the upper back of men and the back and legs of women. Subtypes include lentigo maligna melanoma (best prognosis, face or neck of older individuals), superficial spreading melanoma (most common type, horizontal growth pattern), acral lentigious melanoma (palms, soles, and subungual area of dark skinned individuals), and nodular melanoma (vertical growth pattern with worst prognosis).

* Benign epidermal and dermal lesions include acanthosis nigricans (thickened, hyperpigmented skin in an active and grain that may be associated with internal malignancy), senile keratoses (very common benign squamous-proliferative tan to brown coin-shaped plaques that appear "stuck on" the trunk, head, neck, and extremities of middle-aged and elderly people), and psoriasis (well-demarcated erythematous plaques with silvery scale and pinpoint bleeding after scale removal commonly involving knees, elbows, and scalp, micro shows epidermal hyperplasia, parakeratosis, and Munro abscesses; genetic component and associations with arthritis, enteropathy, and myopathy). Other skin lesions include ichthyosis vulgaris (inherited hyperkeratotic skin), xerosis (itchy, dry skin in elderly), eczema (itchy inflammatory skin disease), polymorphous light eruption (erythematous rash triggered by sun exposure), cutaneous lupus erythematosus ("butterfly" rash due to DNA-anti DNA complex deposition), erythema multiforme (vesiculobullous rash with "targetoid" erythematous lesions), pityriasis rosea (pruritic rash that begins with a "herald patch"), granuloma annulare (erythematous plaques of hands and feet), erythema nodosum (painful subcutaneous nodules involving adipose tissue), and epidermal inclusion cysts (common benign skin cyst filled with keratin).

* Malignant tumors of the skin in addition to melanoma include squamous cell carcinoma (peak at age 60; sun and other risk factors; precursor lesions actinic keratosis and Bowen disease; excision usually curative; variant keratoacanthoma may resolve spontaneously), basal cell carcinoma (most common tumor of adults in the United States; middle-aged or older; sun exposure and other risk factors; variable appearance including pearly papules, nodules, telangiectasia, and ulceration; rarely metastasizes but may be locally aggressive), histiocytosis X (proliferation of Birbeck granule-containing Langerhans cells of skin; unifocal variant; eosinophilic granuloma, multifocal variant; Hand-Schüller-Christian disease, acute disseminated: Letterer-Siwe syndrome).
Red Blood Cell Pathology:
Anemias

RED BLOOD CELL MORPHOLOGY

1. Red cell shapes
   a. Abnormal size: anisocytosis (aniso means unequal)
   b. Abnormal shape: poikilocytosis (poikilo means various)
   c. Elliptocytes may be seen in hereditary elliptocytosis
   d. Spherocytes result from decreased RBC membrane
      i. May be seen in hereditary spherocytosis
      ii. Autoimmune hemolytic anemia
   e. Target cells result from increased RBC membrane. May be seen in hemoglobinopathies, thalassemia, and liver disease
   f. Acanthocytes have irregular spicules on their surfaces. Numerous acanthocytes can be seen in abetalipoproteinemia.
   g. Echinocytes (or burr cells) have smooth undulations on their surface. They may be seen in uremia or more commonly as an artifact.
   h. Schistocytes are RBC fragments (helmet cells are a type of schistocyte). Can be seen in microangiopathic hemolytic anemias or traumatic hemolysis
   i. Bite cells are RBCs with "bites" of cytoplasm being removed by splenic macrophages. Bite cells may be seen in G6PD deficiency.
   j. Teardrop cells (dacrocytes) may be seen in thalassemia and myelofibrosis.
   k. Sickle cells (dperanocytes) are seen in sickle cell anemia.
   l. Rouleaux ("stack of coins") refers to RBCs lining up in a row. Rouleaux are characteristic of multiple myeloma.

2. Red cell inclusions
   a. Basophilic stippling results from cytoplasmic remnants of RNA. May indicate reticulocytosis or lead poisoning
   b. Howell-Jolly bodies are remnants of nuclear chromatin. May occur in severe anemias or patients without spleens
   c. Pappenheimer bodies are composed of iron. May be found in the peripheral blood following splenectomy
   d. Ring sideroblasts have iron trapped abnormally in mitochondria, forming a ring around nucleus. Can be seen in sideroblastic anemia
   e. Heinz bodies result from denatured hemoglobin. Can be seen with G6PD (glucose-6-phosphate dehydrogenase) deficiency
ANEMIAS

1. General
   a. Anemia is a reduction below normal limits of the total circulating red cell mass.
   b. Signs of anemia include palpitations, dizziness, angina, pallor of skin and nails, weakness, claudication, fatigue, and lethargy.
   c. Lab terms
      i. MCV (mean cell volume) is the average volume of a red blood cell.
      ii. MCH (mean cell hemoglobin) is the average content (mass) of hemoglobin per RBC.
      iii. MCHC (mean cell hemoglobin concentration) is the average concentration of hemoglobin in a given volume of packed RBCs.
      iv. RDW (red cell distribution width) is the coefficient of variation of red blood cell volume (RDW is a measure of anisocytosis).
   d. Reticulocytes
      i. Reticulocytes are larger red cells (macrocytic cells) that are spherical and have a bluish color (polychromasia) due to free ribosomal RNA.
      ii. Reticulocytes do not have a nucleus; note that any RBC with a nucleus (nRBC) in peripheral blood is abnormal.
      iii. Maturation into mature RBC takes about 1 day.
      iv. Reticulocyte count: percentage of red cells present in peripheral blood. This is the absolute number of red blood cells present (normal = 0.5% to 1.5%).
      v. Corrected reticulocyte count: (patient’s hct/45) × reticulocyte count
         - Corrects for degree of anemia
         - <2%: poor bone marrow response; >3%: good bone marrow response
      vi. Reticulocyte index: corrected reticulocyte count/2
         - Use if bone marrow reticulocytes (shift cells) are present (polychromasia)
         - Divide by 2 because shift cells take twice as long as reticulocytes to mature (2 days versus 1 day)
   e. Classification of anemia based on color
      i. Normochromic: normal color (central pallor of about a third the diameter of the RBC)
      ii. Hypochromic: decreased color (seen as an increased central pallor of RBC)
      iii. Hyperchromic but is called spherocytosis: increased color (loss of central pallor of RBC)
   f. Classification of anemia based on size (MCV)
2. Pathogenesis of anemia
   a. Blood loss
   b. Hemolytic anemias
      i. Hereditary spherocytosis
      ii. G6PD deficiency
      iii. Sicotic cell disease
      iv. Hemoglobin C disease
      v. Thalassemia
      vi. Paroxysmal nocturnal hemoglobinuria
   c. Immuno-hemolytic anemias
      • Autoimmune hemolytic anemia (AIHA)
      • Cold AIHA
      • Incompatible blood transfusions
      • Hemolytic disease of the newborn
   c. Anemias of diminished erythropoiesis
      i. Megaloblastic anemia (B12 and folate)
      ii. Iron deficiency anemia
      iii. Anemia of chronic disease
iv. Aplastic anemia  
v. Myelophthisic anemia  
vi. Sideroblastic anemia  

MICROCYTIC ANEMIAS

1. Iron deficiency anemia  
a. Normal forms of iron (Fe) and iron metabolism  
   i. Functional iron is found in hemoglobin, myoglobin, and enzymes (catalase and cytochromes).  
   ii. Ferritin is the physiological storage form (plasma ferritin: total body Fe).  
   iii. Hemosiderin: degraded ferritin + lysosomal debris (Prussian blue positive)  
   iv. Iron is transported by transferrin.  
      • Transferrin levels: total iron-binding capacity (TIBC) (normal = 300 mg/dL)  
      • Normal % saturation = one-third saturation (as normal serum iron is 100 mg/dL)  

b. Causes of iron deficiency  
   i. Dietary deficiency is seen in elderly populations and in children and poor.  
   ii. Increased demand is seen in children and pregnant women.  
   iii. Decreased absorption  
      • Generalized malabsorption  
      • After gastrectomy: due to decreased acid, which is needed for ferrous absorption; decreased small intestinal transit time = dumping syndrome  
   iv. Chronic blood loss due to GYN (menstrual bleeding) or GI causes (in the United States, think carcinoma; in the rest of the world, think hookworm).  

c. Sequence of events during iron deficiency  
   i. First is decreased storage iron, which produces  
      • Decreased serum ferritin  
      • Decreased bone marrow iron on Prussian blue stains  
   ii. Next is decreased circulating iron, which causes  
      • Decreased serum iron  
      • Increased TIBC  
      • Decreased % saturation  
   iii. Last is formation of microcytic/hypochromic anemia  
      • Decreased MCV  
      • Decreased MCHC  
      • High RDW  

d. Other symptoms of iron deficiency  
   i. Increased free erythrocyte protoporphyrin (FEP)  
   ii. Epithelial atrophy is seen in Plummer-Vinson syndrome  
   iii. Koilonychia: concave nails (spoon nails) with abnormal ridging and splitting  
   iv. Pica: eating unusual things (e.g., dirt)  

Clinical Correlate
Ferritin is an acute-phase reactant and may be artificially elevated in inflammatory states.
Table 12-1. Iron Panel for Microcytic Anemias

<table>
<thead>
<tr>
<th></th>
<th>Iron Deficiency</th>
<th>AOCD</th>
<th>Thalassemia Minor</th>
<th>Sideroblastic Anemia</th>
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<td>Serum iron</td>
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<tr>
<td>TIBC</td>
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<tr>
<td>% Saturation</td>
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<td>Normal</td>
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<tr>
<td>Serum ferritin</td>
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<td>↑</td>
<td>Normal</td>
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</tbody>
</table>

2. Anemia of chronic disease (AOCD)
   a. Definition: characterized by iron being trapped in bone marrow macrophages leading to decreased utilization of endogenous iron stores
   b. Lab: increased serum ferritin with decreased TIBC
   c. Chronic inflammatory disorders may be associated with increased IL-1, which causes increased lactoferrin, which, in turn, traps iron in bone marrow macrophages

3. Thalassemia syndromes
   a. General definition:
      i. Thalassemias are quantitative, not qualitative, abnormalities of hemoglobin.
         • α-Thalassemia has decreased α-globin chains with relative excess β chains.
         • β-Thalassemia has decreased β-globin chains with relative excess α chains.
      ii. Thalassemia provides a protective advantage to carriers, such as against malaria.

4. α-Thalassemia
   a. Genetics
      i. There are a total of four α-globin chain genes.
      ii. α chains are normally expressed prenatally and postnatally; therefore, there is prenatal and postnatal disease.
      iii. α-Thalassemia is due to gene deletions.
   b. Clinical disease states
      i. Normal: four α genes (αα/αα) and 100% α chains
      ii. Silent carrier: one deletion
         • Total number of α genes: 3 (−/ααα), which produce 75% α chains
         • Individuals are completely asymptomatic and all lab tests normal
      iii. α-Thal trait: two deletions
         • Total number of α genes: 2, which produce 50% α chains
         • Genotype: cis (−/−αα) type is seen in Asians
         • Genotype: trans (−/−αα) type is seen in African Americans (offspring don’t develop H disease or hydrops)
      iv. Hb H disease: three deletions
         • Number of α genes: 1 (−/−/− α), which produces 25% α chains
         • Increased Hb H (β4) forms Heinz bodies, which can be seen with crystal blue stain
      v. Hydrops fetalis: four deletions and is lethal in utero
         • Number of α genes: 0 (−/−/−/−) and 0% α chains
         • Increased Barts hemoglobin (γ4)

Note
Composition of hemoglobins:
• HbA (α2β2)
• HbA2 (α2δ2)
• HbF (α2γ2)
• Hb Bart’s (γ4)
• Hb H (β4)
5. β-Thalassemia
   a. Genetics
      i. There are a total of two β-globin chain genes.
      ii. They are expressed postnatally only (therefore only postnatal disease and not prenatal).
      iii. Mechanism: mainly due to point mutations, which form either some β chains (β+) or none (β0)
   b. β-Thal minor
      i. Asymptomatic
      ii. Increased hemoglobin A2 (8%) and increased hemoglobin F (5%)
   c. β-Thal intermedia has a severe anemia, but no transfusions needed
   d. β-Thal major (Cooley anemia)
      i. Patients are normal at birth.
      ii. Symptoms develop at about 6 months as hemoglobin F levels decline.
      iii. Severe hemolytic anemia results from decreased RBC life span.
         • Intramedullary destruction results in “ineffective erythropoiesis.”
         • Hemolysis causes jaundice and an increased risk of pigment (bilirubin) gallstones.
         • Lifelong transfusions are required, which result in secondary hemochromatosis.
         • Congestive heart failure (CHF) is the most common cause of death.
      iv. Erythroid hyperplasia in the bone marrow causes “crewcut” skull x-ray and increased size of maxilla (“chipmunk face”).
   v. Peripheral blood
      • Microcytic/hypochromic anemia
      • Numerous target cells and increased reticulocytes
   vi. Hemoglobin electrophoresis: ↑ hemoglobin F (90%), ↑ hemoglobin A2, ↓ hemoglobin A

6. Sideroblastic anemia
   a. Definition: a disorder in which the body has adequate iron stores, but is unable to incorporate the iron into hemoglobin. Associated with ring sideroblasts (accumulated iron in mitochondria of erythroblasts) in bone marrow
   b. May be either pyridoxine (vitamin B6) responsive or pyridoxine unresponsive; the latter is a form of myelodysplastic syndrome (refractory anemia with ring sideroblasts)
   c. Peripheral blood may show dimorphic RBC population.
   d. Lab: increased serum iron, ferritin, FEP, and % saturation of TIBC with decreased TIBC

NORMOCYTIC ANEMIAS

1. Anemias of blood loss
   a. Acute blood loss may cause shock or death.
   b. If the patient survives, the resulting hemodilution caused by shift of water from the interstitium will lower the hematocrit.
   c. There will be a marked reticulocytosis in 5–7 days.
d. Chronic blood loss, such as from the GI tract or from the GYN system, may result in iron deficiency anemia.

2. Hemolytic anemias
   a. Intravascular (IV) hemolysis
      i. Release of hemoglobin into the blood causes hemoglobinemia and hemoglobinuria.
      ii. Increased bilirubin from RBCs causes jaundice and an increased risk of pigment (bilirubin) gallstones.
      iii. Hemoglobin may be oxidized to methemoglobin, which causes methemoglobinemia and methemoglobinuria.
      iv. Markedly decreased hemoglobin-binding proteins in the blood, such as haptoglobin and hemopexin, are characteristic.
      v. No splenomegaly
   b. Extravascular (EV) hemolysis
      i. Splenomegaly results if the extravascular hemolysis occurs in spleen.
      ii. Hepatomegaly results if the extravascular hemolysis occurs in liver.
      iii. Increased bilirubin and decreased haptoglobin occur, but not as much as with IV hemolysis.
      iv. Absence of hemoglobinemia, hemoglobinuria, and methemoglobin formation

![Figure 12-2. DIC with Microangiopathic Hemolytic Anemia](https://commons.wikimedia.org/wiki/Anemia)

3. Sickle cell disease
   a. Definition: an inherited blood disorder leading to the formation of hemoglobin S and increased propensity for the affected red blood cells to become sickle-shaped and occlude small vessels.
b. Genetics
   i. Abnormality: single nucleotide change in codon causes valine (neutral) to
      replace normal glutamic acid (acidic) at the sixth position of the β-globin
      chain.
   ii. Heterozygous (AS): trait
       • About 8% of African Americans are heterozygous for hemoglobin S.
       • Patients with sickle trait have fewer symptoms than those with sickle disease.
       • Have resistance to Plasmodium falciparum infection (malaria)
   iii. Homozygous (SS): disease (sickle cell anemia)

   c. Factors affecting formation of irreversibly sickled red blood cells
   i. Increased concentration (dehydration) makes symptoms worse; decreased
      concentration (with thalassemia) makes symptoms better.
   ii. Decreased pH decreases oxygen affinity and makes symptoms worse.
   iii. Increased hemoglobin F makes symptoms better (rationale for therapy with
      hydroxyurea, which increases blood hemoglobin F levels).
   iv. Presence of hemoglobin C (SC: double-heterozygote individual) makes symp-
      toms better

   d. Increased RBC destruction causes a severe hemolytic anemia.
   i. Erythroid hyperplasia in the bone marrow
   ii. Increased bilirubin leads to jaundice and gallstone (pigment) formation.

   e. Capillary thrombi result from sickle cells blocking small vessels and may cause
   i. Vaso-occlusive (painful) crisis
   ii. Hand-foot syndrome (swelling) in children
   iii. Autosplenectomy, which is seen in older children and adults
       • Howell-Jolly bodies will appear in peripheral blood after autosplenectomy.
       • Results in increased incidence of infections (encapsulated organisms)
   iv. Increased incidence of Salmonella osteomyelitis (leg pain)
   v. Leg ulcers
   vi. Risk of aplastic crisis (especially with parvovirus B19 infection)
   vii. Emergencies: priapism and acute chest syndrome

   f. Lab tests for hemoglobin S
   i. Sickling test (metabisulfite test, which can't tell sickle cell disease from sickle
      cell trait)
   ii. Hemoglobin electrophoresis
   iii. Prenatal diagnosis: genetic testing (MstII endonuclease)

   g. Therapy includes hydroxyurea (increases hemoglobin F)

4. Hemoglobin C disease
   a. Abnormality: single nucleotide change in a codon causes lysine (basic) to replace
      normal glutamic acid (acidic) at the beta 6 position.
   b. Signs: mild normochromic-normocytic anemia, splenomegaly, target cells, and
      rod-shaped crystals in RBCs (the latter being characteristic)

5. Glucose-6-phosphate dehydrogenase deficiency
   a. Definition: a genetic disorder affecting the hexose monophosphate shunt leading
      to decreased production of reduced glutathione and increased susceptibility of red
      blood cells to oxidative injuries
Red Blood Cell Pathology: Anemias

b. Pathogenesis
i. Deficiency of glucose-6-phosphate dehydrogenase (G6PD) results in decreased levels of the antioxidant glutathione (GSH).
ii. RBCs are sensitive to injury by oxidant stresses leading to hemolysis.
iii. Deficiency of G6PD is not due to decreased synthesis but rather to defective protein folding, resulting in a protein having a decreased half-life.
c. X-linked inheritance; patient populations include
i. African Americans (A+ type)
   • Hemolysis is secondary to acute oxidative stress such as oxidative drugs (primarily, sulfonamides, anti-TB drugs), and more typically by viral or bacterial infections.
   • Hemolysis is intermittent (even if drug is continued) because only older RBCs have decreased levels of G6PD.
ii. Mediterranean type
   • Associated with favaism due to ingestion of fava beans
   • Has more severe hemolysis because all RBCs have decreased G6PD activity in that there is both decreased synthesis and decreased stability

d. Oxidation of hemoglobin forms Heinz bodies.
i. Heinz bodies cannot be seen with normal peripheral blood stains (Wright-Giemsa).
ii. Need supravital stains (methylene blue and crystal violet) to see Heinz bodies
iii. Heinz bodies are “eaten” by splenic macrophages (extravascular hemolysis), which may form bite cells.

6. Hereditary spherocytosis (HS)
a. Definition: autosomal dominant disorder that is due to a defect involving ankyrin and spectrin (most commonly affecting ankyrin molecule) in RBC membrane, which causes a decrease in the RBC surface membrane (spherocytosis)
b. Spherocytes are not flexible and are removed in spleen by macrophages (i.e., extravascular hemolysis), which causes
i. Splenomegaly with a mild to moderate hemolytic anemia
ii. Chronic hemolysis produces increased bilirubin and an increased risk for jaundice and pigment gallstones.
iii. Increased risk for acute red-cell aplasia due to parvovirus B19 infection
c. Lab tests
   i. Increased osmotic fragility
   ii. Normal MCH with increased MCHC
d. Treatment is splenectomy

7. Autoimmune hemolytic anemia (AIHA)
a. Warm AIHA
   i. Antibodies are IgG that are usually against Rh antigens and are active at 37°C
   ii. RBCs are removed by splenic macrophages, producing splenomegaly.
   iii. Etiology
      • Most cases are idiopathic
      • Autoimmune diseases (such as SLE)
      • Chronic lymphocytic leukemia (CLL)

Bridge to Biochemistry

G6PD is the rate-limiting enzyme in the hexose-monophosphate shunt (HMP).
G6PD normally produces NADPH, which keeps glutathione reduced.
Glutathione protects by breaking down hydrogen peroxide.

Clinical Correlate

Differential diagnosis of spherocytes in the peripheral blood includes warm AIHA (autoimmune hemolytic anemia) and hereditary spherocytosis. Use the osmotic fragility test (HS) and direct Coombs test (AIHA) to tell them apart.
8. Paroxysmal nocturnal hemoglobinuria (PNH)
   a. Definition: a hemolytic anemia caused by an acquired intrinsic defect in the cell membrane, especially in red cells, white cells, and platelets
   b. Abnormality: decreased glycosyl phosphatidylinositol (GPI)–linked proteins, especially decay accelerating factor (DAF)
      i. The function of DAF is to inhibit the activation of the complement cascade by breaking down C3 convertase.
      ii. Deficiency of DAF results in increased complement activity.
      iii. All cells in blood have increased sensitivity to the lytic actions of complement.
   c. Symptoms are episodes (paroxysms) of hemolysis at night.
   d. Acidosis in vivo, which occurs during sleep (breathing slowly retains CO₂) and exercise (lactic acidosis), causes activation of complement.
   e. PNH is a clonal stem cell disorder that therefore affects all cell lines.
   f. Pancytopenia in peripheral blood: anemia, leukopenia, thrombocytopenia
   g. Complications: increased risk for aplastic anemia, leukemia, and venous thrombosis
   h. Lab tests for PNH
      i. Sucrose in vitro (sucrose lysis test)
      ii. Acidosis in vitro (Ham test)

9. Pyruvate kinase deficiency
   a. The most common enzyme deficiency in the glycolytic pathway
   b. The enzyme normally converts phosphoenolpyruvate to pyruvate.
   c. Deficiency leads to decreased ATP with resulting damage to the erythrocyte membrane.
   d. Clinically, there is a hemolytic anemia with jaundice from birth.

10. Hereditary elliptocytosis
    a. Definition: a mild, hereditary, hemolytic anemia caused by a defect in spectrin.
    b. It is characterized by osmotically fragile ovoid erythrocytes (“elliptocytes”).

11. Aplastic anemia
    a. Definition: the term used when marrow failure causes a pancytopenia of the blood
    b. Aplastic anemia is the end pathway of many different processes including idiopathic (most common), medications (alkylating agents, chloramphenicol), chemical agents (benzene, insecticides), infection (EBV, CMV, parovirus, hepatitis), and whole body radiation (therapeutic or nuclear exposure).

MACROCYTIC ANEMIAS

1. Megaloblastic anemias
   a. Basic cause is impaired DNA synthesis (delayed mitoses), while RNA is not impaired; this produces a nuclear-cytoplasmic asynchrony that affects all rapidly proliferating cell lines, including cells of bone marrow, GI tract, and GYN
b. Examples of enlarged proliferating cells:
   i. RBCs have megaloblastic maturation.
      - Megaloblasts in bone marrow form macro-ovalocytes in peripheral blood.
      - Autohemolysis in bone marrow (ineffective erythropoiesis) will cause increased bilirubin and lactate dehydrogenase (LDH).
   ii. WBC changes
      - Giant metamyelocytes in bone marrow
      - Hypersegmented neutrophils (>5 lobes) in peripheral blood
   iii. Note: Platelets are not increased in size.

2. Megaloblastic anemia due to vitamin B_{12} (cobalamin) deficiency
   a. Causes of B_{12} deficiency
      i. Dietary deficiency
         - Rare because B_{12} is stored in the liver and it takes years to develop dietary deficiency
         - Seen only in strict vegetarians (diet with no animal proteins, milk, or eggs)
      ii. Decreased absorption, which may be caused by any of the following:
         - Decreased IF associated with gastrectomy or pernicious anemia
         - Pancreatic insufficiency (pancreatic proteases normally break down B_{12}-R complexes in duodenum)
         - Intestinal malabsorption due to parasites (fish tapeworm, a.k.a. *Diphyllobothrium latum*), bacteria (blind-loop syndrome), or Crohn disease of ileum
   b. Signs and symptoms of B_{12} deficiency
      i. Weakness due to anemia (megaloblastic anemia)
      ii. Sore (“beefy”) tongue due to generalized epithelial atrophy
      iii. Subacute combined degeneration of the spinal cord (SCDSC): demyelination of the posterior and lateral portion of the spinal cord
         - Posterior (sensory) tracts cause loss of vibration and position
         - Lateral involves dorsal spinocerebellar tracts (arm and leg dystaxia) and corticospinal tracts (spastic paralysis)
   c. Lab tests
      i. Low serum B_{12} level and increased serum homocysteine
      ii. Increased methylmalonic acid in urine
      iii. Schilling test:
         - Pernicious anemia: abnormal with correction by IF
         - Method: intramuscular vitamin B_{12}, then give oral radioactive vitamin B_{12}, and measure urine for radioactive vitamin B_{12}
   d. Treatment: intramuscular vitamin B_{12}, which will cause increased reticulocytes in about 5 days

3. Megaloblastic anemia due to folate deficiency
   a. Causes include
      i. Decreased intake
         - Dietary deficiency takes only months to develop
         - Seen in chronic alcoholics and elderly (“tea and toast” diet)

Note

Normal Sequence of B_{12} Absorption
1. Dietary B_{12} binds to salivary R-binding.
2. B_{12}-R complex broken by pancreatic proteases.
3. Free B_{12} binds to intrinsic factor (IF), which is secreted by gastric parietal cells.
4. B_{12}-IF complex absorbed by ileal mucosal epithelial cells.
5. B_{12} transported in blood bound to transcobalamin II.
ii. Decreased absorption: intestinal malabsorption (folate is absorbed in the upper small intestine)

iii. Increased requirement for folate
   - Pregnancy (folate deficiency during pregnancy is an important cause of neural tube defects)
   - Infancy

iv. Decreased utilization: folate antagonists used in chemotherapy such as methotrexate

b. Signs and symptoms of folate deficiency
   i. Megaloblastic anemia
   ii. But no neurologic symptoms (i.e., no SCIDSC)

c. Lab tests
   i. Low serum folate levels and increased serum homocysteine

d. Treatment: folate

POLYCYTHEMIA VERA

1. Polycythemia vera
   a. Due to a clonal expansion of a multipotent myeloid stem cell that primarily produces extra erythrocytes
   b. Also produces lesser degrees of granulocytes (neutrophils, eosinophils, basophils), mast cells, and platelets
   c. Characterized clinically by increased RBC mass, absolute leukocytosis, thrombocytosis, decreased erythropoietin, splenomegaly, hypercellular marrow, thrombotic events (related to blood viscosity), and gout (related to increased blood cell turnover)

2. Secondary polycythemia
   a. Refers to increased red cell mass due to compromised ability of blood to supply oxygen to tissues
   b. Causes include COPD and cyanotic congenital heart disease
   c. Erythropoietin levels can be appropriately high.
   d. May also be caused by inappropriately high erythropoietin levels, e.g., renal cell carcinoma excreting erythropoietin is the typical cause

3. Relative polycythemia
   a. Refers to an increased red cell count secondary to decreased plasma volume (typically due to dehydration)
   b. Red cell mass, erythropoietin, and blood oxygen content are normal.
Chapter Summary

* Red blood cells can have a variety of abnormal shapes or contain inclusions, either of which may suggest particular diagnoses.

* Anemia is the reduction below normal limits of the total circulating red cell mass, which may lead to palpitations, dizziness, angina, skin pallor, weakness, or other symptoms. Laboratory measures used in the evaluation of anemia include MCV, MCH, MCHC, RDW, and reticulocyte count.

* Anemias can be classified based on size and red cell color. They can also be classified based on pathogenesis, including broad categories of blood loss, hemolytic anemias, and anemias of diminished erythropoiesis.

* Iron deficiency anemia is a microcytic anemia seen most often in the elderly and poor population, children, pregnant women, and patients with chronic blood loss. Iron deficiency anemia is characterized by decreased serum iron, increased TIBC, decreased percentage saturation, and decreased serum ferritin.

* Anemia of chronic disease can be seen in patients with a variety of chronic systemic diseases and is characterized by decreased serum iron, decreased TIBC, decreased percentage saturation, and increased serum ferritin.

* Thalassemias are anemias due to quantitative abnormalities of synthesis of hemoglobin chains, and are subclassified as alpha thalassemias and beta thalassemias. Alpha-thalassemia has four clinical forms depending upon the number of alpha-globin genes affected: silent carrier, alpha-thalassemia trait, HbH disease, and hydrops fetalis. Beta-thalassemia has three clinical presentations: beta-thalassemia minor, beta-thalassemia intermedia, and beta-thalassemia major.

* Sideroblastic anemias characteristically have ringed sideroblasts in the bone marrow; some cases are a form of myelodysplastic syndrome.

* Anemia of blood loss occurs when a patient survives acute blood loss and undergoes hemodilution that lowers the hematocrit. Chronic cases may develop superimposed iron deficiency anemia.

* Hemolytic anemias can be due to either intravascular or extravascular hemolysis.

* Sickle cell anemia is due to a single nucleotide change in the beta-globin chain and is an important disease of African Americans; it clinically presents as either sickle cell trait or sickle cell anemia. Patients with sickle cell anemia are vulnerable to a variety of complications related to sickled cells blocking small blood vessels.

* Hemoglobin C disease is also related to a single nucleotide change in a globin gene but produces milder disease than sickle cell anemia.

* Glucose-6-phosphate dehydrogenase deficiency is an enzyme deficiency that causes red cells to lyse under oxidant stresses.

* Hereditary spherocytosis is an autosomal dominant disorder due to an abnormal membrane-associated protein, spectrin, which leads to spherical erythrocyte morphology with mild to moderate hemolytic anemia.

* Autoimmune hemolytic anemias can be idiopathic or related to other autoimmune diseases, leukemias and lymphomas, or medications.

(Continued)
Chapter Summary (continued)

* Paroxysmal nocturnal hemoglobinuria produces episodic hemolysis as a result of increased red-cell sensitivity to the lytic actions of complement. Pyruvate kinase deficiency is a hereditary cause of hemolytic anemia due to a deficiency of a glycolytic pathway enzyme, leading to decreased ATP and resulting in erythrocyte membrane damage. Hereditary elliptocytosis causes mild anemia. Aplastic anemia is a common end pathway of many different disease processes that destroy the marrow's ability to produce blood cells.

* Megaloblastic anemias occur when there is impaired DNA synthesis, which leads to delayed mitoses. Important causes include vitamin B₁₂ deficiency and folate deficiency.

* Polycythemia vera is a clonal disease leading to increased red cells (dominant process) accompanied by lesser degrees of increased granulocytes and platelets. Secondary polycythemia is polycythemia due to increased erythropoietin, which can be either "appropriate" if it helps for a tissue oxygenation problem, or "inappropriate" if the erythropoietin is high because it is secreted by a tumor. Relative polycythemia is the term used for increased hematocrit in the absence of increased red cell mass and is usually due to decreased plasma volume (as in dehydration).
Vascular Pathology

VASCULITIS

1. Polyaartelitis nodosa (PAN)
   a. Epidemiology
      i. Young adults
      ii. Male > female
   b. Distribution of disease
      i. Systemic vasculitis—any organ except lung
      ii. Kidney, heart, GI tract, muscle, etc.
      iii. Small and medium size arteries
   c. Clinical features
      i. Symptoms are varied and depend on the system involved.
      ii. Low-grade fever (fever of unknown origin [FUO]), weight loss, and malaise
      iii. Hematuria, renal failure, hypertension
      iv. Abdominal pain, diarrhea, and GI bleeding
      v. Myalgia and arthralgia
   d. Pathology
      i. Segmental necrotizing vasculitis
      ii. Three stages
         • Acute lesions—fibrinoid necrosis and neutrophils
         • Healing lesions—fibroblast proliferation
         • Healed lesions—nodular fibrosis and loss of internal elastic lamina
      iii. Sequela
         • Thrombosis and infarction
         • Arteritis (kidneys, heart, and GI tract)
   e. Lab findings
      i. Hepatitis B antigen (HBsAg) positive in 30% of cases
      ii. Perinuclear antineutrophil cytoplasmic autoantibodies (P-ANCA)
         • Autoantibody against myeloperoxidase
         • Correlates with disease activity
         • P-ANCA is only found in the microscopic form of polyarteritis (microscopic polyangitis)
   f. Diagnosis: arterial biopsy
   g. Treatment: corticosteroids and cyclophosphamide
h. Prognosis
   i. Untreated—fatal in most cases
   ii. Treated—90% long-term remission rate

2. Churg-Strauss syndrome (allergic granulomatosis and angiitis)
   a. Variant of PAN
   b. Associated with bronchial asthma
   c. Systemic vasculitis with granulomas and eosinophilia
   d. Involves the lung, spleen, kidney, etc.
   e. P-ANCA may be present.

3. Wegener granulomatosis
   a. Epidemiology
      i. Rare; males > females
      ii. Peak incidence: ages 40–60
   b. Distribution of disease
      i. Necrotizing vasculitis with granulomas
      ii. Classically involves the nose, sinuses, lungs, and kidneys
      iii. Small-size arteries, capillaries, and veins
   c. Clinical features
      i. Bilateral pneumonitis with nodular and cavitary pulmonary infiltrates
      ii. Chronic sinusitis
      iii. Nasopharyngeal ulcerations
      iv. Renal disease
         • Focal necrotizing glomerulonephritis
         • Crescentic glomerulonephritis
   d. Micro: fibrinoid necrosis, neutrophils, and granulomas
   e. Lab findings
      i. Cytoplasmic antineutrophil cytoplasmic autoantibodies (C-ANCA)
         • Autoantibody against proteinase 3
         • Correlates with disease activity
   f. Diagnosis: biopsy
   g. Treatment: immunosuppressive drugs (cyclophosphamide)
   h. Prognosis
      i. Untreated—80% 1-year mortality rate
      ii. Treated—90% long-term remission

4. Temporal arteritis (giant cell arteritis)
   a. Epidemiology
      i. Most common form of vasculitis
      ii. Female > male
      iii. Primarily affects the elderly population
      iv. Associated with HLA-DR4
   b. Distribution of disease
      i. Small and medium-sized arteries
      ii. Cranial arteries (temporal, facial, and ophthalmic arteries)
      iii. Aortic arch—giant cell aortitis (uncommon)
c. Clinical features
   i. Throbbing headache
   ii. Tender, firm temporal arteries
   iii. Visual disturbances
      • Blurred or double vision
      • Visual loss
   iv. Facial pain
   v. Fever, malaise, weight loss, muscle aches, anemia
   vi. Polymyalgia rheumatica: systemic flu-like symptoms and joint involvement

d. Lab: elevated ESR

e. Pathology
   i. Segmental granulomatous vasculitis
   ii. Multinucleated giant cells and fragmentation of the internal elastic lamina
   iii. Intimal fibrosis with lumenal narrowing

f. Diagnosis
   i. Temporal arterial biopsy
   ii. Classic presentation or rapid onset may be treated empirically.

g. Treatment: corticosteroids

h. Prognosis
   i. Treated—dramatic response to steroids
   ii. Untreated—blindness due to occlusion of ophthalmic artery

5. Takayasu arteritis (pulseless disease)

a. Epidemiology
   i. Most common in Asia
   ii. Affects young and middle-aged women (ages 15–45)

b. Distribution of disease
   i. Medium-sized to large arteries
   ii. Aortic arch and major branches

c. Pathology
   i. Granulomatous vasculitis with extensive intimal fibrosis
   ii. Irregular fibrous thickening of the wall of the aortic arch
   iii. Narrowing of the orifices of the major arterial branches

d. Clinical features
   i. Loss of pulse in the upper extremities
   ii. Ocular manifestations
      • Visual loss or field defects
      • Retinal hemorrhages
   iii. Neurologic abnormalities

e. Treatment: steroids

f. Prognosis: variable course

6. Buerger disease (thromboangiitis obliterans)

a. Epidemiology
   i. Occurs in young males, usually under 40 years old
ii. Associated with heavy cigarette smoking
iii. Common in Israel, India, Japan, and South America

b. Distribution of disease
i. Small and medium-sized arteries and veins
ii. Involves the extremities

c. Pathology
i. Recurrent neutrophilic vasculitis with microabscesses
ii. Segmental thrombosis leads to vascular insufficiency

d. Clinical features
i. Severe pain (claudication) in the affected extremity
ii. Thrombophlebitis
iii. Secondary Raynaud phenomenon
iv. Ulceration and gangrene

e. Treatment: smoking cessation

7. Kawasaki disease (mucocutaneous lymph node syndrome)

a. Epidemiology
i. Commonly affects infants and young children (age <4)
ii. Japan, Hawaii, and U.S. mainland

b. Clinical features
i. Acute febrile illness
ii. Conjunctivitis; erythema and erosions of the oral mucosa
iii. Generalized maculopapular skin rash
iv. Lymphadenopathy

c. Distribution of disease
i. Large, medium-sized, and small arteries
ii. Coronary artery commonly affected (70%)

d. Pathology
i. Segmental necrotizing vasculitis
ii. Weakened vascular wall may undergo aneurysm formation

e. Prognosis
i. Self-limited course
ii. Mortality rate of 1–2% due to rupture of a coronary aneurysm or coronary thrombosis

RAYNAUD DISEASE VERSUS PHENOMENON

1. Primary Raynaud phenomenon (Raynaud disease)

a. Young women
b. Episodic small artery vasospasm in the extremities, nose, or ears
c. Results in blanching and cyanosis of fingers or toes
d. Precipitated by cold temperature and emotions
e. No underlying disease or pathology
2. Secondary Raynaud phenomenon
   a. Arterial insufficiency secondary to an underlying disease
   b. Examples: scleroderma (CREST), SLE, Buerger disease, atherosclerosis, etc.

**ARTERIOSCLEROSIS**

1. Mönckeberg medial calcific sclerosis
   a. Medial calcification of medium-sized (muscular) arteries
   b. Femoral, tibial, radial, and ulnar arteries
   c. Asymptomatic; may be detected by X-ray

2. Arteriolosclerosis
   a. Definition: sclerosis of arterioles
   b. Affects small arteries and arterioles
   c. Micro
      i. Hyaline arteriolosclerosis: pink, glassy arterial wall thickening with luminal narrowing (benign hypertension, diabetes, and aging)
      ii. Hyperplastic arteriolosclerosis: smooth-muscle proliferation resulting in concentric ("onion skin") wall thickening and luminal narrowing (malignant hypertension)

3. Atherosclerosis
   a. Definition: lipid deposition and intimal thickening of large and medium-sized (elastic and muscular) arteries, resulting in fatty streaks and atheromatous plaques over a period of decades (a type of chronic inflammatory condition)
   b. Distribution of disease: aorta, coronary, carotid, cerebral, iliac, and popliteal arteries

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**In a Nutshell**

**Arteriosclerosis**

Definition: a group of diseases that result in arterial wall thickening ("hardening of the arteries")

- Mönckeberg
- Arteriolosclerosis
- Atherosclerosis

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**Table 13-1. Major and Minor Risk Factors for Atherosclerosis**

<table>
<thead>
<tr>
<th>Major Risk Factors</th>
<th>Minor Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia</td>
<td>Male gender</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Sedentary lifestyle</td>
</tr>
<tr>
<td>Smoking</td>
<td>Stress (type A personality)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Elevated homocysteine</td>
</tr>
<tr>
<td>Obesity</td>
<td>Oral contraceptive use</td>
</tr>
<tr>
<td></td>
<td>Increasing age</td>
</tr>
<tr>
<td></td>
<td>Familial/genetic factors</td>
</tr>
</tbody>
</table>

|                    | Fatty streak (clinically reversible)      |
|                    | i. Gross: flat, yellow intimal streak    |
|                    | ii. Micro: lipid-laden macrophages (foam cells) |
|                    | Atheromatous plaque                      |
|                    | i. Gross: raised, yellow-white plaques   |
|                    | ii. Micro                               |
|                    | • Fibrous cap: collagen, smooth muscle, lymphocytes, and foam cells |
|                    | • Necrotic core (atheroma): cholesterol clefts, lipid, foam cells, and necrotic debris |
e. Complicated atheromatous plaques (clinically irreversible)
   i. Dystrophic calcification (brittle eggshell quality)
   ii. Ulceration and atheroemboli
   iii. Plaque rupture with superimposed thrombus
f. Clinical complications
   i. Ischemic heart disease (MIs)
   ii. Cerebrovascular accidents (CVA)
   iii. Atheroemboli (transient ischemic attacks [TIAs] and renal infarcts)
   iv. Aneurysm formation
   v. Peripheral vascular disease
   vi. Mesenteric artery occlusion

HYPERTENSION (HTN)

1. Definition: an elevated blood pressure leading to end-organ damage, or a sustained
diastolic pressure >90 mm Hg and/or a systolic pressure >140 mm Hg

<table>
<thead>
<tr>
<th>The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) Report defines blood pressure as:</th>
<th>Systolic Blood Pressure (mm Hg)</th>
<th>Diastolic Blood Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120–139</td>
<td>80–89</td>
</tr>
<tr>
<td>Stage I Hypertension</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Stage II Hypertension</td>
<td>≥160</td>
<td>≥100</td>
</tr>
</tbody>
</table>
2. Incidence
   a. Very common: 25% of U.S. population
   b. African Americans > Caucasians; risk increases with age
3. Etiology
   a. Idiopathic (essential) primary HTN (95%)
   b. Secondary HTN (5%)
      i. Renal disease
      ii. Pheochromocytoma, etc.
4. Benign hypertension
   a. Accounts for 95% of the cases of HTN
   b. Mild to moderate elevations in blood pressure causing end-organ damage
   c. Asymptomatic silent disease
   d. No organ is spared
   e. Micro: hyaline arteriolosclerosis
   f. Late manifestations
      i. Concentric left ventricular hypertrophy
      ii. Congestive heart failure
      iii. Accelerated atherosclerosis (major risk factor)
      iv. Myocardial Infarction
      v. Aneurysm formation, rupture, and dissection
      vi. Intracerebral hemorrhage (major risk factor)
      vii. Chronic renal failure
5. Malignant (accelerated) HTN
   a. Accounts for 5% of the cases of HTN
   b. Markedly elevated pressures (e.g., systolic pressure greater than 180 mm Hg and/or diastolic >120 mm Hg) causing end-organ damage
   c. Funduscopic exam
      i. Retinal hemorrhages and exudates
      ii. Papilledema
   d. Gross: kidney has petechial hemorrhages ("flea-bitten" appearance)
   e. Micro
      i. Hyperplastic arteriolosclerosis ("onion skin")
      ii. Necrotizing arteriolitis: fibrinoid necrosis of vessel walls
   f. Medical emergency: if untreated most patients will die within 2 years from renal failure, intracerebral hemorrhage, or chronic heart failure (CHF)
ANEURYSMS AND ARTERIOVENOUS FISTULAS

1. Aneurysms
   a. Definition: congenital or acquired weakness of the vessel wall media, resulting in a localized dilatation or outpouching
   b. Complications
      i. Thrombus formation and thromboembolism
      ii. Compression of nearby structures
      iii. Rupture or dissection may cause sudden death.

![Berry aneurysm in the Circle of Willis](image)

![Dissecting aortic aneurysm](image)

![Coronary artery aneurysm](image)

![Fusiform aneurysm of the abdomen](image)

**Figure 13-2. Location of Aneurysms**

2. Atherosclerotic aneurysms
   a. Weakening of media secondary to atheroma formation
   b. Occur in the abdominal aorta below the renal arteries
   c. Associated with hypertension
   d. Half of aortic aneurysms > 6 cm in diameter will rupture within 10 years.

3. Syphilitic aneurysms
   a. Involves the ascending aorta
   b. Syphilitic (luetie) aortitis causes an obliteratorve endarteritis of the vasa vasorum, leading to ischemia and smooth-muscle atrophy of the aortic media.
   c. May dilate the aortic valve ring, causing aortic insufficiency
4. Aortic dissecting aneurysm
   a. Definition: blood from the vessel lumen enters an intimal tear and dissects through
      the layers of the media
   b. Etiology: degeneration (psicic medial degeneration) of the tunica media
   c. Presents with severe tearing pain
   d. May compress and obstruct the aortic branches (e.g., renal or coronary arteries)
   e. HTN and Marfan syndrome are predisposing factors.
5. Berry aneurysm
   a. Congenital aneurysm of the circle of Willis
6. Microaneurysms: small aneurysms commonly seen in HTN and diabetes
7. Mycotic aneurysms: aneurysms usually due to bacterial infections
8. Arteriovenous (AV) fistulas
   a. Definition: a direct communication between a vein and an artery without an interven-
      ving capillary bed
   b. Etiology: may be congenital or acquired (e.g., trauma)
   c. Potential complications
      i. Shunting of blood may lead to low output heart failure.
      ii. Risk of rupture and hemorrhage

VENOUS DISEASE

1. Deep vein thrombosis (DVT)
   a. Clinical features
      i. Deep leg veins (90%): iliac, femoral, popliteal veins
      ii. Often asymptomatic: commonly missed diagnosis
      iii. Unilateral leg swelling, warmth, erythema, Homans sign (increased resistance to
           passive dorsiflexion of the ankle by the examiner)
   b. Diagnosis: detected by doppler "duplex" ultrasound
   c. Major complication: pulmonary embolus
2. Varicose veins
   a. Definition: dilated, tortuous veins caused by increased intraluminal pressure
   b. Superficial veins of the lower extremities (lack of structural support from superficial
      fat and/or incompetent valve(s))
      i. Female > male; common in pregnancy
      ii. Occurs in 15% of the U.S. population
      iii. Aggravated by prolonged standing or sitting
      iv. Edema, thrombosis, stasis dermatitis, and ulcerations
      v. Rarely a source of emboli
   c. Esophageal varices
      i. Due to portal hypertension usually caused by cirrhosis
      ii. Life-threatening hemorrhage
   d. Anal region (hemorrhoids)
      i. Constipation and pregnancy
      ii. May bleed (streaks of red blood on hard stools)
      iii. Thrombosis (painful)
VASCULAR NEOPLASMS

1. Hemangiomas
   a. Extremely common, benign vascular tumors
   b. Most common tumor in infants
   c. Occur on the skin, mucous membranes, or internal organs
   d. Major types: capillary and cavernous hemangiomas
   e. May spontaneously regress

2. Hemangioendothelioma
   a. Associated with von Hippel-Lindau disease
   b. Multiple tumors involving the cerebellum, brain stem, spinal cord, and retina

3. Glomus tumor (glomangioma)
   a. Benign, small, painful tumor of the glomus body
   b. Usually occurs under fingernails

4. Kaposi sarcoma
   a. Low-grade malignant tumor of endothelial cells
   b. Associated with Kaposi-sarcoma–associated virus (HHV8)
   c. Gross
      i. Multiple red-purple patches, plaques, or nodules
      ii. May remain confined to the skin or may disseminate
   d. Micro
      i. Proliferation of spindle-shaped endothelial cells
      ii. Slit-like vascular spaces
      iii. Extravasated RBCs
   e. Classic European form
      i. Older men of Eastern European or Mediterranean origin
      ii. Red-purple skin plaques on the lower extremities
   f. Transplant-associated form
      i. Occurs in patients on immunosuppression for organ transplants
      ii. Involves skin and viscera
      iii. May regress with reduction of immunosuppression
   g. African form
      i. Occurs in African children and young men
      ii. Generalized lymphatic spread is common
   h. AIDS-associated form
      i. Most common in homosexual male AIDS patients
      ii. Aggressive form with frequent widespread visceral dissemination
      iii. Common sites: skin, GI tract, lymph nodes, and lungs
      iv. Responsive to chemotherapy and interferon-alpha
      v. Rarely causes death

5. Angiosarcomas (hemangiosarcoma)
   a. Malignant vascular tumor with a high mortality
   b. Most commonly occur in skin, breast, liver, and soft tissues
   c. Liver angiosarcomas are associated with vinyl chloride, arsenic, and thorotrast.
Chapter Summary

* Polyarteritis nodosa is a segmental necrotizing vasculitis that can affect any organ, except the lung. The symptoms vary with the organ involved.

* Churg-Strauss syndrome is a variant of polyarteritis nodosa with associated bronchial asthma, granuloma formation, and eosinophilia.

* Wegener granulomatosis is a necrotizing vasculitis with granulomas that classically involves the nose, sinuses, lungs, and kidneys.

* Temporal arteritis is a segmental granulomatous vasculitis with a predilection for involving cranial arteries. Headache, facial pain, and visual disturbances occur. Untreated temporal arteritis may cause blindness.

* Takayasu arteritis is a granulomatous vasculitis with massive intimal fibrosis that tends to involve the aortic arch and its major branches. It may produce blindness or loss of pulse in the upper extremities.

* Buerger disease is a neutrophilic vasculitis that tends to involve the extremities (potentially causing gangrene) of young men who smoke heavily.

* Kawasaki disease is a febrile lymphadenopathy with rash with an associated segmental necrotizing vasculitis with a predilection for the coronary arteries.

* Raynaud disease is an idiopathic small artery vasospasm that causes blanching and cyanosis of the fingers and toes; the term secondary Raynaud phenomenon is used when similar changes are observed secondary to a systemic disease such as scleroderma or systemic lupus erythematosus.

* Würmleberg medial calcific sclerosis is an asymptomatic medial calcification of medium-sized arteries.

* Arteriosclerosis refers to small artery and arteriolar changes leading to luminal narrowing that are most often seen in patients with diabetes, hypertension, and aging.

* Atherosclerosis is lipid deposition and intimal thickening of large and medium-sized arteries, resulting in fatty streaks and atheromatous plaques. Clinical complications of atherosclerosis include ischemic heart disease, cerebrovascular accidents, aneurysm formation, peripheral vascular disease, and mesenteric artery occlusion.

* Hypertension is defined as an elevated blood pressure leading to end-organ damage, or sustained diastolic pressure >90 mm Hg and/or systolic pressure >140 mm Hg. Benign hypertension is a common, initially silent, disease that may eventually produce cardiac disease, accelerated atherosclerosis, aneurysm formation, and renal and CNS damage. Malignant hypertension is much less common than benign hypertension and is defined as markedly elevated pressures (e.g., systolic pressure greater than 180 mm Hg, or diastolic >120 mm Hg) causing rapid end-organ damage. Untreated patients often die within 2 years from renal failure, intracerebral hemorrhage, or chronic heart failure.

* An aneurysm is defined as a congenital or acquired weakness of the vessel wall media, resulting in a localized dilation or outpouching. Complications of aneurysms include thrombus formation, compression of adjacent structures, and rupture with risk of sudden death.

* Atherosclerotic aneurysms are associated with hypertension and tend to involve the abdominal aorta.

(Continued)
Chapter Summary (continued)

* Syphilitic aneurysms tend to involve the ascending aorta and develop secondary to an obliterative endarteritis of the vasa vasorum, which is the blood supply of the aortic media.

* Aortic dissecting aneurysms occur when blood from the vessel lumen enters an intimal tear and dissects through the layers of the media, which have often previously been damaged by cystic medial degeneration.

* Berry aneurysms are congenital aneurysms of the vessels near the circle of Willis. Rupture of these aneurysms may cause subarachnoid hemorrhage.

* Deep vein thrombosis usually involves the deep leg veins and may be asymptomatic. The major complication is pulmonary embolus.

* Varicose veins are dilated, tortuous veins caused by increased intraluminal pressure. Common sites include the superficial veins of the lower extremities, esophageal varices, and hemorrhoids.

* Hemangiomas are extremely common, benign vascular tumors that may involve the skin, mucous membranes, or internal organs.

* Hemangioblastosomas are vascular tumors associated with von Hippel-Lindau disease that tend to involve the central nervous system and retina.

* Glomus tumors are small, painful vascular tumors most often found under the fingernails.

* Kaposi sarcoma is a low-grade malignant tumor of endothelial cells that appears to have a viral etiology (HHV8) and in the United States is found most often in AIDS patients.

* Angiosarcoma is a malignant vascular tumor with a high mortality that occurs most commonly in skin, breast, liver, and soft tissues.
Cardiac Pathology

ISCHEMIC HEART DISEASE

1. General
   a. Definition: cardiac ischemia usually secondary to coronary artery disease (CAD)
   b. Most common cause of death in the United States
   c. Most common in middle-age men and postmenopausal women

2. Angina pectoris
   a. Definition: transient cardiac ischemia without cell death resulting in substernal chest pain
   b. Stable angina
      i. Most common type of angina
      ii. Caused by coronary artery atherosclerosis with luminal narrowing greater than 75%
      iii. Chest pain is brought on by increased cardiac demand (exertional or emotional).
      iv. EKG: ST segment depression (subendocardial ischemia)
      v. Relieved by rest or nitroglycerin (vasodilatation)
   c. Prinzmetal variant angina
      i. Caused by coronary artery vasospasm
      ii. Episodic chest pain often occurring at rest
      iii. EKG: transient ST segment elevation (transmural ischemia)
      iv. Relieved by nitroglycerin (vasodilatation)
   d. Unstable or crescendo angina
      i. Caused by formation of a nonocclusive thrombus in an area of coronary atherosclerosis
      ii. Increasing frequency, intensity, and duration of episodes
      iii. Occurs at rest
      iv. High risk for myocardial infarction

3. Myocardial infarction (MI)
   a. Definition: localized area of cardiac muscle coagulative necrosis due to ischemia
   b. Most common cause of death in the United States
   c. Mechanism
      i. Coronary artery atherosclerosis with plaque rupture and superimposed thrombus formation
      ii. Coronary artery spasm
Clinical Correlate

Atypical presentations of MI with little or no chest pain are seen most frequently in elderly patients, diabetics, women, and postsurgical patients.

d. Distribution of coronary artery thrombosis
   i. Left anterior descending (LAD) = 45%
   ii. Right coronary artery (RCA) = 35%
   iii. Left circumflex coronary artery (LCA) = 15%

e. Transmural infarction
   i. Most common type of infarction
   ii. Ischemic necrosis of >50% of myocardial wall

f. Subendocardial infarction: ischemic necrosis of <50% of myocardial wall

g. Clinical presentation
   i. Sudden onset of severe “crushing” substernal chest pain
   ii. Often radiates to the left arm, jaw, and neck
   iii. Chest heaviness, tightness, and shortness of breath
   iv. Diaphoresis, nausea, and vomiting
   v. Jugular venous distension (JVD)
   vi. Anxiety and often have a “feeling of impending doom”

Table 14-1. Serum Markers Used to Diagnose Myocardial Infarctions

<table>
<thead>
<tr>
<th></th>
<th>Elevated by</th>
<th>Peak</th>
<th>Returns to Normal by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac-specific troponin I &amp; T</td>
<td>3–6 h</td>
<td>16 h</td>
<td>7–10 days</td>
</tr>
</tbody>
</table>
h. EKG
   i. ST segment elevation
   ii. Q waves representing myocardial coagulative necrosis develop in 24 to 48 hrs.
   i. Gross and microscopic sequence of changes
   i. The microscopic and gross changes represent a spectrum that is preceded by biochemical changes going from aerobic metabolism to anaerobic metabolism within minutes.
   ii. The time intervals are variable and depend on the size of the infarct, as well as other factors.

Table 14-2. Gross Sequence of Changes

<table>
<thead>
<tr>
<th>Survival Time</th>
<th>Predominant Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–18 h</td>
<td>No visible gross change</td>
</tr>
<tr>
<td>18–24 h</td>
<td>Vague pallor and softening</td>
</tr>
<tr>
<td>1–7 days</td>
<td>Yellow pallor</td>
</tr>
<tr>
<td>7–28 days</td>
<td>Central pallor with a red border</td>
</tr>
<tr>
<td>Months</td>
<td>White, firm scar</td>
</tr>
</tbody>
</table>

Table 14-3. Microscopic Sequence of Changes

<table>
<thead>
<tr>
<th>Survival Time</th>
<th>Predominant Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–4 h</td>
<td>Wavy myocyte fibers and contraction bands</td>
</tr>
<tr>
<td>4–24 h</td>
<td>Coagulative necrosis</td>
</tr>
<tr>
<td>1–3 days</td>
<td>Neutrophilic infiltrate</td>
</tr>
<tr>
<td>3–7 days</td>
<td>Macrophages</td>
</tr>
<tr>
<td>7–28 days</td>
<td>Granulation tissue</td>
</tr>
<tr>
<td>6 weeks</td>
<td>Fibrotic scar</td>
</tr>
</tbody>
</table>

j. Complications
   i. Cardiac arrhythmias that may lead to sudden cardiac death
   ii. Congestive heart failure
   iii. Cardiogenic shock (>40–50% myocardium is necrotic)
   iv. mural thrombus and thromboembolism
   v. Fibrinous pericarditis
   vi. Cardiac rupture (most common 4–7 days post-MI)
      • Ventricular free wall → cardiac tamponade
      • Interventricular septum → left to right shunt
      • Papillary muscle → mitral insufficiency
   vii. Ventricular aneurysm
Clinical Correlate

Auscultation of a friction rub is characteristic of pericarditis. Pericarditis is most common 2–3 days after infarction but may also occur several weeks later (Dressler syndrome—a rare autoimmune reaction (type II) where the necrotic heart muscle induces the immune system to generate autoantibodies to cardiac self-antigens).

4. Sudden cardiac death
   a. Definition: death within 1 hour of the onset of symptoms
   b. Mechanism: fatal cardiac arrhythmia (usually ventricular fibrillation)
   c. Etiology
      i. Coronary artery disease (80%)
      ii. Hypertrophic cardiomyopathy
      iii. Mitral valve prolapse
      iv. Aortic valve stenosis
      v. Congenital heart abnormalities
      vi. Myocarditis

5. Chronic ischemic heart disease
   a. Definition: the insidious onset of progressive congestive heart failure with no history of angina pectoris or myocardial infarction
   b. Diffuse myocardial fibrosis due to chronic ischemic injury from severe atherosclerotic coronary artery disease

Clinical Correlate

Clinically, the degree of orthopnea is often quantified in terms of the number of pillows the patient needs in order to sleep comfortably (e.g., “three-pillow orthopnea”).

CONGESTIVE HEART FAILURE

1. Congestive heart failure (CHF)
   a. Definition: insufficient cardiac output to meet the metabolic demand of the body’s tissues and organs
   b. Final common pathway for many cardiac diseases
   c. Increasing incidence in the United States
   d. Complications
      i. Forward failure = decreased organ perfusion
      ii. Backward failure = passive congestion of organs
   e. Right- and left-sided heart failure often occur together.

2. Left heart failure
   a. Etiology
      i. Ischemic heart disease
      ii. Hypertension
      iii. Myocardial diseases
      iv. Aortic or mitral valve disease
   b. Gross
      i. Increased heart weight
      ii. Left ventricular hypertrophy and dilatation
      iii. Heavy, edematous lungs
   c. Presentation: dyspnea, orthopnea, paroxysmal nocturnal dyspnea, rales, and S3 gallop
   d. Micro
      i. Cardiac myocyte hypertrophy with “enlarged pleiotropic nuclei”
      ii. Pulmonary capillary congestion and alveolar edema
      iii. Intra-alveolar hemosiderin-laden macrophages (“heart failure cells”)
e. Complications
   i. Passive pulmonary congestion and edema
   ii. Activation of renin-angiotensin-aldosterone system leading to 2° hyperaldosteronism
   iii. Cardiogenic shock
3. Right heart failure
   a. Etiology
      i. Most commonly caused by left-sided heart failure
      ii. Pulmonary or tricuspid valve disease
      iii. Cor pulmonale
   b. Presentation: jugular venous distention (JVD), hepatosplenomegaly, dependent edema, ascites, weight gain, and pleural and pericardial effusions
   c. Gross: RVH and dilatation
   d. Complications
      i. Chronic passive congestion of the liver
      ii. Cardiac sclerosis/cirrhosis (only with long-standing congestion)

VALVULAR HEART DISEASE
1. Degenerative calcific aortic valve stenosis
   a. Common valvular abnormality
   b. Definition: age-related dystrophic calcification, degeneration, and stenosis of the aortic valve
   c. Common in congenital bicuspid aortic valves
   d. Results in concentric left ventricular hypertrophy (LVH) and CHF
   e. Increased risk of sudden death
   f. Treatment: aortic valve replacement
2. Mitral valve prolapse
   a. Epidemiology
      i. Young women
      ii. Affects 5–10% of the U.S. population
      iii. Associated with Marfan syndrome
   b. Asymptomatic with a mid-systolic click on auscultation
   c. Gross: enlarged, floppy mitral valve leaflets that prolapse into the left atrium
   d. Micro: myxomatous degeneration
   e. Complications
      i. — Infectious endocarditis and septic emboli
      ii. Rupture of chordae tendineae and mitral insufficiency
      iii. Sudden death (rare)
3. Rheumatic valvular heart disease/acute rheumatic fever
   a. Definition: rheumatic fever is a systemic recurrent inflammatory disease, triggered by a pharyngeal infection with Group A β-hemolytic streptococci
   b. Mechanism: in genetically susceptible individuals, the infection results in production of antibodies that cross-react with cardiac antigens (type II hypersensitivity reaction)

Note

Cor pulmonale = Right-sided heart failure caused by pulmonary hypertension from intrinsic lung disease:
Lung disease → pulmonary hypertension → ↑ right ventricular pressure → right ventricular hypertrophy (RVH) → right-sided heart failure.
c. Epidemiology
   i. Children (ages 5–15 years)
   ii. Decreasing incidence in the United States

d. Clinical findings
   i. Symptoms occur 2–3 weeks after a pharyngeal infection
   ii. Lab: elevated antistreptolysin O (ASO) titers
   iii. Jones criteria

Table 14-4. Jones Criteria of Rheumatic Fever

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migratory polyarthritis</td>
<td>Fever</td>
</tr>
<tr>
<td>Pancarditis</td>
<td>Arthralgias</td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
<td>Elevated acute phase reactants</td>
</tr>
<tr>
<td>Skin rash (erythema marginatum)</td>
<td></td>
</tr>
<tr>
<td>Sydenham chorea</td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis of rheumatic fever requires: two major or one major and two minor

e. Acute rheumatic heart disease
   i. Myocarditis—*Aschoff body*: fibrinoid necrosis surrounded by macrophages (*Anitschkow cells*), lymphocytes, and plasma cells
   ii. Fibrinous pericarditis
   iii. Endocarditis
      • Involves mitral and aortic valves
      • Fibrin vegetations along the lines of closure
      • MacCallum plaques: left atrial endocardial thickening

f. Chronic rheumatic heart disease
   i. Mitral and aortic valvular fibrosis
      • Valve thickening and calcification
      • *Fusion of the valve commissures*
      • *Chordae tendineae are short, thickened, and fused.*
   ii. Complications
      • Mitral and/or aortic stenosis and/or regurgitation and CHF
      • Infectious endocarditis

4. Infectious bacterial endocarditis
   a. Definition: bacterial infection of the cardiac valves, characterized by *vegetations* on the valve leaflets
   b. Risk factors: rheumatic heart disease, mitral valve prolapse, bicuspid aortic valve, degenerative calcific aortic stenosis, congenital heart disease, artificial valves, indwelling catheters, dental procedures, immunosuppression, and intravenous drug use
   c. Acute endocarditis
      i. High virulence organism: *Staphylococcus aureus*
      ii. Can colonize a normal valve

Clinical Correlate

Endocarditis involving the right side of the heart is highly suggestive of intravenous drug use.
iii. Produces large destructive vegetations (fibrin, platelets, bacteria, and neutrophils)
iv. Prognosis: poor; mortality = 50%

d. **Subacute endocarditis**
   i. Low virulence organism: *Streptococcus group viridans*
   ii. Usually colonize a previously damaged valve

e. **Clinical presentation**
   i. Fever, chills, weight loss, and cardiac murmur
   ii. Systemic emboli
   iii. Roth spots: retinal emboli
   iv. Osler nodes: painful, red subcutaneous nodules on the fingers and toes
   v. Janeway lesions: painless, red lesions on the palms and soles
   vi. Splinter fingernail hemorrhages

f. **Diagnosis:** serial blood cultures

g. **Complications**
   i. Septic emboli
   ii. Valve damage resulting in insufficiency and CHF
   iii. Myocardial abscess
   iv. Dehiscence of an artificial heart valve

5. **Marantic endocarditis**
   a. Synonym: nonbacterial thrombotic endocarditis (NBTE)
   b. Definition: small, *sterile vegetations* along the valve leaflet line of closure in patients with a *debilitating disease*
   c. Complication: embolism, secondarily becoming infected

**CONGENITAL HEART DISEASE**

1. **Congenital heart disease**
   a. Most common cause of childhood heart disease in the United States
   b. Etiology
      i. Idiopathic (90%)
      ii. Genetic association—trisomies, cri du chat, Turner syndrome, etc.
      iii. Viral infection (especially congenital rubella)
      iv. Drugs and alcohol

2. **Coarctation of the aorta**
   a. Definition: segmental narrowing of the aorta
   b. **Pseudoclastic coarctation (infantile-type)**
      i. Associated with Turner syndrome
      ii. Severe narrowing of aorta *proximal* to the ductus arteriosus
      iii. Usually associated with a patent ductus arteriosus (PDA), which supplies blood to aorta distal to the narrowing
      iv. Right ventricular hypertrophy
      v. Presentation: infant with CHF and weak pulses and cyanosis in the lower extremities
      vi. Poor prognosis without surgical correction

**Bridge to Microbiology**

*Viridans streptococci*
- Alpha-hemolytic
- Beta-resistant
- Optochin-resistant
c. **Postductal coarctation (adult-type)**
   i. Narrowing of the aorta *distal* to the ductus arteriosus
   ii. Presentation: child or adult with *hypertension* in the *upper extremities* and *hypotension* and weak pulses in the *lower extremities*
   iii. Collateral circulation via the internal mammary and intercostal arteries
   iv. Chest x-ray: notching of the ribs due to bone remodel as a consequence of increased blood flow through the intercostal arteries

d. **Complications**
   i. Congestive heart failure
   ii. Intracerebral hemorrhage
   iii. Dissecting aortic aneurysm

<table>
<thead>
<tr>
<th>Table 14.5. Comparison of Left Versus Right Shunt Congenital Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Right → Left Shunt</strong></td>
</tr>
<tr>
<td>Early cyanosis (blue babies)</td>
</tr>
<tr>
<td>Blood shunted past the lungs</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
</tr>
<tr>
<td>Transposition of the great vessels</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
</tr>
</tbody>
</table>

3. **Tetralogy of Fallot**
   a. Most common cause of cyanotic heart disease
   b. Classic tetrad
      i. *Pulmonary outflow obstruction/stenosis*
      ii. *Right ventricular hypertrophy*
      iii. VSD
      iv. *Overriding aorta*
   c. Clinical: cyanosis, shortness of breath (SOB), digital clubbing, and polycythemia
   d. Prognosis: progressive pulmonary outflow stenosis and cyanosis over time
   e. Treatment: surgical correction
4. Transposition of the great arteries
a. Definition: abnormal development of the truncocoval septum results in inversion of the aorta and pulmonary arteries with respect to the ventricles
b. Risk increased in infants of diabetic mothers
c. Develop early cyanosis and right ventricular hypertrophy
d. To survive, infants must have mixing of blood by a VSD, ASD, or PDA
e. Poor prognosis without surgery

5. Truncus arteriosus
a. Definition: failure to develop a dividing septum between the aorta and pulmonary artery, resulting in a common trunk
b. Blood flow from the pulmonary trunk to the aorta
c. Clinical: early cyanosis and CHF
d. Poor prognosis without surgery

6. Tricuspid atresia
a. Definition: absence of a communication between the right atrium and ventricle due to developmental failure to form the tricuspid valve
b. Associated defects: right ventricular hypoplasia and an ASD
c. Poor prognosis without surgery

7. Ventricular septal defect (VSD)
   a. Second most common congenital heart defect (most common congenital heart defect is a bicuspid aortic valve)
   b. Definition: direct communication between the ventricular chambers
   c. Small VSD
      i. May be asymptomatic and close spontaneously
      ii. May produce a jet stream that damages the endocardium and increases the risk of infectious endocarditis
Bridge to Embryology

In utero the ductus arteriosus is kept open by low arterial oxygen saturation and elevated prostaglandin E2 (PGE2) levels. Functional closure occurs in the first 2 days of life due to increased oxygen saturation and decreased PGE2. The ductus arteriosus becomes the ligamentum arteriosum.

d. Large VSD may lead to secondary pulmonary hypertension, RVH, reversal of the shunt, and late cyanosis (Eisenmenger complex)
e. Auscultation: systolic murmur
f. VSDs are commonly associated with other heart defects
g. Treatment: surgical correction of large defects

8. Atrial septal defect (ASD)
   a. Definition: direct communication between the atrial chambers
   b. Most common type: ostium secundum
   c. Complications
      i. Eisenmenger syndrome
      ii. Paradoxical emboli

9. Patent ductus arteriosus (PDA)
   a. Definition: direct communication between the aorta and pulmonary artery due to the continued patency of the ductus arteriosus after birth
   b. Associated with prematurity and congenital rubella infections
   c. Clinical: machinery murmur, late cyanosis, and CHF
   d. Complication: Eisenmenger syndrome

PRIMARY CARDIOMYOPATHIES (DIAGNOSIS OF EXCLUSION)

1. Dilated cardiomyopathy
   a. Definition: cardiac enlargement with dilatation of all four chambers resulting in progressive congestive heart failure
   b. Most common form of cardiomyopathy
   c. Etiology
      i. Idiopathic (majority of cases)
      ii. Alcohol
      iii. Drug related—Adriamycin (doxorubicin) and cocaine
      iv. Viral myocarditis—Coxsackievirus B and enteroviruses
      v. Parasitic infections—Chagas disease
      vi. Pregnancy related
   d. Pathogenesis: the underlying etiology leads to destruction of myocardial contractility affecting systolic function
   e. Echocardiogram: decreased ejection fraction
   f. Presentation: progressive CHF
   g. Complications: mural thrombi and cardiac arrhythmias
   h. Prognosis: poor; 5-year survival = 25%
   i. Treatment: heart transplantation

2. Hypertrophic cardiomyopathy
   a. Synonyms: asymmetrical septal hypertrophy, idiopathic hypertrophic subaortic stenosis (IHSS)
   b. Etiology
      i. Hereditary: autosomal dominant disorder (>50% of cases)
      ii. Idiopathic
c. Pathogenesis: the increased synthesis of actin and myosin leads to asymmetrical hypertrophy and decreased compliance affecting diastolic function.

d. Common cause of sudden cardiac death in young athletes.

e. Gross
   i. Asymmetrical cardiac hypertrophy, which is most prominent in the ventricular septum.
   ii. The ventricular outflow tract is often obstructed by the septal hypertrophy.
   f. Micro: cardiac myofiber hypertrophy and disarray.

3. Restrictive cardiomyopathy
   a. Definition: uncommon form of cardiomyopathy caused by diseases that produce restriction of cardiac filling during diastole.
   b. Etiology
      i. Amyloidosis
      ii. Sarcoidosis
      iii. Endomyocardial fibroelastosis
      iv. Loeffler endomyocarditis
   c. Pathogenesis: increased deposition of material leads to decreased compliance affecting diastolic function.

CARCINOID HEART DISEASE

1. Carcinoid heart disease
   a. Definition: right-sided endocardial and valvular fibrosis secondary to exposure to serotonin in patients with carcinoid tumors that have metastasized to the liver.
   b. Plaque-like thickening (endocardial fibrosis) of the endocardium and valves of the right side of the heart.
   c. Carcinoid syndrome
      i. Skin flushing
      ii. Diarrhea
      iii. Cramping
      iv. Bronchospasm and wheezing
      v. Telangiectasias
   d. Diagnosis: urinary 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of the breakdown of serotonin via monoamine oxidase.

CARDIAC TUMORS

1. Cardiac myxoma
   a. Benign tumor usually arising within the left atrium near the fossa ovalis.
   b. Micro: stellate-shaped cells within a myxoid background.
   c. Complications
      i. Tumor emboli
      ii. “Ball-valve” obstruction of the valves.

2. Cardiac rhabdomyoma
   a. Benign tumor usually arising within the myocardium.
   b. Associated with tuberous sclerosis.

In a Nutshell

Tuberous Sclerosis
- Autosomal dominant
- Multiple hamartomas
- Cortical tubers
- Renal angiomylipomas
- Cardiac rhabdomyomas
- Pulmonary hamartomas
Chapter Summary

* Ischemic heart disease, the most common cause of death in the United States, is the consequence of cardiac ischemia usually secondary to coronary artery disease.

* Angina pectoris refers to transient cardiac ischemia (without cell death) resulting in substernal pain. Variants of angina include stable angina, Prinzmetal variant angina, and unstable angina.

* Myocardial infarction is a localized area of cardiac muscle coagulative necrosis due to ischemia and can occur as the result of either coronary artery atherosclerosis with superimposed thrombus formation or coronary artery spasm. Myocardial infarction often presents with sudden onset of severe "crushing" substernal chest pain that may radiate to the left arm, jaw, and neck. EKG changes and elevation of cardiac-specific troponin I/T in the serum to confirm the diagnosis. Myocardial infarction has a wide variety of complications that can cause death.

* Congestive heart failure is insufficient cardiac output to meet the metabolic demands of the body's tissues and organs. Left heart failure can complicate ischemic heart disease, hypertension, myocardial diseases, and aortic or mitral valve disease. It is associated with left ventricular hypertrophy and dilatation, passive pulmonary congestion and edema, activation of the renin-angiotensin-aldosterone system leading to hyperaldosteronism, and cardiogenic shock. Right heart failure can complicate left heart failure, pulmonary or tricuspid valvular disease, and cor pulmonale. It causes jugular venous distension, hepatosplenomegaly, dependent edema, and ascites.

* Degenerative calcific aortic valve stenosis, the most common valvular abnormality, is an age-related dystrophic calcification, degeneration, and stenosis of the aortic valve that can cause concentric left ventricular hypertrophy, congestive heart failure, and an increased risk of sudden death.

* Mitral valve prolapse is a myxomatous degeneration of the mitral valve that causes the valve leaflets to become enlarged and floppy.

* Rheumatic fever is a systemic inflammatory disease, triggered by a pharyngeal infection with Group A beta-hemolytic streptococci, that in genetically susceptible individuals results in the production of antibodies that cross-react with cardiac antigens. Acute rheumatic heart disease can produce myocarditis, pericarditis, and endocarditis. Chronic rheumatic heart disease can damage the mitral and aortic valves, secondarily predisposing for mitral stenosis, congestive heart disease, and infective endocarditis.

* Infective bacterial endocarditis is a bacterial infection of the cardiac valves, characterized by vegetations on the valve leaflets. Risk factors include previous damage to valves, congenital heart disease, and sources of bacteremia. Acute endocarditis is caused by high-virulence organisms, notably *Streptococcus viridans*, and produces large destructive lesions with a high mortality rate. Subacute endocarditis is caused by low-virulence organisms, notably *Vibrio* streptococci, and usually involves previously damaged valves.

* Marantic endocarditis refers to the formation of small, sterile fibrin vegetations along the valve leaflet line of closure in patients with debilitating diseases.

* Congenital heart disease is the most common cause of childhood heart disease in the United States and may be idiopathic or associated with genetic disease, infection, or drug and alcohol use.

* Coarctation of the aorta is a segmental narrowing of the aorta that is subclassified, depending upon the level at which the narrowing occurs, into preductal coarctation (poorer prognosis, association with Turner syndrome) and postductal coarctation (late onset).

(Continued)
Chapter Summary (continued)

* Tetralogy of Fallot is the most common cause of cyanotic heart disease and is characterized by a classic tetrad of pulmonary outflow obstruction/stenosis, right ventricular hypertrophy, ventricular septal defect, and overriding aorta.

* Transposition of the great arteries is an abnormal development of the intracardiac septum that results in inversion of the aorta and pulmonary arteries with respect to the ventricles. Transposition of the great arteries has a poor prognosis without surgery.

* Truncus arteriosus is a failure to develop a dividing septum between the aorta and the pulmonary artery, resulting in a common trunk. Truncus arteriosus has a poor prognosis without surgery.

* Tricuspid atresia is the absence of a communication between the right atrium and ventricle due to developmental failure to form the tricuspid valve. Tricuspid atresia has a poor prognosis without surgery.

* Ventricular septal defect is the second most common congenital heart defect and consists of a direct communication between the ventricular chambers. The prognosis varies with the size of the defect.

* Atrial septal defect is a direct communication between the atrial chambers whose most common type involves the ostium secundum.

* Patent ductus arteriosus is a direct communication between the aorta and pulmonary artery due to the continued patency of the ductus arteriosus after birth.

* Dilated cardiomyopathy is the most common form of primary cardiomyopathy and consists of cardiac enlargement with dilatation of all four chambers due to diminished contractility, resulting in progressive congestive heart failure and/or arrhythmias. The 5-year survival rate is 25%.

* Hypertrophic cardiomyopathy is an asymmetric cardiac hypertrophy that is most prominent in the ventricular septum, where it may obstruct the ventricular outflow tract, with resulting increased risk of sudden cardiac death, particularly in young athletes.

* Restrictive cardiomyopathy is an uncommon form of cardiomyopathy caused by diseases such as amyloidosis and sarcoidosis that produce restriction of cardiac filling during diastole.

* Carcinoid heart disease is a right-sided endocardial and valvular fibrosis secondary to exposure to serotonin in patients with carcinoid tumors that have metastasized to the liver.

* Cardiac myxoma is a benign tumor, usually arising within the left atrium near the fossa ovalis. It can cause tumor emboli and ball-valve obstruction of valves.

* Cardiac rhabdomyoma is a benign tumor, usually arising within the myocardium. It is associated with tuberous sclerosis.
ATELECTASIS

1. Definition: area of collapsed or nonexpanded lung
2. Major types
   a. Obstruction/resorption atelectasis
      i. Collapse of lung due to resorption of air distal to an obstruction
      ii. Examples: aspiration of a foreign body, chronic obstructive pulmonary disease (COPD), or postoperative
   b. Compression atelectasis due to fluid, air, blood, or tumor in the pleural space
   c. Contraction (scar) atelectasis due to fibrosis and scarring of the lung
   d. Patchy atelectasis
      i. Due to a lack of surfactant
      ii. Examples: hyaline membrane disease of newborn or acute (adult) respiratory distress syndrome (ARDS)
3. Predisposed to infection due to decreased mucociliary clearance
4. Reversible disorder

PULMONARY INFECTIONS

1. Bacterial pneumonia
   a. Definition: acute inflammation and consolidation (solidification) of the lung due to a bacterial agent
   b. Clinical signs and symptoms
      i. Fever and chills
      ii. Productive cough with yellow-green (pus) or rusty (bloody) sputum
      iii. Tachypnea
      iv. Pleuritic chest pain
      v. Decreased breath sounds, rales, and dullness to percussion
   c. Lab: elevated WBC count with a left shift
   d. Chest x-ray
      i. Lobar: lobar or segmental consolidation (opacification)
      ii. Bronchopneumonia: patchy opacification
      iii. Pleural effusion
   e. Clinical keys: identification of the organism and early treatment with antibiotics

Bridge to Anatomy

Pores of Kohn are collateral connections between air spaces through which infections and neoplastic cells can spread.
f. **Lobar pneumonia**
   i. Consolidation of entire lobe
   ii. Organism: *Streptococcus pneumoniae* (95%) or *Klebsiella*
      - Alpha-hemolytic
      - Bile soluble
      - Optochin sensitive
      - Lancet-shaped diplococci
   iii. Four classic phases
      - Congestion: active hyperemia and edema
      - Red hepatization: neutrophils and hemorrhage
      - Grey hepatization: degradation of red blood cells
      - Resolution: healing
   iv. Micro: intra-alveolar suppurative inflammation (neutrophils) and edema

g. **Bronchopneumonia**
   i. Scattered patchy consolidation centered around bronchioles
   ii. Tends to be bilateral, multilobar, and basilar
   iii. Affects the young, old, and terminally ill

   v. Micro: acute inflammation of bronchioles and surrounding alveoli

h. **Diagnosis**
   i. Sputum gram stain and culture
   ii. Blood cultures

   i. Treatment: empiric antibiotic treatment modified by the results of cultures and organism sensitivities

j. **Complications of pneumonia**
   i. Fibrous scarring and pleural adhesions
   ii. Lung abscess
   iii. Empyema (pus in a body cavity)
   iv. Sepsis

2. **Lung abscess**
   a. Definition: localized collection of neutrophils (pus) and necrotic pulmonary parenchyma
   b. **Etiology**
      i. Aspiration
         - Most common
         - Tends to involve right lower lobe
         - Mixed oral flora (anaerobic/aerobic)
      ii. Following a pneumonia, especially *S. aureus* and *Klebsiella*
      iii. Postobstructive
      iv. Septic emboli
   c. **Complications**
      i. Empyema
ii. Pulmonary hemorrhage  
iii. Secondary amyloidosis  

3. **Atypical pneumonia**  
   a. Definition: *interstitial pneumonia* without consolidation  
   b. Organisms  
      i. *Mycoplasma pneumoniae*  
      ii. Influenza virus  
      iii. Parainfluenza  
      iv. Respiratory syncytial virus (RSV), especially in young children  
      v. Adenovirus  
      vi. Cytomegalovirus (CMV), especially in immunocompromised  
      vii. Varicella  
      viii. Many others  
   c. More common in children and young adults  
   d. Chest x-ray: diffuse interstitial infiltrates  
   e. Lab: elevated cold agglutinin titer (*Mycoplasma*)  
   f. Micro: lymphoplasmacytic inflammation within the alveolar septum  
   g. Complications  
      i. Superimposed bacterial infections  
      ii. Reye syndrome: viral illness (influenza/varicella) + aspirin  

4. **Tuberculosis**  
   a. Increasing incidence in the United States, secondary to AIDS  
   b. Inhalation of aerosolized bacilli  
   c. Clinical presentation  
      i. Fevers and night sweats  
      ii. Weight loss  
      iii. Cough  
      iv. Hemoptysis  
   d. Micro: caseating granulomas with acid-fast bacilli  
   e. Lab: positive skin test (PPD)  
   f. Primary pulmonary tuberculosis  
      i. Initial exposure  
      ii. Ghon focus: subpleural caseous granuloma above or below the interlobar fissure  
      iii. Ghon complex: Ghon focus + hilar lymph node granuloma  
      iv. Most lesions (95%) will undergo fibrosis and calcification  
   g. Secondary pulmonary tuberculosis  
      i. Reactivation or reinfection  
      ii. Simon focus: granuloma at lung apex (high oxygen tension)  
   h. Progressive pulmonary tuberculosis  
      i. Cavitary tuberculosis  
      ii. Miliary pulmonary tuberculosis  
      iii. Tuberculous bronchopneumonia
i. Disseminated to different organ systems via hematogenous route often resulting in
a miliary pattern within each affected organ
i. Meninges
ii. Cervical lymph nodes (scrofula) and larynx
iii. Liver/spleen, kidneys, adrenals, ileum
iv. Lumbar vertebrae bone marrow (Pott disease)
v. Fallopian tubes and epididymis

SARCOIDOSIS

1. Definition: a systemic granulomatous disease of uncertain etiology and it is a diagnosis
   of exclusion
2. Epidemiology
   a. Unknown etiology
   b. Females > males, age: 20–60
   c. Most common in African American women
3. Clinical presentation
   a. May be asymptomatic
   b. Cough, shortness of breath (SOB)
   c. Fatigue, malaise
   d. Skin lesions
   e. Eye irritation or pain
   f. Fever/night sweats
4. Noncaseating granulomas occur in any organ of the body.
   a. Lung: diffuse scattered granulomas
   b. Lymph nodes: hilar and mediastinal adenopathy
   c. Skin, liver/spleen, heart, CNS, GI tract
   d. Eye: Mikulicz syndrome: involvement of uvea and parotid
   e. Bone marrow: especially in the phalanges
5. Lab: elevated serum angiotensin converting enzyme (ACE)—ACE is synthesized by
   endothelial cells and macrophages
6. X-ray: bilateral hilar lymphadenopathy
7. Micro
   a. Noncaseating granulomas
   b. Schaumann bodies: laminated dystrophic calcifications
   c. Asteroid bodies: stellate giant-cell cytoplasmic inclusions
8. Diagnosis of exclusion
9. Prognosis: favorable with a variable clinical course


**OBSTRUCTIVE VERSUS RESTRICTIVE LUNG DISEASE**

Table 15-1. Obstructive Versus Restrictive Lung Disease

<table>
<thead>
<tr>
<th>Obstructive Airway Disease</th>
<th>Restrictive Lung Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition:</strong></td>
<td></td>
</tr>
<tr>
<td>Increased resistance to airflow secondary to obstruction of airways</td>
<td>Decreased lung volume and capacity</td>
</tr>
<tr>
<td><strong>Pulmonary function tests (spirometry):</strong></td>
<td></td>
</tr>
<tr>
<td>FEV₁/FVC ratio is decreased</td>
<td>Decreased TLC and VC</td>
</tr>
</tbody>
</table>

**Examples:**

- **Chronic obstructive airway disease**
  - Asthma
  - Chronic bronchitis
  - Emphysema
  - Bronchectasis

- **Chest wall disorders**
  - Obesity, kyphoscoliosis, polio, etc.

- **Interstitial/infiltrative diseases**
  - ARDS, pneumoconiosis
  - Pulmonary fibrosis

Table 15-2. Summary of Obstructive Versus Restrictive Pattern

<table>
<thead>
<tr>
<th>Variable</th>
<th>Obstructive Pattern, e.g., Emphysema</th>
<th>Restrictive Pattern, e.g., Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lung capacity</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>FEV₁</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Forced vital capacity</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>↓</td>
<td>↑ or normal</td>
</tr>
<tr>
<td>Peak flow</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Functional residual capacity</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Residual volume</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

**OBSTRUCTIVE PULMONARY DISEASE**

1. **Chronic bronchitis**
   a. Definition: a clinical diagnosis of a persistent cough and copious sputum production for at least 3 months in 2 consecutive years
   b. Highly associated with smoking (99%)
   c. Clinical findings
      i. Cough, sputum production, dyspnea, frequent infections
      ii. Hypoxia, cyanosis, weight gain

KAPLAN MEDICAL 159
d. Micro

i. Hypertrophy and hyperplasia of bronchial mucous glands (Reid index equals the submucosal gland thickness divided by the bronchial wall thickness between the ciliated pseudostratified columnar epithelium and the perichondrium; normal ratio is 0.4 or less)

ii. Increased numbers of goblet cells

iii. Hypersecretion of mucus

iv. Bronchial squamous metaplasia and dysplasia (smokers)

e. Complications

i. Increased risk for recurrent infections

ii. Secondary pulmonary HTN leading to right heart failure (cor pulmonale)

iii. Lung cancer

2. Emphysema

a. Definition: destruction of alveolar septa resulting in enlarged air spaces and a loss of elastic recoil

b. Etiology

i. Protease/antiprotease imbalance

ii. Proteases (including elastase) are produced by neutrophils and macrophages, which are stimulated by smoke and pollution.

iii. Antiproteases include α-1-antitrypsin, α-1-macroglobulin, and secretory leukoprotease inhibitor.

<table>
<thead>
<tr>
<th>Centriacinar (Centrilobular)</th>
<th>Panacinar (Panlobular)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal respiratory bronchioles involved, distal alveoli spared</td>
<td>Entire acinus involved</td>
</tr>
</tbody>
</table>

Most common type (95%)

Associated with smoking, air pollution | α-1-Antitrypsin deficiency

Distribution: worst in apical segments of upper lobes | Distribution: entire lung; worse in bases of lower lobes

c. Gross

i. Overinflated, enlarged lungs

ii. Enlarged, grossly visible air spaces

iii. Formation of apical blebs and bullae (centriacinar type)

d. Clinical findings

i. Progressive dyspnea

ii. Pursing of lips and use of accessory respiratory muscles to breathe

iii. Barrel chest (increased anterior-posterior diameter)

iv. Weight loss

3. Asthma

a. Definition: hyperreactive airways, resulting in episodic bronchospasm when triggered by certain stimuli
b. Extrinsic (type I hypersensitivity reaction)
   i. Allergic (atopic)
      • Most common type
      • Childhood and young adults; (+) family history
      • Allergens: pollen, dust, food, molds, animal dander, etc.
   ii. Occupational exposure: fumes, gases, and chemicals

c. Intrinsic (unknown mechanism)
   i. Respiratory infections (usually viral)
   ii. Stress
   iii. Exercise
   iv. Cold temperatures
   v. Drug induced (aspirin)

d. Asthma attack: wheezing, severe dyspnea, coughing

e. Status asthmaticus: potentially fatal unrelenting attack

f. Sputum cytology
   i. *Curschmann spirals*: twisted mucous plugs admixed with sloughed epithelium
   ii. Eosinophils
   iii. Charcot-Leyden crystals: composed of eosinophil membrane protein

g. Micro
   i. Mucous plugs
   ii. Hypertrophy of mucous glands with goblet cell hyperplasia
   iii. Inflammation (especially with eosinophils)
   iv. Edema
   v. Hypertrophy and hyperplasia of bronchial wall smooth muscle
   vi. Thickened basement membranes

4. Bronchiectasis
   a. Definition: abnormal permanent airway dilatation due to chronic necrotizing inflammation
   b. Clinical findings include cough, fever, malodorous purulent sputum, and dyspnea
   c. Causes
      i. Bronchial obstruction: foreign body, mucous, tumor, etc.
      ii. Necrotizing pneumonias
      iii. Cystic fibrosis
      iv. Kartagener syndrome
         • Autosomal recessive
         • Immotile cilia due to defect of dynein arms (primary ciliary dyskinesia)
         • Bronchiectasis, chronic sinusitis, situs inversus (a congenital condition
           where the major visceral organs are anatomically reversed compared with
           their normal anatomical positions)
   d. Gross: dilated bronchi and bronchioles extending out to the pleura
   e. Complications: abscess, septic emboli, cor pulmonale, secondary amyloidosis
Figure 15-1. Cross-Section of Bronchiectasis

Figure 15-2. Structure of the Axoneme of a Cilium
INFLITRATIVE RESTRICTIVE LUNG DISEASES
(DIFFUSE INTERSTITIAL DISEASES)

1. Acute respiratory distress syndrome (ARDS)
   a. Synonyms: diffuse alveolar damage (DAD), shock lung, acute lung injury
   b. Definition: diffuse damage of alveolar epithelium and capillaries, resulting in progressive respiratory failure that is unresponsive to oxygen treatment
   c. Causes: shock, sepsis, trauma, gastric aspiration, radiation, oxygen toxicity, drugs, pulmonary infections, and many others
   d. Clinical presentation: dyspnea, tachypnea, hypoxemia, cyanosis, and use of accessory respiratory muscles
   e. X-ray: bilateral lung opacity ("white out")
   f. Gross: heavy, stiff, noncompliant lungs
   g. Micro
      i. Interstitial and intra-alveolar edema
      ii. Interstitial inflammation
      iii. Loss of type I pneumocytes
      iv. Hyaline membrane formation (composed of cellular debris of dead pneumocytes, and fibrin-rich edema)
   h. Treatment
      i. Treat the underlying cause
      ii. Oxygen, positive end-expiratory pressure (PEEP), and mechanical ventilation
   i. Prognosis: overall mortality 50%
2. Respiratory distress syndrome of the newborn
   a. Synonym: hyaline membrane disease of newborns
   b. Associated with
      i. Prematurity (gestational age of <28 weeks has a 60% incidence)
      ii. Maternal diabetes
      iii. Multiple births
      iv. C-section delivery
   c. Defect: deficiency of surfactant
   d. Clinical presentation: often normal at birth, but within a few hours develop increasing respiratory effort, tachypnea, nasal flaring, use of accessory muscle of respiration, an expiratory grunt, cyanosis
   e. X-ray: "ground-glass" reticulogranular densities
   f. Lab: lecithin-sphingomyelin ratio <2
   g. Micro: atelectasis and hyaline membrane formation
   h. Treatment: surfactant replacement and oxygen
   i. Prognosis: overall mortality ~30%
   j. Complications of oxygen treatment in newborns
      i. Bronchopulmonary dysplasia
      ii. Retrolental fibroplasia (retinopathy of prematurity)
   k. Prevention: delay labor and corticosteroids to mature the lung

Bridge to Anatomy
Type II pneumocytes play an important role in repair in lung injury.
3. Occupation-associated pneumoconiosis
   
a. Pneumoconioses
   
i. Definition: fibrosing pulmonary diseases caused by inhalation of an aerosol (mineral dusts, particles, vapors, or fumes)
   
ii. Key factors
       • Type of aerosol and its ability to stimulate fibrosis
       • Dose and duration of exposure
       • Size of the particle – less than 10 microns to get access to the alveolar sac

b. Coal worker’s pneumoconiosis
   
i. Occupation: coal mining
   
ii. Anthracosis
       • Carbon pigment (anthracotic pigment) accumulates in macrophages along the pleural lymphatics and interstitium.
       • Asymptomatic
   
iii. Simple coal worker’s pneumoconiosis
       • Synonym: black lung disease
       • Coal-dust macules and nodules in the upper lobes
       • Little pulmonary dysfunction
   
iv. Complicated coal worker’s pneumoconiosis
       • Progressive massive fibrosis
       • Increasing respiratory distress occurs
       • Secondary pulmonary hypertension and cor pulmonale

v. Caplan syndrome: pneumoconiosis plus rheumatoid arthritis

c. Asbestosis
   
i. Family of crystalline silicates
       • Serpentine
         – Curved, flexible fibers
         – Most common type: chrysotile
       • Amphibole
         – Straight, brittle fibers
         – Types: crocidolite, tremolite, and amosite
         – More pathogenic and highly associated with mesotheliomas
   
ii. Occupations: shipyard workers, insulation and construction industries, brake-lining
   
iii. Lung pathology
       • Diffuse interstitial fibrosis, which is most severe in the lower lobes
       • Asbestos bodies that may become coated with iron (ferruginous bodies)
       • Slowly progressive dyspnea
       • Secondary pulmonary hypertension and cor pulmonale
       • Parietal pleural plaques (acellular type I collagen deposition) in a symmetrical distribution involving the domes of the diaphragm and anterolateral chest walls
   
iv. Fibrous pleural adhesions

Clinical Correlate

Dietary drugs fenfluramine and phentermine have been associated with primary pulmonary hypertension.
v. Pleural plaques
vi. Bronchogenic carcinoma
   • Most common tumor in asbestos-exposed individuals
   • Synergistic effect of smoking and asbestos exposure
vii. Malignant mesotheliomas
   • Rare, highly malignant neoplasm
   • Occupational exposure to asbestos in 90% of cases
   • Presents with recurrent pleural effusions, dyspnea, chest pain
   • Gross: encases and compresses the lung
   • Micro: carcinomatous and sarcomatous elements (biphasic pattern)
   • EM: long, thin microvilli
   • Poor prognosis
viii. Increased risk of laryngeal, stomach, and colon cancers
ix. *Family members also have increased risk of cancer* due to worker bringing home clothing covered with asbestos fibers
x. Caplan syndrome
d. Silicosis
   i. Occupations: sandblasters, metal grinders, miners
   ii. Exposure to silicon dioxide (silica)
   iii. Pathology
      • Dense nodular fibrosis of the upper lobes
      • Birefringent silica particles can be seen with polarized light.
      • May develop progressive massive fibrosis
   iv. Clinical course
      • X-ray: fibrotic nodules in the upper zones
      • Insidious onset of dyspnea
      • Slowly progressive despite cessation of exposure
v. Increased risk of secondary tuberculosis
vi. Caplan syndrome
e. Berylliosis
   i. Occupation: aerospace industry and nuclear reactors
   ii. Etiology
      • Beryllium exposure
      • Genetic susceptibility
      • Type IV hypersensitivity reaction, resulting in granuloma formation
   iii. Acute exposure: acute pneumonitis
   iv. Chronic exposure
      • Pulmonary noncaseating granulomas and fibrosis
      • Hilar lymph node granulomas
      • Systemic granulomas

In a Nutshell

Horner Syndrome
   • Ptosis
   • Miosis
   • Anhidrosis
   • Enophthalmos
VASCULAR DISORDERS

1. Pulmonary edema
   a. Definition: fluid accumulation within the lungs usually due to disruption of Starling forces or endothelial injury
   b. Increased hydrostatic pressure: left-sided heart failure, mitral valve stenosis, fluid overload
   c. Decreased oncotic pressure: nephrotic syndrome or liver disease
   d. Increased capillary permeability: infections, drugs (bleomycin, heroin), shock, radiation
   e. Gross: wet, heavy lungs; usually worse in lower lobes
   f. Micro: intra-alveolar fluid, engorged capillaries, hemosiderin-laden macrophages (heart-failure cells)

2. Pulmonary emboli (PE) and pulmonary infarction (see Chapter 5 for discussion)

3. Pulmonary hypertension
   a. Definition: increased pulmonary artery pressure, usually due to increased vascular resistance or blood flow
   b. Etiology
      i. COPD and interstitial disease (hypoxic vasoconstriction)
      ii. Multiple ongoing pulmonary emboli
      iii. Mitral stenosis and left heart failure
      iv. Congenital heart disease with left to right shunts (ASD, VSD, PDA)
      v. Primary (idiopathic) HTN, typically in young women
   c. Pathology
      i. Pulmonary artery atherosclerosis
      ii. Small artery medial hypertrophy and intimal fibrosis
      iii. Plexogenic pulmonary arteriopathy
      iv. Complication: right ventricular hypertrophy → failure (cor pulmonale)

PULMONARY NEOPLASIA

1. Bronchogenic carcinoma
   a. Epidemiology
      i. Leading cause of cancer death among both men and women
      ii. Increasing in women (increased smoking) in the past few decades
      iii. Occurs most commonly from 50–80 years of age
   b. Major risk factors
      i. Cigarette smoking
      ii. Occupational exposure (asbestosis, uranium mining, radiation, etc.)
      iii. Air pollution
      iv. Chronic pulmonary fibrosing conditions (e.g., idiopathic pulmonary fibrosis, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, collagen vascular diseases [e.g., SLE, rheumatoid arthritis], pneumonoconioses)
c. Common genetic mutations
   i. Oncogenes
      • L-myc: small cell carcinomas
      • K-ras: adenocarcinomas
   ii. Tumor suppressor gene p53 and the retinoblastoma gene

d. Clinical features
   i. Cough, sputum production, weight loss, anorexia, fatigue, dyspnea, hemoptysis, and chest pain
   ii. Obstruction may produce focal emphysema, atelectasis, bronchiectasis, or pneumonia.

e. Adenocarcinoma (35%)
   i. More commonly seen in women; less closely associated with smoking than squamous cell
   ii. Gross: peripheral gray-white mass with pleural puckering
   iii. May develop in areas of parenchymal scarring (scar carcinoma)
   iv. Micro: tumor forms glands and may produce mucin

f. Bronchioloalveolar carcinoma (5%)
   i. Subset of adenocarcinoma
   ii. Arises from terminal bronchioles or alveolar walls
   iii. Gross: peripheral mucinous gray-white nodules
   iv. Micro: columnar tumor cells grow along the walls of pre-existing alveoli

g. Squamous cell (30%)
   i. Males > females; strongly related to smoking
   ii. Gross: usually centrally located, gray-white bronchial mass
   iii. Arises from bronchial epithelium after a progression: metaplasia \( \rightarrow \) dysplasia \( \rightarrow \) carcinoma in situ \( \rightarrow \) invasive carcinoma
   iv. Micro
      • Invasive nests of squamous cells
      • Intercellular bridges (desmosomes)
      • Keratin production ("squamous pearls")

h. Small cell (oat cell) carcinoma (20%)
   i. Males > females; strong association with smoking
   ii. Very aggressive: rapid growth and early dissemination
   iii. Gross: central, gray-white masses
   iv. Micro: small round or polygonal cells in clusters
   v. EM: cytoplasmic dense-core neurosecretory granules
   vi. Commonly associated with paraneoplastic syndromes

i. Large cell carcinoma (10%)
   i. Micro: large anaplastic cells without evidence of differentiation

j. Intrathoracic spread
   i. Lymph nodes (50%): hilar, bronchial, tracheal, and mediastinal
   ii. Pleural involvement (adenocarcinoma)
   iii. Pancoast tumor (apical tumor) causing Horner syndrome
iv. Superior vena cava syndrome
   • Obstruction of the superior vena cava by tumor
   • Distended head and neck veins
   • Plethora
   • Facial and upper arm edema
v. Esophageal obstruction: dysphagia
vi. Recurrent laryngeal nerve involvement: hoarseness
vii. Phrenic nerve damage: diaphragmatic paralysis
k. Extrathoracic sites of metastasis: adrenal (>50%), liver, brain, and bone
l. Paraneoplastic syndromes
i. Endocrine/metabolic syndromes
   • ACTH → Cushing syndrome
   • ADH → SIADH
   • PTH → hypercalcemia (squamous cell carcinomas)
ii. Eaton-Lambert syndrome (See Skeletal Muscle and Peripheral Nerve Pathology
    Chapter 29)
iii. Acanthosis nigricans (See Skin Pathology Chapter 11)
iv. Hypertrophic pulmonary osteoarthropathy
   • Periosteal new bone formation
   • Clubbing
   • Arthritis
m. Treatment
   i. Non-small cell lung cancer: surgery
   ii. Small cell lung cancer: chemotherapy and radiation
n. Prognosis: poor; overall 5-year survival: 10%

2. Bronchial carcinoids
   a. Younger age group; age <40
   b. Gross: polypoid intrabronchial mass
   c. Micro: small, round, uniform cells growing in nests (organoid pattern)
   d. EM: cytoplasmic dense core neurosecretory granules

3. Laryngeal squamous cell carcinoma
   a. Risk factors: smoking, alcohol, and frequent cord irritation
   b. Symptoms: hoarseness, difficulty swallowing, pain, hemoptysis, and eventual respira-
      tory compromise
   c. Complications: direct extension, metastases, and infection

4. Metastatic carcinoma to the lung
   a. Most common malignant neoplasm in the lung
   b. Gross: multiple, bilateral, scattered nodules
   c. Common primary sites: breast, stomach, pancreas, colon
DISEASES OF THE PLEURAL CAVITY

1. Pleural effusion
   a. Definition: accumulation of fluid in the pleural cavity
   b. Empyema: pus in pleural space
   c. Chylothorax: Chylous fluid in pleural space secondary to obstruction of thoracic duct, usually by tumor

2. Pneumothorax
   a. Definition: air in the pleural cavity
   b. Traumatic penetrating chest wall injuries
   c. Spontaneous: pneumothorax often occurs in typically tall young adults due to a rupture of apical blebs
   d. Tension: pneumothorax results in a life-threatening shift of thoracic organs across midline

3. Mesothelioma
   a. Rare, highly malignant neoplasm
   b. Occupational exposure to asbestos in almost 90% of cases
   c. Recurrent pleural effusions, dyspnea, chest pain
   d. Gross: the tumor encases and compresses the lung
   e. Micro: carcinomatous and sarcomatous elements (biphasic pattern)
   f. EM: long, thin microvilli
   g. Poor prognosis
Chapter Summary

* Atelectasis is an area of collapsed or unexpanded lung and can occur secondary to obstruction, compression, contraction, or lack of surfactant.

* Bacterial pneumonia is an acute inflammation and consolidation (solidification) of the lung due to a bacterial agent. Lobar pneumonia causes consolidation of an entire lobe and is most commonly caused by infection with Streptococcus pneumoniae. Bronchopneumonia causes scattered patchy consolidation centered around bronchioles and can be due to a wide variety of bacterial agents.

* Lung abscess is a localized collection of neutrophils (pus) and necrotic pulmonary parenchyma and may occur following aspiration, pneumonia, obstruction, or septic emboli.

* Atypical pneumonia causes interstitial pneumonitis without consolidation and can be due to viral agents and Mycoplasma pneumoniae.

* Tuberculosis causes caseating granulomas containing acid-fast mycobacteria. Primary tuberculosis can produce a Ghon complex, characterized by a subpleural caseous granuloma above or below the lobar tissue accompanied by hilar lymph node granulomatous inflammation. Secondary tuberculosis tends to involve the lung apex. Progressive pulmonary tuberculosis can take the forms of cavitory tuberculosis, miliary pulmonary tuberculosis, and tuberculous bronchopneumonia. Miliary tuberculosis can also spread to involve other body sites.

* Sarcoidosis is a granulomatous disease of unknown etiology that produces clinical disease somewhat resembling tuberculosis.

* Obstructive airway disease is characterized by increased resistance to airflow secondary to obstruction of airways, whereas restrictive lung disease is characterized by decreased lung volume and capacity.

* Chronic obstructive pulmonary disease includes chronic bronchitis, emphysema, asthma, and bronchiectasis. Chronic bronchitis is a clinical diagnosis made when persistent cough and copious sputum production have been present for at least 3 months in 2 consecutive years. Emphysema is associated with destruction of respiratory bronchioles or alveolar septa, resulting in enlarged air spaces and a loss of elastic recoil, and producing overinflated, enlarged lungs. Asthma is due to hyperreactive airways, resulting in episodic bronchospasm when triggered by stimuli that may include allergens, respiratory infections, stress, exercise, cold temperatures, and drugs. Bronchiectasis is an abnormal permanent airway dilatation due to chronic necrotizing infection; most patients have underlying lung disease such as bronchial obstruction, necrotizing pneumonias, cystic fibrosis, or Kartagener syndrome.

* Acute respiratory distress syndrome is due to diffuse damage to the alveolar epithelium and capillaries, resulting in progressive respiratory failure that is unresponsive to oxygen treatment. Causes include shock, sepsis, trauma, gastric aspiration, radiation, oxygen toxicity, drugs, pulmonary infections, and many others.

* Respiratory distress syndrome of the newborn causes respiratory distress within hours of birth and is seen in infants with deficiency of surfactant secondary to prematurity, maternal diabetes, multiple births, or c-section delivery.

* Pulmonary edema is fluid accumulation within the lungs that can be due to many causes, including left-sided heart failure, mitral valve stenosis, fluid overload, nephrotic syndrome, liver disease, infections, drugs, shock, and radiation.

(Continued)
Chapter Summary (continued)

* Most pulmonary emboli arise from deep vein thrombosis in the leg and may be asymptomatic, cause pulmonary infarction, or cause sudden death.

* Pulmonary hypertension is increased pulmonary artery pressure, usually due to increased vascular resistance or blood flow. Pulmonary hypertension can be primary (idiopathic) or related to underlying COPD, interstitial disease, pulmonary emboli, mitral stenosis, left heart failure, and congenital heart disease with left to right shunt.

* Bronchogenic carcinoma is the leading cause of cancer deaths among both men and women. Major risk factors are cigarette smoking, occupational exposures, air pollution, and "scarring." Histologic types include adenocarcinoma, bronchioloalveolar carcinoma, squamous cell carcinoma, small-cell carcinoma, and large-cell carcinoma. Other tumors of importance include bronchial carcinoids, metastatic carcinoma to the lung, and laryngeal squamous cell carcinoma.

* Pleural effusion is the accumulation of fluid in the pleural cavity. Pneumothorax is air in the pleural cavity.

* Mesotheliomas are rare, highly malignant neoplasms that can involve the pleura and are closely related to prior asbestos exposure.

* Pneumoconiosis is a fibrosing pulmonary disease caused by inhalation of an aerosol, such as mineral dust, particles, vapors, or fumes.

* Coal worker's pneumoconiosis (black lung disease) can range in severity from slight pulmonary dysfunction to progressive massive fibrosis leading to increasing respiratory distress and cor pulmonale. Caplan syndrome is the term used for the combination of pneumoconiosis (due to many different agents) and rheumatoid arthritis.

* Asbestos can cause pulmonary fibrosis, bronchogenic carcinoma, and malignant mesotheliomas. Silicosis can cause pulmonary fibrosis and an increased risk of tuberculosis. Berylliosis can cause either an acute pneumonitis or granulomatous disease with fibrosis of the lungs.
CONGENITAL ANOMALIES OF THE KIDNEY

1. Renal agensis
   a. Bilateral agensis
      i. Ultrasound: oligohydramnios
      ii. Potter facies: flattened nose, low-set ears, and recessed chin
      iv. Pulmonary hypoplasia
      v. Incompatible with life
   b. Unilateral agensis
      i. The remaining kidney undergoes compensatory hypertrophy.
      ii. Patients often have adequate renal function.
      iii. May develop progressive glomerular sclerosis

2. Hypoplasia
   a. Failure of a kidney (usually unilateral) to develop to normal weight
   b. There is a decreased number of calyces and lobes.

3. Horseshoe kidney
   a. Common congenital anomaly; it is found in 1 in 750 autopsies
   b. Gross: fusion of the kidneys, usually at the lower pole
   c. Patients have normal renal function but may be predisposed to renal calculi.

4. Abnormal locations
   a. Most common abnormal location is a pelvic kidney
   b. The ectopic kidney usually has normal function.
   c. Tortuosity of ureters may predispose to pyelonephritis.

CYSTIC DISEASE

1. Autosomal recessive polycystic kidney disease
   a. Synonym: childhood polycystic kidney disease
   b. Clinical features
      i. Rare autosomal recessive disease
      ii. Presents in infancy with progressive and often fatal renal failure
   c. Gross
      i. Bilaterally enlarged kidneys
      ii. Multiple small cysts in the cortex and medulla
iii. The cysts are oriented in a radial fashion with their long axis at right angles to the renal capsule.

iv. Cysts occur in the collecting ducts of the nephron.

d. May also have multiple hepatic cysts and congenital hepatic fibrosis

2. **Autosomal dominant polycystic kidney disease**
   a. Synonym: adult polycystic kidney disease
   b. Incidence: affects 1 in 1,000 people
   c. Genetics
      i. Autosomal dominant inheritance
      ii. Mutation of *PKD1* gene on chromosome 16
      iii. The *PKD1* gene produces a transmembrane protein called polycystin 1.
      iv. Other mutations involve *PKD2* and *PKD3* genes.
   d. Clinical features
      i. Asymptomatic with normal renal function until middle age
      ii. Presents with renal insufficiency, hematuria, and hypertension
      iii. Abdominal masses and flank pain
      iv. Most patients develop end-stage renal failure by their seventh decade.
   e. Diagnosis: ultrasound and CT scans
   f. Gross
      i. Massive bilateral kidney enlargement with large bulging cysts
      ii. Cysts are filled with serous, turbid, or hemorrhagic fluid.
   g. Micro: functioning nephrons are present between the cysts; cysts arise from the tubular structures of the nephron
   h. Extrarenal manifestations
      i. Liver cysts
      ii. Berry aneurysms of the circle of Willis
      iii. Mitral valve prolapse
      iv. Colonic diverticula
3. Renal dysplasia
   a. The most common renal cystic disease in children
   b. Causes an enlarged renal mass with cartilage and immature collecting ducts
   c. It may progress clinically to renal failure.
4. Medullary sponge kidney disease
   a. Causes multiple cysts of collecting ducts with a "Swiss cheese" appearance
   b. May predispose to recurrent urinary tract infections, hematuria, and renal stones
5. Acquired polycystic disease
   a. Is seen in renal dialysis patients
   b. Is associated with a small risk of developing renal cell carcinoma
6. Simple retention cysts of the kidney
   a. Are common in adults and occasionally cause hematuria

GLomerular Diseases

1. Diagnosis of glomerular diseases
   a. Clinical syndrome

Table 16-1. Clinical Syndromes in Glomerular Disease

<table>
<thead>
<tr>
<th>Nephritic Syndrome</th>
<th>Nephrotic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematuria (RBC casts)</td>
<td>Severe proteinuria (&gt;3.5 g/day)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Hypoalbuminemia (&lt;3 g/dl)</td>
</tr>
<tr>
<td>Azotemia</td>
<td>Generalized edema</td>
</tr>
<tr>
<td>Oliguria</td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Proteinuria (&lt;3.5 g/day)</td>
<td>Lipiduria</td>
</tr>
</tbody>
</table>
b. Renal biopsy
   i. Light microscopy (LM)
   ii. Immunofluorescence (IF)
   iii. Electron microscopy (EM)

Figure 16-2. Transmission Electron Micrograph Demonstrating Podocytes

PRIMARY GLOMERULOPATHIES (NEPHRITIC)
1. Acute poststreptococcal glomerulonephritis
   a. Synonyms: acute proliferative GN, postinfectious GN
   b. Clinical features
      i. Decreasing in incidence in the United States
      ii. Children affected more frequently than adults
      iii. Occurs 2–4 weeks after a streptococcal infection of the throat or skin
      iv. Organism: β-hemolytic group A streptococci
      v. May be caused by other bacteria, viruses, and parasites and systemic diseases (SLE and polyarteritis nodosa [PAN])
      vi. Nephritic syndrome
c. Laboratory studies
   i. Elevated antistreptolysin O (ASO) titers
   ii. Low serum complement

d. Light microscopy
   i. Hypercellular glomeruli with neutrophils and monocytes
   ii. Red cell casts in the renal tubules

e. Immunofluorescence: granular deposits of IgG, IgM, and C3 throughout the glomerulus

f. Electron microscopy: subepithelial (humps) immune complex deposits

g. Treatment: conservative fluid management

h. Prognosis
   i. Children
      - Complete recovery in >95% of cases
      - Rapidly progressive glomerulonephritis (RPGN) (1%)
      - Chronic glomerulonephritis (2%)
   ii. Adults
      - Complete recovery (60%)
      - RPGN/chronic renal disease (40%)

. Goodpasture syndrome (anti-GBM disease)

a. Definition: production of antibodies directed against basement membrane (anti-GBM antibodies), which result in damage of the lungs and the kidney

   i. The Goodpasture antigen is the noncollagenous component of type IV collagen.

b. Clinical features
   i. Males > females
   ii. Peak incidence: ages 20–40 years
   iii. Pulmonary involvement typically precedes the renal disease.
   iv. Present with pulmonary hemorrhage and recurrent hemoptysis
   v. Most develop RPGN

c. Light microscopy: hypercellularity, crescents, and fibrin

d. Immunofluorescence: smooth and linear pattern of IgG and C3 in the glomerular basement membrane (GBM)

f. Treatment: plasma exchange, steroids, and cytotoxic drugs

g. Prognosis
   i. Poor
   ii. Pulmonary hemorrhage may be severe and life threatening.
   iii. RPGN leading to renal failure
   iv. Early aggressive treatment may prevent end-stage renal failure.

. Rapidly progressive glomerulonephritis (RPGN)

a. Synonym: crescentic glomerulonephritis

b. Clinical feature: rapid progression to severe renal failure in weeks or months

Note

The characteristic finding in RPGN is the formation of crescents within Bowman space. The crescents are composed of fibrin, parietal epithelial cells, monocytes, and macrophages.
c. Occurs in several clinical settings
   i. Following Goodpasture syndrome
   ii. Following other forms of glomerulonephritis (post-streptococcal, SLE, Berger disease)
   iii. Associated with vasculitis (i.e., Wegner granulomatosis)
   iv. Idiopathic

d. Light microscopy
   i. Hypercellular glomeruli
   ii. Crescent formation in Bowman space

e. Immunofluorescence
   i. Variable
   ii. May show granular or linear deposits of immunoglobulin and complement

f. Electron microscopy
   i. Variable
   ii. May or may not have electron-dense deposits
   iii. GBM disruption and discontinuity is commonly seen.

g. Prognosis: poor with rapid progression to acute renal failure and end-stage renal disease

4. IgA nephropathy (Berger disease)
   a. Clinical features
      i. Most common cause of glomerulonephritis in the world
      ii. Common in France, Japan, Italy, and Austria
      iii. Affects children and young adults (mostly males)
      iv. Recurrent gross hematuria
      v. Onset may follow a respiratory infection.
      vi. Predominantly nephritic
      vii. Associated with celiac sprue and Henoch-Schönlein purpura
   b. Pathogenesis: The mechanism is unknown. There is a possible entrapment of circulating immune complexes with activation of the alternate complement pathway. There is also a possible genetic predisposition.

c. Light microscopy
   i. Variable
   ii. Normal or mesangial proliferation

d. Immunofluorescence: mesangial deposits of IgA and C3

e. Electron microscopy: mesangial immune complex deposits

f. Prognosis: many cases slowly progress to renal failure over 25 years

5. Membranoproliferative glomerulonephritis (MPGN)
   a. Types of MPGN
      i. Type I
      ii. Type II (dense deposit disease)
   b. Clinical features
      i. May be nephritic, nephrotic, or mixed!
      ii. MPGN may be secondary to many systemic disorders (SLE, endocarditis), chronic infections (HBV, HCV, HIV), and malignancies (chronic lymphocytic leukemia).
c. Lab
   i. Decreased serum C3
   ii. C3 nephritic factor (MPGN type II)
d. Light microscopy
   i. Lobulated appearance of the glomeruli
   ii. Mesangial proliferation and capillary wall thickening due to the mesangial and endothelial cell proliferation and/or deposition of subendothelial immune complex deposits
   iii. Splitting of the basement membrane ("tram-tracking") may be seen with a silver or periodic acid-Schiff (PAS) stain
e. Immunofluorescence
   i. Type I: granular pattern of C3 often with IgG, C1q, and C4
   ii. Type II: granular and linear pattern of C3
f. Electron microscopy
   i. Type I: subendothelial and mesangial immune complex deposits
   ii. Type II: dense deposits within the GBM
g. Prognosis
   i. Slowly progressive course, resulting in chronic renal failure over the course of 10 years
   ii. High incidence of recurrence in transplants

6. Alport syndrome
   a. Definition: a rare X-linked disorder caused by a defect in type IV collagen that is characterized by hereditary nephritis, hearing loss, and ocular abnormalities
   b. Genetics
      i. X-linked
      ii. The most common mutation causing Alport syndrome is in the COL4A5 gene coding for the alpha-5 chain of type 4 collagen.
   c. Clinical features
      i. Gross or microscopic hematuria begins in childhood.
      ii. Hearing loss leading to sensorineural deafness
      iii. Various ocular abnormalities of the lens and cornea can occur.
   d. Electron microscopy: alternating thickening and thinning of basement membrane is seen with splitting of the lamina densa
   e. Alport syndrome is a progressive disease that ultimately results in renal failure.

**PRIMARY GLOMERULOPATHIES (NEPHROTIC)**

1. Membranous glomerulonephritis
   a. Most common cause of nephrotic syndrome in adults
   b. Etiology
      i. Most (85%) cases are idiopathic.
      ii. Drugs (penicillamine)
      iii. Infections (hepatitis virus B and C, syphilis, etc.)
      iv. Systemic diseases (SLE, diabetes mellitus, etc.)
      v. Associated with malignant carcinomas of the lung and colon

---

**Note**

"Tram-Tracking"
This double contour appearance is caused by the splitting of the GBM by extension of the mesangial cell processes into the capillary loop.
vi. There may be a genetic predisposition.

c. Light microscopy
   i. There is a diffuse thickening of the capillary walls.
   ii. Basement membrane projections ("spikes") are seen on silver stains.

d. Immunofluorescence: granular and linear pattern of IgG and C3

e. Electron microscopy
   i. Subepithelial deposits along the basement membranes
   ii. Effacement of podocyte foot processes

f. Prognosis
   i. Variable course
   ii. Spontaneous remission
   iii. Persistent proteinuria
   iv. End-stage renal disease

2. Minimal change disease
   a. Synonyms: lipid nephrosis, nui disease
   b. Clinical features
      i. Most common cause of nephrotic syndrome in children
      ii. Peak incidence: ages 2–6 years
      iii. Diagnosis of exclusion
   c. Light microscopy
      i. Normal glomeruli
      ii. Lipid accumulation in proximal tubule cells (lipoid nephrosis)
   d. Immunofluorescence: negative; no immune deposits
   e. Electron microscopy
      i. Effacement of epithelial (podocyte) foot processes
      ii. Micronucleus transformation
      iii. No immune complex deposits
   f. Treatment: corticosteroids
   g. Prognosis
      i. Excellent
      ii. Dramatic response to steroids in children
      iii. Majority have a complete recovery

3. Focal segmental glomerulosclerosis
   a. Clinical features
      i. African Americans > Caucasians
      ii. Occurs in all ages
      iii. Nephrotic syndrome
   b. Etiology
      i. Idiopathic (primary)
      ii. Associated with loss of renal tissue
      iii. Superimposed on other glomerular diseases, such as IgA nephropathy
      iv. Sickle cell anemia
      v. Heroin use
vi. AIDS
vii. Morbid obesity
c. Light microscopy
   i. **Focal segmental sclerosis and hyalinization of glomeruli**
   ii. Initially affects the glomeruli along the medullary border
d. Immunofluorescence: IgM and C3 deposits in the sclerotic segments
e. Electron microscopy
   i. Nonsclerotic regions exhibit effacement of foot processes.
   ii. Sclerotic segments show increased mesangial matrix.
f. Treatment
   i. Poor response to steroids
   ii. High rate of recurrence in renal transplants
g. Prognosis
   i. Poor; children do better than adults
   ii. Most progress to chronic renal failure

**SECONDARY GLOMERULONEPHRITIS**

1. Definition: glomerulonephritis secondary to other disease processes

2. Diabetes
   a. Causes nodular glomerulosclerosis, hyaline arteriolosclerosis, and diabetic microangiopathy
   b. Clinically, may develop microalbuminuria that can progress to nephrotic syndrome

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**Note**

**Focal:** only some of the glomeruli are affected

**Segmental:** only a portion of the glomerular tuft exhibits sclerosis

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*Figure 16-3. Histopathology of Nodular Glomerulosclerosis (Kimmelstiel-Wilson Syndrome), Kidney*
3. Systemic lupus erythematosus
   a. Can cause a wide variety of patterns of damage to the kidney with clinical features that can include hematuria, nephritic syndrome, nephrotic syndrome, hypertension, and renal failure

**CHRONIC GLOMERULONEPHRITIS**

1. Definition: the final stage of many forms of glomerular disease and is characterized by progressive renal failure, uremia, and ultimately death
2. Clinical features
   a. Anemia, anorexia, and malaise
   b. Proteinuria, hypertension, and azotemia
3. Gross: small, shrunken kidneys
4. Micro: hyalination of glomeruli, interstitial fibrosis, atrophy of tubules, and a lymphocytic infiltrate
5. Urinalysis shows *broad, waxy casts*.
6. Treatment: dialysis and renal transplantation

**DISEASES OF THE TUBULES AND INTERSTITIUM**

1. Acute tubular necrosis (ATN)
   a. Definition: acute renal failure associated with potentially reversible injury to the tubular epithelium
   b. Clinical features
      i. ATN is the most common cause of acute renal failure in the United States.
      ii. Oliguria and elevation of blood urea nitrogen (BUN) and creatinine
      iii. Metabolic acidosis and hyperkalemia
      iv. Urinalysis shows *dirty brown granular casts and epithelial casts*.
   c. Ischemic ATN
      i. Is the most common cause of ATN
      ii. Is due to decreased blood flow caused by severe hemorrhage, severe renal vasoconstriction, hypotension, dehydration, or shock
   d. Nephrotoxic ATN—Caused by:
      i. Drugs (e.g., polymyxin, methicillin, gentamicin, sulfonamides)
      ii. Radiographic contrast agents
      iii. Heavy metals (e.g., mercury, lead, gold)
      iv. Organic solvents (e.g., carbon tetrachloride, chloroform, methyl alcohol)
      v. Ethylene glycol (antifreeze)
      vi. Mushroom poisoning
      vii. Phenol
      viii. Pesticides
      ix. Myoglobin
   e. Prognosis: excellent if the patient survives the disease responsible for the ATN
2. Acute and chronic pyelonephritis
   a. Definition: bacterial infection involving the renal pelvis, tubules, and interstitium
b. Pathogenesis
   i. Ascending infection is the most common route
   ii. Organisms
      • Gram-negative enteric bacilli
      • *Escherichia coli*, proteus, klebsiella, enterobacterium
   iii. Predisposing factors: urinary obstruction, vesicoureteral reflux, pregnancy, 
        urethral instrumentation, diabetes mellitus, benign prostatic hypertrophy, and 
        other renal pathology
   c. Clinical features
      i. Females >> males
      ii. Fever, chills, and malaise
      iii. Dysuria, frequency, and urgency
      iv. Costovertebral angle tenderness
      v. Urinalysis shows pyuria and WBC casts
   d. Micro: acute inflammation of the interstitium and tubules, or chronic inflammation 
      with fibrosis, which may progress to renal failure

3. Tubulointerstitial nephritis
   a. Definition: an acute or chronic inflammation of tubules and interstitium
   b. Pathogenesis: can be due to many causes, including medications, infections, acute 
      pyelonephritis, systemic lupus erythematosus, lead poisoning, urate nephropathy, and 
      multiple myeloma

4. Analgesic nephropathy
   a. The most common cause of chronic drug-induced tubular interstitial nephritis
   b. May cause renal papillary necrosis, hypertension, chronic renal failure, and transitional cell carcinoma of the renal pelvis and bladder

5. Urate nephropathy
   a. Due to deposition of urate crystals (secondary to leukemia treatment, lead poisoning, and gout) in renal tubules and interstitium
   b. May produce acute renal failure

UROLITHIASIS

1. Renal calculi
   a. Incidence
      i. Occurs in up to 6% of the population
      ii. Men are affected more often than women.
   b. Stone composition
      i. Calcium oxalate stones (75%)
      ii. Magnesium ammonium phosphate ("struvite") stones
         • Associated with infection by urea-splitting bacteria (proteus)
         • Often form large staghorn calculi
      iii. Uric acid stones are seen in gout, leukemia, and in patients with acidic urine.
      iv. Cystine stones
   c. Pathology
      i. Most stones are unilateral.
      ii. Are formed in the calyx, pelvis, and urinary bladder

Clinical Correlate
It may be difficult to distinguish cystitis from pyelonephritis. The presence of fever, costovertebral angle tenderness, and WBC casts in the urine are helpful clues to the diagnosis of pyelonephritis.
d. Clinical features
i. Calcium stones are radiopaque and can be seen on x-ray.
ii. Renal colic may occur if small stones pass into the ureters.
iii. May cause hematuria, urinary obstruction, and predispose to infection

TUMORS OF THE KIDNEY

1. Benign tumors of the kidney
   a. Cortical adenomas
      i. Common finding at autopsy
      ii. Small encapsulated cortical nodules measuring less than 3 cm
   b. Angiomyolipomas
      i. Hamartomas composed of fat, smooth muscle, and blood vessels
      ii. Common in patients with tuberous sclerosis

2. Renal cell carcinoma (RCC)
   a. Synonym: hypernephroma
   b. Incidence
      i. Males > females
      ii. They are most common in ages 50–70 years.
   c. Risk factors
      i. Cigarette smoking
      ii. Chronic analgesic use
      iii. Asbestos exposure
      iv. Chronic renal failure and acquired cystic disease
      v. von Hippel-Lindau disease (VHL tumor suppressor gene)
   d. Gross
      i. Large, solitary yellow mass found most commonly in the upper pole
      ii. Areas of necrosis and hemorrhage are commonly present.
      iii. The tumor often invades the renal vein and may extend into the inferior cava and heart.
   e. Micro
      i. Clear cell carcinoma
         • Polygonal cells with clear cytoplasm
         • Most common type
      ii. Papillary carcinoma
      iii. Chromophobe carcinoma
      iv. Sarcomatoid RCC (poor prognosis)
   f. Clinical features
      i. "Classic" triad (10%): hematuria, palpable mass, and flank pain
      ii. Paraneoplastic syndromes from ectopic hormone production
         • Polycythemia (erythropoietin production)
         • Hypertension (renin production)
         • Cushing syndrome (corticosteroid synthesis)
• Hypercalcemia (PTH-like hormone)
• Feminization or masculinization (gonadotropin release)

iii. May cause secondary amyloidosis, a leukemoid reaction, or eosinophilia
iv. There is a high incidence of metastasis on initial presentation.

3. Wilms tumor (nephroblastoma)
   a. Peak age: 2–5 years
   b. Risk factors
      i. WAGR syndrome (Wilms tumor, aniridia, genital anomalies, and mental retardation)
      ii. Beckwith-Wiedemann syndrome—increased risk of childhood cancers (e.g., renal cell carcinoma, neuroblastoma) and congenital anomalies (e.g., macroglossia, macrosomia, midline abdominal wall defects [e.g., omphalocele, umbilical hernia], ear creases or ear pits and neonatal hypoglycemia, hemihypertrophy)
   c. Tumor suppressor genes
      • WT-1 (11p13)
      • WT-2 (11p15)
   d. Presents as a large abdominal mass
   e. Gross: large, solitary tan mass
   f. Micro
      i. Metanephric blastema
      ii. Epithelial elements (immature glomeruli and tubules)
      iii. Stroma
   g. Treatment: surgery, chemotherapy, and radiation
   h. Prognosis: excellent; long-term survival rate of 90%

4. Transitional cell carcinomas
   a. Can involve the renal pelvis as well as the urinary bladder

**CHRONIC RENAL FAILURE**

1. Is the end stage of many different renal diseases
2. It is characterized pathologically by bilaterally shrunken kidneys.
3. Clinically, it causes progressive irreversible azotemia, normocytic anemia, platelet dysfunction, renal osteodystrophy, and hypertension.

**VASCULAR DISORDERS OF THE KIDNEY**

1. Renal artery stenosis
   a. Renal artery stenosis of any etiology causes decreased blood flow to the involved kidney with resulting secondary hypertension that is often not responsive to antihypertensive medications; treatment is usually surgical
   b. Atheromatous plaque is the most common cause of renal artery stenosis.
   c. Dysplastic lesions are an important additional cause of renal artery stenosis.
      i. Dysplastic lesions can take several forms that are all termed “fibromuscular dysplasia.”
ii. The most common of these forms include medial fibroplasia with aneurysms (most common form, causes alternating stenosis and aneurysms in "string of beads" pattern), perimedial fibroplasia (involves the outer media), and medial dissection (medial fibrosis with dissecting aneurysms); all three occur in middle-aged adults.

d. Miscellaneous diseases that can affect the renal arteries (with or without stenosis) include congenital anomalies, Takayasu arteritis, and radiation injuries.

2. Benign nephrosclerosis
   a. Is due to hypertension
   b. Causes hyaline arteriolosclerosis, tubular atrophy, interstitial fibrosis, and glomerulosclerosis
   c. Laboratory findings include mild proteinuria, hematuria, and azotemia.

3. Malignant (accelerated) hypertension
   a. Can cause fibrinoid necrosis of arterioles, glomerulitis, and hyperplastic arteriolosclerosis
   b. Clinical features
      i. Malignant hypertension causes cerebral edema, papilledema, retinal hemorrhage, intracerebral hemorrhage, and oliguric acute renal failure.

4. Renal infarction
   a. Etiology
      i. Can be due to thrombi from the left side of the heart, atheroembolic disease, and vasculitis
   b. Clinical features
      i. Presents with sudden onset of flank pain and hematuria

5. Sickle cell anemia
   a. Can cause medullary infarctions due to blockage of blood flow in the medullary vessels, which can cause asymptomatic hematuria, loss of urine concentrating ability, renal papillary necrosis, and pyelonephritis

6. Diffuse cortical necrosis
   a. Can occur with obstetric emergencies and DIC
   b. Can cause anuria

**OBSTRUCTIVE DISORDERS OF THE URINARY SYSTEM**

1. Hydronephrosis
   a. Characterized by dilation of ureter and renal pelvis
   b. Is a common complication of urinary tract obstruction
   c. Specific causes include renal stones, retroperitoneal fibrosis, benign prostatic hyperplasia, and cervical cancer.

**URETERAL DISORDERS**

1. Congenital anomalies
   a. Includes double ureters and congenital megaureter
2. Ureteritis cystica
   a. Definition: term used when chronic inflammation causes formation of small mucosal cysts in the ureter
   b. This condition can predispose for adenocarcinoma of the ureter.
3. Renal stones
   a. Commonly lodge in the ureters
4. Retroperitoneal fibrosis
   a. Usually an idiopathic condition that causes severe fibrosis of the retroperitoneal area that can entrap the ureters
   b. Some cases show sclerosing conditions in other body sites.
5. Transitional cell carcinoma
   a. Is the most common ureteral carcinoma

**URINARY BLADDER PATHOLOGY**

1. Cystitis
   a. Etiology
      i. Organisms: fecal flora (*Escherichia coli*, proteus, klebsiella, enterobacterium)
      ii. Radiation cystitis
      iii. Chemotherapy agents such as cyclophosphamide (hemorrhagic cystitis)
   b. Clinical features
      i. Females >> males
      ii. Frequency, urgency, dysuria, and suprapubic pain
      iii. Systemic signs (e.g., fever, chills, malaise) are uncommon.
   c. Predisposing factors: benign prostatic hypertrophy, bladder calculi, and cystocele
2. Urinary bladder tumors
   a. Most common type: transitional cell carcinoma
   b. Epidemiology
      i. Males > females
      ii. Increasing in incidence
      iii. Peak incidence is between 40 and 60 years of age
   c. Risk factors include
      i. Cigarette smoking
      ii. Occupational exposure to naphthylamine
      iii. Bladder infection with *Schistosoma haematobium*
         * Common in Egypt
         * Tend to develop squamous cell carcinomas
d. Clinical features
   i. Bladder cancer usually presents with painless hematuria.
   ii. It may also cause dysuria, urgency, frequency, hydronephrosis, and pyelonephritis.

e. Prognosis
   i. Bladder cancer has a high incidence of recurrence.
   ii. The prognosis depends on the tumor grade and stage.

f. Other bladder tumors include papillomas, adenocarcinoma, and embryonal rhabdomyosarcoma.

3. Congenital anomalies of the bladder
   a. Exstrophy of the bladder
      i. A developmental failure of the formation of the abdominal wall and bladder
         that leaves the bladder open at the body surface
   b. Urachal cyst remnants
      i. May permit drainage of urine from a newborn's umbilicus, and also may be a
         cause of bladder adenocarcinoma

4. Miscellaneous bladder conditions
   a. Acquired diverticuli
      i. Can complicate urinary tract outlet obstruction due to benign prostatic hyperplasia or other causes
   b. Cystocele
      i. Definition: the term used for prolapse of the bladder into the vagina
      ii. It is common in middle-aged to elderly women.
c. Cystitis cystica and glandularis
   i. Causes formation of small cysts and glands in the bladder mucosa related to chronic inflammation
   ii. It is associated with an increased risk of adenocarcinoma.

Chapter Summary

* Renal agenesis is the failure of one or both kidneys to develop. Bilateral renal agenesis is incompatible with life, but persons with unilateral agenesis may have adequate renal function. Other congenital anomalies of the kidney include hypoplasia, horseshoe kidney, and abnormal locations.

* Autosomal recessive polycystic kidney disease presents in infancy with progressive renal failure. Autosomal dominant polycystic kidney disease presents in adulthood with renal insufficiency, hematuria, and hypertension. The kidneys may be massively enlarged by the time of diagnosis. Renal dysplasia is the most common renal cystic disease in children and may cause a renal mass and renal failure. Medullary sponge kidney may cause a “Swiss cheese” appearance to the kidney and predisposes for infection, hematuria, and stones. Acquired polycystic disease is seen in renal dialysis patients. Simple retention cysts are common in adult kidneys.

* Glomerular diseases can present with either nephritic syndrome or nephrotic syndrome. Nephritic syndrome is characterized by hematuria, hypertension, azotemia, oliguria, and proteinuria less than 3.5 g/day. Nephrotic syndrome is characterized by severe proteinuria greater than 3.5 g/day, hypoalbuminemia, generalized edema, hyperlipidemia, and lipiduria.

* Acute post-streptococcal glomerulonephritis is associated with subepithelial immune complex deposits (subepithelial humps) by electron microscopy, occurs 2–4 weeks after a streptococcal infection of the throat or skin, and usually causes nephritic syndrome in children.

* Goodpasture syndrome is characterized by a smooth and linear pattern of IgG and C3 by immunofluorescence. It is the result of damage by autoantibodies to the basement membranes of the lungs and kidneys and is characterized clinically by pulmonary hemorrhage and rapidly progressive glomerulonephritis.

* Rapidly progressive glomerulonephritis is characterized microscopically by hypercellular glomeruli with crescent formation in Bowman space. Clinically, it features rapid progression to severe renal failure in weeks or months. It can be seen idiopathically or as a complication of renal disease due to Goodpasture syndrome, other forms of glomerulonephritis, or vasculitis.

* IgA nephropathy is characterized by mesangial deposits of IgA and C3, is the most common cause of glomerulonephritis worldwide, and tends to produce recurrent gross hematuria in children and young adults.

* Membranoproliferative glomerulonephritis is characterized microscopically by mesangial proliferation and basement membrane splitting and clinically may produce a nephritic pattern, a nephrotic pattern, or a mixed pattern.

* Membranous glomerulonephritis is characterized by diffuse thickening of capillary walls and basement membrane projections (spikes) visible with silver stains and is the most common cause of nephrotic syndrome in adults.

* Minimal change disease is characterized by effacement of epithelial (podocyte) foot processes visible with electron microscopy and is the most common cause of nephrotic syndrome in children.

(Continued)
Chapter Summary (continued)

* Focal segmental glomerulosclerosis is characterized by focal segmental sclerosis and hyalinization of glomeruli and is a cause of nephrotic syndrome that can occur idiopathically or secondary to other glomerular diseases, sickle cell anemia, heroin use, AIDS, and morbid obesity.

* Secondary glomerulonephritis can be caused by diabetes mellitus and systemic lupus erythematosus.

* Chronic glomerulonephritis with small, shrunken kidneys is the final stage of many forms of glomerular diseases and is characterized by progressive renal failure, uremia, and ultimately death.

* Acute tubular necrosis is acute renal failure associated with reversible injury to the tubular epithelium and can be due to ischemia or nephrotoxins.

* Acute and chronic pyelonephritis is a bacterial infection involving the renal pelvis, tubules, and interstitium and is most commonly due to Escherichia coli, Proteus, Klebsiella, or Enterobacter.

* Renal calculi are common and may be composed of calcium oxalate, struvite, uric acid, or cystine. Clinically, stones may cause renal colic, hematuria, urinary obstruction, and a predisposition for infection.

* Benign tumors of the kidney include cortical adenomas and angiomyolipomas. Renal cell carcinoma tends to produce a large solitary renal mass in middle-aged to older adults and may cause hematuria, palpable mass, flank pain, and paraneoplastic syndromes.

* Wilms tumor is a childhood malignancy that presents with a large abdominal mass. It now has an excellent long-term prognosis.

* Vascular diseases of the kidney include renal artery stenosis (decreased blood flow to the kidney leading to secondary hypertension), benign nephrosclerosis (which develops secondary to ordinary hypertension), hyperplastic arteriolosclerosis (which develops secondary to malignant hypertension), renal infarction (from emboli from the left side of the heart and secondary to sickle cell anemia), and diffuse cortical necrosis (secondary to obstetric emergencies and DIC).

* Ureteral disorders include congenital anomalies, ureteritis, cystic disease, stones lodged in a ureter, retroperitoneal fibrosis, and transitional cell carcinoma.

* Cystitis, or urinary bladder inflammation, can be due to bacterial infection, radiation, or chemotherapy; cystitis clinically produces frequency, urgency, dysuria, and suprapubic pain.

* Transitional cell carcinoma is the most common type of bladder tumor and usually presents with painless hematuria. Other bladder tumors include papillomas, adenocarcinoma, and embryonal rhabdomyosarcoma.

* Congenital anomalies of the bladder include exstrophy and urachal cyst remnants.

* Other bladder conditions include acquired diverticuli, cystocele, and cystitis cystica and glandularis.
Gastrointestinal Tract Pathology

ESOPHAGUS

1. Congenital and mechanical disorders
   a. Tracheoesophageal fistula
      i. Definition: congenital connection between the esophagus and trachea
      ii. Often associated with esophageal atresia
      iii. Often discovered soon after birth because of aspiration
   b. Esophageal webs
      i. Definition: weblike protrusions of the esophageal mucosa into the lumen
      ii. Presentation: dysphagia
      iii. Plummer-Vinson syndrome
         • Middle-aged women
         • Esophageal webs
         • Iron deficiency anemia
         • Increased risk of carcinoma
      iv. Schatzki ring: weblike narrowing at gastroesophageal junction
   c. Achalasia
      i. Definition: failure of the lower esophageal sphincter (LES) to relax with swallowing
      ii. Etiology
         • Unknown in most cases
         • South America: → Chagas disease
      iii. Presentation: progressive dysphagia
      iv. Gross: esophageal dilation proximal to the LES
      v. Barium swallow: “bird-beak” sign
      vi. Micro: loss of ganglion cells in the myenteric plexus
      vii. Treatment: LES balloon dilation or myotomy
      viii. Increased risk of esophageal carcinoma

2. Hematemesis and esophageal bleeding
   a. Mallory-Weiss syndrome
      i. Definition: laceration at the gastroesophageal junction produced by severe prolonged vomiting
      ii. Most common cause: acute ingestion and/or alcoholism
      iii. Presentation: hematemesis
      iv. Gross: linear lacerations at the gastroesophageal junction
      v. Complications: Boerhaave syndrome: esophageal rupture (rare)

Clinical Correlate
The most common type of tracheoesophageal fistula:

In a Nutshell
Mallory-Weiss tears versus esophageal varices:
Although both are associated with alcohol abuse and can present with hematemesis, Malling-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.
b. **Esophageal varices**
   i. Definition: dilated submucosal veins in the lower third of the esophagus, usually secondary to portal hypertension
   ii. Most common cause: cirrhosis
   iii. Presentation
       • Asymptomatic
       • Massive hematemesis when ruptured
   iv. Complication: potentially fatal hemorrhage
   v. Treatment: band ligation, sclerotherapy, or balloon tamponade

3. **Esophagitis**
   a. **Gastroesophageal reflux disease (reflux esophagitis)**
      i. Definition: esophageal irritation and inflammation due to reflux of gastric secretions into the esophagus
      ii. Presentation: heartburn and regurgitation
      iii. Complications
          • Bleeding
          • Stricture
          • Bronchospasm and asthma
          • Barrett esophagus
   b. **Barrett esophagus**
      i. Definition: metaplasia of the squamous esophageal mucosa to a more protective columnar type (intestinal metaplasia) because of chronic exposure to gastric secretions
      ii. Incidence is increasing
      iii. Cause: gastroesophageal reflux disease (GERD)
      iv. Gross: irregular gastroesophageal (GE) junction with tongues of red granular mucosa extending up into the esophagus
      v. Increased risk of dysplasia and esophageal adenocarcinoma

4. **Esophageal carcinoma**
   a. **Squamous cell carcinoma (SCC) of the esophagus**
      i. Epidemiology
         • SCC is the most common type of esophageal cancer in the world, but not in the United States.
         • Males > females: age usually >50
         • African Americans > Caucasians
      ii. Risk factors
         • Heavy smoking and alcohol use
         • Achalasia
         • Plummer-Vinson syndrome
         • Tylosis
         • Prior lye ingestion
iii. Presentation
   - Often asymptomatic until late in the course
   - Progressive dysphagia
   - Weight loss and anorexia
   - Bleeding
   - Hoarseness or cough (advanced cancers)
iv. Diagnosis: endoscopy and biopsy
v. Treatment: surgery
vi. Prognosis: poor

b. Adenocarcinoma of the esophagus
   i. More common than SCC in the United States
   ii. Caucasians > African Americans
   iii. Arises in the distal esophagus
   iv. Associated with Barrett esophagus and dysplasia
   v. Prognosis: poor

STOMACH

1. Congenital disorders
   a. Pyloric stenosis
      i. Definition: congenital stenosis of the pylorus due to marked muscular hypertrophy of the pyloric sphincter, resulting in gastric outlet obstruction
      ii. Males > females
      iii. Associated with Turner and Edwards syndromes
      iv. Presentation
         - Onset of regurgitation and vomiting in the second week of life
         - Waves of peristalsis are visible on the abdomen
         - Palpable oval abdominal mass
      v. Treatment: surgery
   b. Congenital diaphragmatic hernia
      i. Definition: congenital defect in the diaphragm, resulting in herniation of the abdominal organs into the thoracic cavity
      ii. The stomach is the most commonly herniated organ due to left-sided congenital diaphragmatic hernia.
      iii. Often associated with intestinal malrotation
      iv. Complications: significant lung hypoplasia

Clinical Correlate

Pyloric stenosis is congenital hypertrophy of the pylori, which presents with projectile vomiting and a palpable abdominal "olive."
2. hypertrophic gastropathy
   a. Ménétrier disease
      i. Middle-aged men
      ii. Gross: enlarged rugal folds in the body and fundus
      iii. Micro: Profound hyperplasia of surface mucous cells with glandular atrophy
      iv. Decreased acid production
      v. Protein losing enteropathy
      vi. Increased risk of gastric cancer
   b. Zollinger-Ellison syndrome
      i. Definition: pancreatic gastrinoma producing gastrin
      ii. Gross: enlarged rugal folds
      iii. Increased acid secretion
      iv. Presentation: multiple intractable peptic ulcers

3. Acute inflammation and stress ulcers
   a. Acute hemorrhagic gastritis
      i. Definition: acute inflammation, erosion, and hemorrhage of the gastric mucosa due to a breakdown of the mucosal barrier and acid-induced injury
      ii. Etiology
         • Chronic aspirin or NSAID use
         • Alcohol use
b. Gastric stress ulcers
   i. Gross: multiple, small, round, superficial ulcers of the stomach and duodenum
   ii. Etiology
       • NSAID use
       • Severe stress
       • Sepsis
       • Shock
       • Severe burns or trauma (Curling ulcers)
       • Elevated intracranial pressure (Cushing ulcers)
   iii. High incidence in intensive care unit (ICU) patients
   iv. Complication: bleeding

4. Chronic gastritis
   a. Definition: chronic inflammation of the gastric mucosa eventually leading to atrophy (chronic atrophic gastritis)
   b. Fundic type (type A)
      i. Autoimmune atrophic gastritis
         • Involves the body and the fundus
         • Autoantibodies to parietal cells and/or intrinsic factor
         • Loss of parietal cells
         • Decreased acid secretion
         • Increased serum gastrin (G-cell hyperplasia)
         • Pernicious anemia: megaloblastic anemia due to lack of intrinsic factor and $B_{12}$ malabsorption
      ii. Gross: loss of rugal folds in the body and fundus
      iii. Micro:
         • Mucosal atrophy with loss of glands and parietal cells
         • Chronic lymphoplasmacytic inflammation
         • Intestinal metaplasia
      iv. Increased risk of gastric carcinoma
   c. Antral type (type B)
      i. Helicobacter pylori gastritis
      ii. Most common form of chronic gastritis in the United States

Clinical Correlate

Ability of H. pylori to produce urease is clinically used for detection by the [$^{13}$C]-urea breath test and clofazimine (CLO) tests. Other methods of detection include biopsy (histologic identification is the gold standard) and serology.
iii. *Helicobacter pylori*
   - Curved, gram-negative rods
   - Urease producing
   - Risk of infection increases with age
   - Associated with chronic gastritis (type B)
   - Associated with duodenal and gastric peptic ulcers
   - Associated with gastric carcinoma

iv. Micro
   - *H. pylori* organisms are visible in the mucous layer of the surface epithelium.
   - Foci of acute inflammation
   - Chronic inflammation with lymphoid follicles
   - Intestinal metaplasia

v. Increased risk of gastric carcinoma

5. Chronic peptic ulcer (benign ulcer)
   a. Peptic ulcer
      i. Definition: ulcers of the distal stomach and proximal duodenum caused by gastric secretions (hydrochloric acid and pepsin) and impaired mucosal defenses
   ii. Etiology
       - Chronic NSAID and aspirin use
       - Steroids
       - Smoking
       - *H. pylori* infection
   iii. Two major locations (see b and c below)
   iv. Diagnosis: endoscopy ± biopsy
   v. Treatment
       - Acid suppression: *H₂* blocker, proton pump inhibitor, etc.
       - Eradication of *H. pylori*
   vi. Complications
       - Hemorrhage
       - Iron deficiency anemia
       - Penetration into adjacent organs
       - Perforation (x-ray shows free air under the diaphragm)
       - Pyloric obstruction

b. Duodenal peptic ulcer
   i. More common than gastric ulcers
   ii. Associations
       - *H. pylori* (~100%)
       - Increased gastric acid secretion
       - Increased rate of gastric emptying
       - Blood group O
       - Multiple endocrine neoplasia (MEN) type I and Zollinger-Ellison syndromes
       - Cirrhosis and COPD
   iii. Location: anterior wall of the proximal duodenum
iv. Classic presentation: burning epigastric pain 1–3 hours after eating, which is relieved by food

c. **Gastric peptic ulcer**
   i. Associated with *H. pylori* (75%)
   ii. Location: lesser curvature of the antrum
   iii. Gross
       • Small (<3 cm), solitary ulcers
       • Round or oval shape
       • Sharply demarcated, “punched-out” ulcers
       • Overhanging margins
       • Radiating mucosal folds
   iv. Classic presentation: burning epigastric pain, which worsens with eating

6. **Gastric carcinoma (malignant ulcer)**
   a. Gastric carcinoma
      i. Epidemiology
         • Decreasing incidence in the United States
         • Japan > United States
      ii. Risk factors
         • Dietary factors
            Smoked fish and meats
            Pickled vegetables
            Nitrosamines
            Benzpyrene
            Decreased intake of fruits and vegetables
         • *H. pylori* infection
         • Chronic atrophic gastritis
         • Smoking
         • Blood type A
         • Bacterial overgrowth in the stomach
         • Prior subtotal gastrectomy
         • Ménétrier disease
      iii. Presentation
         • Often (90%) asymptomatic until late in the course
         • Weight loss and anorexia
         • Epigastric abdominal pain mimicking a peptic ulcer
         • Early satiety
         • Occult bleeding and iron deficiency anemia
      iv. Location: lesser curvature of the antrum
      v. Gross
         • Large (>3 cm), irregular ulcer
         • Heaped-up margins and a necrotic ulcer base
         • May also occur as a flat or polypoid mass
      vi. Intestinal type—micro: gland-forming adenocarcinoma
vii. Diffuse type
   • Diffuse infiltration of stomach by poorly differentiated tumor cells
   • *Signet-ring cells*: nucleus is displaced to the periphery by intracellular mucin
   • *Linitis plastica*: thickened "leather bottle"-like stomach

viii. Metastasis
   • *Virchow* (sentinel) node: left supraclavicular lymph node
   • *Krukenberg* tumor: spread to the ovary

ix. Diagnosis: endoscopy and biopsy

x. Treatment: gastrectomy

xi. Prognosis: poor; overall 5-year survival 20%

**SMALL AND LARGE INTESTINES**

1. Mechanical obstruction
   a. **Volvulus**
      i. Definition: twisting of a segment of bowel on its vascular mesentery, resulting in intestinal obstruction and infarction
      ii. Often associated with congenital abnormalities such as intestinal malrotation
      iii. Locations: sigmoid colon and small bowel
      iv. Complications: infarction and peritonitis
   b. **Intussusception**
      i. Definition: telescoping of a proximal segment of the bowel into the distal segment
      ii. Most common in infants and children
      iii. In adults it may be associated with a mass or tumor.
      iv. Presentation: intestinal obstruction, abdominal pain, and "currant-jelly" stools
      v. Complication: infarction of the intussuscepted segment
   c. **Incarcerated hernia**
      i. Definition: segment of bowel becomes imprisoned within a hernia
      ii. Complications: intestinal obstruction and infarction
   d. **Hirschsprung disease**
      i. Synonym: congenital aganglionic megacolon
      ii. Definition: *congenital absence of ganglion cells* in the rectum and sigmoid colon, resulting in intestinal obstruction
      iii. Presentation
         • Males > females
         • Delayed passage of meconium
         • Constipation, abdominal distension, and vomiting
         • Associated with Down syndrome
      iv. Gross
         • Affected segment is narrowed.
         • Proximal dilatation (megacolon)
      v. Micro: absence of ganglion cells in Auerbach and Meissner plexuses

**Note**

Acquired megacolon may be caused by Chagas disease or ulcerative colitis (toxic megacolon).
vi. Diagnosis: rectal biopsy
vii. Treatment: resection of affected segment

2. Malabsorption syndromes
   a. Celiac sprue
      i. Synonyms: gluten-sensitive enteropathy, nontropical sprue
      ii. Definition: hypersensitivity to gluten (and gliadin), resulting in loss of small bowel villi and malabsorption
      iii. Genetic predisposition: HLA-B8, DR3, and DQ
      iv. Micro
         • Loss of villi
         • Increased intraepithelial lymphocytes
         • Increased plasma cells in the lamina propria
      v. Presentation
         • Usually presents in childhood with malabsorption
         • Abdominal distention, bloating, and flatulence
         • Diarrhea, steatorrhea, and weight loss
   vi. Associated with dermatitis herpetiformis
   vii. Treatment: dietary restriction of gluten

Bridge to Anatomy
Auerbach plexus = myenteric ganglia
Meissner plexus = submucosal ganglia

Figure 17-2. Celiac

b. Tropical sprue
   i. Definition: malabsorptive disease of unknown etiology (infection and/or nutritional deficiency) affecting travelers to tropical regions, such as the Caribbean and South America
   ii. Micro: similar to celiac sprue
   iii. Treatment: antibiotics, vitamin B12, and folate
c. Whipple disease
   i. Definition: rare infectious disease involving many organs, including small intestines, joints, lung, heart, liver, spleen, and CNS
   ii. Caucasian males; age 30–50 years
   iii. Organism: *Tropheryma whipplei*
   iv. Presentation: malabsorption, weight loss, and diarrhea
   v. Micro: small bowel lamina propria is filled with macrophages stuffed with PAS-positive, Gram-positive, rod-shaped bacilli
   vi. Treatment: antibiotics

3. Inflammatory bowel disease
   a. Three major categories
      i. Crohn disease (CD) (synonym: regional enteritis)
      ii. Ulcerative colitis (UC)
      iii. Colitis of indeterminate type
   b. Epidemiology
      i. Females > males
      ii. Caucasians > non-Caucasians
      iii. Age distribution
         - CD: bimodal with peaks at ages 10–30 and 50–70 years
         - UC: peaks at age 20–30 years
      iv. Increasing incidence
      v. Ulcerative colitis is more common than Crohn disease.
   c. Presentation
      i. Episodes of bloody diarrhea or stools with mucus
      ii. Crampy lower abdominal pain
      iii. Fever
      iv. Perianal fistulas (CD)
      v. Extraintestinal manifestations (UC > CD)
      vi. CD of the small bowel may present with malabsorption.
      vii. CD may mimic appendicitis.
   d. Diagnosis
      i. Diagnosis of exclusion
      ii. Endoscopy and biopsy
## Table 17-1. Crohn Disease Versus Ulcerative Colitis

<table>
<thead>
<tr>
<th></th>
<th>Crohn Disease</th>
<th>Ulcerative Colitis</th>
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<tbody>
<tr>
<td>Most common site</td>
<td>Terminal ileum</td>
<td>Rectum</td>
</tr>
<tr>
<td>Distribution</td>
<td>Mouth to anus</td>
<td>Rectum → colon “back-wash” ileitis</td>
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<tr>
<td>Spread</td>
<td>Discontinuous/“skip”</td>
<td>Continuous</td>
</tr>
<tr>
<td>Gross features</td>
<td>• Focal aphthous ulcers with intervening normal mucosa</td>
<td>Extensive ulceration</td>
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<tr>
<td></td>
<td>• Linear fissures</td>
<td>Pseudopolyps</td>
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<td></td>
<td>• Cobblestone appearance</td>
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<td></td>
<td>• Thickened bowel wall</td>
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<td></td>
<td>• “Creeping fat”</td>
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<tr>
<td>Micro</td>
<td>Noncaseating granulomas</td>
<td>Crypt abscesses</td>
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<tr>
<td>Inflammation</td>
<td>Transmural</td>
<td>Limited to mucosa and submucosa</td>
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<tr>
<td>Complications</td>
<td>• Strictures</td>
<td>Toxic megacolon</td>
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<td>• “String sign” on barium studies</td>
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<td></td>
<td>• Obstruction</td>
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<td>• Fistulas</td>
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<td></td>
<td>• Sinus tracts</td>
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<td>Genetic association</td>
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<td>HLA-B27</td>
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<tr>
<td>Extraintestinal manifestations</td>
<td>Uncommon</td>
<td>Common (e.g., arthritis, spondylitis, primary sclerosing cholangitis, erythema nodosum, pyoderma gangrenosum)</td>
</tr>
<tr>
<td>Cancer risk</td>
<td>Slight 1-3%</td>
<td>5-25%</td>
</tr>
</tbody>
</table>

4. Miscellaneous conditions
   a. Ischemic bowel disease
      i. Definition: decreased blood flow and ischemia of the bowel secondary to atherosclerosis with thrombosis, thromboembolism, or reduced cardiac output from shock
      ii. Most common in older individuals
      iii. Presentation: abdominal pain and bloody diarrhea
      iv. Distribution: tends to affect watershed areas (e.g., splenic flexure)
      v. Gross: hemorrhagic infarction
      vi. Treatment: surgical resection
      vii. Prognosis: poor; over 50% mortality

---

*Bridge to Anatomy*

The splenic flexure of the colon receives blood from both the superior and inferior mesenteric arteries.
b. **Hemorrhoids**
   i. Definition: tortuous, dilated submucosal veins caused by increased venous pressure
   ii. Risk factors
      • Constipation and prolonged straining during bowel movements
      • Pregnancy
      • Cirrhosis
   iii. Complications
      • Thrombosis (painful)
      • Bleeding (streaks of bright red blood on hard stool)

c. **Angiodysplasia**
   i. Definition: arteriovenous malformations of the intestines
   ii. Common in individuals over age 55
   iii. Occur in the cecum and right colon
   iv. Presentation: multiple episodes of rectal bleeding
   v. Associated with Osler-Weber-Rendu syndrome and the CREST syndrome
   vi. Treatment: surgical resection

d. **Melanosis coli**
   i. Common with laxative abuse
   ii. Gross: black pigmentation of the colon due to the ingestion of the laxative pigment by macrophages in the mucosal and submucosa
   iii. Can mimic colitis or malignancy

e. **Pseudomembranous colitis (antibiotic-associated colitis)**
   i. Definition: acute colitis characterized by the formation of inflammatory pseudomembranes in the intestines
   ii. Organism: *Clostridium difficile*, can also be due to ischemic bowel disease
   iii. Often brought on by a course of broad-spectrum antibiotics (especially clindamycin and ampicillin)
   iv. Presentation: diarrhea, fever, and abdominal cramps
   v. Gross: yellow-tan mucosal membranes
   vi. Micro:
      • Superficial colonic necrosis with an overlying pseudomembrane
      • Pseudomembranes are mushroom-shaped inflammatory exudates composed of neutrophils, mucin, fibrin, and necrotic cellular debris.
   vii. Diagnosis: detection of *C. difficile* toxin in the stool
   viii. Treatment: vancomycin or *metronidazole*

f. **Appendicitis**
   i. Most commonly caused by obstruction of the appendix by a fecalith
   ii. Clinical findings
      • Appendicitis often starts with periumbilical pain that subsequently localizes to the right lower quadrant.
      • Nausea, vomiting, and a fever may also be present.
   iii. Lab: elevated WBC count
   iv. Gross: a fibrinopurulent exudate may be seen on the appendiceal serosa.
v. Micro: neutrophils are present within the mucosa and muscular wall (muscularis propria) of the appendix
vi. A complication is appendiceal rupture leading to peritonitis.

5. Diverticula
a. Meckel diverticulum
   i. Definition: congenital small bowel diverticulum
   ii. Remnant of the vitelline (omphalomesenteric) duct
   iii. “Rule of 2s”
      • 2% of the normal population
      • 2 feet from the ileocecal valve
      • 2 cm in length
      • 2 years old or younger at the time of diagnosis
      • 2% of carcinoid tumors occur in a Meckel diverticulum
   iv. Presentation
      • Most are asymptomatic
      • May contain rests of ectopic gastric mucosa and present with intestinal bleeding

b. Colonic diverticulosis
   i. Definition: acquired outpouching of the bowel wall, characterized by herniation of the mucosa and submucosa through the muscularis propria (pseudo-diverticulum)
   ii. Epidemiology
      • Extremely common in the United States
      • Incidence increases with age
   iii. Risk factor: low-fiber diet leads to increased intraluminal pressure
   iv. Location: most common in the sigmoid colon
   v. Presentation
      • Often asymptomatic
      • Constipation alternating with diarrhea
      • Left lower quadrant abdominal cramping and discomfort
      • Occult bleeding and an iron deficiency anemia
      • Lower GI hemorrhage
   vi. Complications
      • Diverticulitis
      • Fistulas
      • Perforation and peritonitis

6. Neoplasia
a. Adenomatous colonic polyp
   i. Definition: benign neoplasm of the colonic mucosa that has the potential to progress to colonic adenocarcinoma
   ii. Presentation
      • Commonly asymptomatic
      • Occult bleeding and iron deficiency anemia

Note
Given that only two layers of the bowel wall are involved, these acquired outpouchings are technically pseudodiverticula.

Clinical Correlate
It is estimated to take roughly 10 years to progress from adenoma to carcinoma, which makes colonoscopy an effective tool for identifying and removing adenomas before they progress to an invasive malignancy.
iii. Prognostic features
   - Tubular versus villous histology
   - Pedunculated versus sessile appearance
   - Size of polyps
   - Degree of dysplasia

iv. Diagnosis
   - Hemoccult positive stools
   - Endoscopy

b. Familial adenomatous polyposis (FAP)
i. Synonym: adenomatous polyposis coli (APC)

ii. Genetics
   - Autosomal dominant
   - APC gene on chromosome 5q21

iii. Develop thousands of colonic adenomatous polyps

iv. Diagnosis: discovery of more than 100 adenomatous polyps on endoscopy

v. Complication: by age 40, virtually 100% will develop an invasive adenocarcinoma
   and increased risk for developing duodenal adenocarcinoma and adenocarcinoma of the papilla of Vater.

c. Gardner syndrome

i. Autosomal dominant

ii. Variant of FAP characterized by
   - Numerous colonic adenomatous polyps
   - Multiple osteomas
   - Fibromatosis
   - Epidermal inclusion cysts
d. Turcot syndrome
   i. Rare variant of FAP characterized by
      • Numerous colonic adenomatous polyps
      • CNS tumors (gliomas)

e. Hereditary nonpolyposis colorectal cancer (HNPCC)
   i. Synonym: Lynch syndrome
   ii. Genetics
      • Autosomal dominant
      • Mutation of DNA nucleotide mismatch repair gene
   iii. Colon cancer
   iv. Increased risk of endometrial and ovarian carcinoma

f. Peutz-Jeghers syndrome
   i. Autosomal dominant
   ii. Multiple hamartomatous polyps (primarily in the small intestine)
   iii. Melanin pigmentation of the oral mucosa
   iv. Increased risk of cancer of the lung, pancreas, breast, and uterus

g. Colonic adenocarcinoma
   i. Third most common tumor in terms of incidence and mortality in the United States
   ii. Risk factors
      • Low-fiber diet
      • Diet low in fruits and vegetables
      • High red meat and animal fat consumption
      • Adenomatous polyps
      • Hereditary polyposis syndromes
      • Lynch syndrome
      • Ulcerative colitis
   iii. Genetics
      • Multiple mutations are involved.
      • APC gene
      • K-ras oncogene
      • DCC gene (deleted in colorectal cancer—a tumor suppressor gene [18q21- qter region] that is a cellular adhesion molecule)
      • p53 gene

Table 17-2. Right-Sided Cancer Versus Left-Sided Cancer

<table>
<thead>
<tr>
<th>Gross</th>
<th>Right-Sided Cancer</th>
<th>Left-Sided Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polypoid mass</td>
<td></td>
<td>Circumferential growth producing a “napkin-ring” configuration</td>
</tr>
</tbody>
</table>

| Barium studies | Polypoid mass       | “Apple-core” lesion                      |

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Bleeding</th>
<th>Change in bowel habits</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Occult blood in stool</td>
<td></td>
<td>• Constipation or diarrhea</td>
</tr>
<tr>
<td>• Iron deficiency anemia</td>
<td></td>
<td>• Reduced caliber stools</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Obstruction</td>
</tr>
</tbody>
</table>
iv. Diagnosis
   - Hemoccult positive stool
   - Endoscopy with biopsy
v. Pattern of spread
   - Lymphatic spread to mesenteric lymph nodes
   - Distant spread to liver, lungs, and bone
vi. Staging: modified Dukes (Astatler-Coller) staging system
vii. Treatment
   - Surgical resection
   - Chemotherapy for metastatic disease
   - Monitor CEA levels

Table 17-3. The Modified Dukes Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Extent of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Limited to the mucosa and submucosa</td>
</tr>
<tr>
<td>B1</td>
<td>Invasion into but not through the muscularis propria</td>
</tr>
<tr>
<td>B2</td>
<td>Invasion through the muscularis propria</td>
</tr>
<tr>
<td>C1</td>
<td>Positive lymph nodes; invasion into but not through the muscularis propria</td>
</tr>
<tr>
<td>C2</td>
<td>Positive lymph nodes; invasion through the muscularis propria</td>
</tr>
<tr>
<td>D</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

h. Carcinoid tumors
   i. Neuroendocrine tumor often producing serotonin
   ii. Locations: appendix (most common) and terminal ileum
   iii. Metastasis to the liver may result in carcinoid heart disease
   iv. Carcinoid syndrome
      - Diarrhea
      - Cutaneous flushing
      - Bronchospasm and wheezing
      - Fibrosis
   v. Diagnosis: urinary 5-HIAA (5-hydroxyindoleacetic acid)

Note
Histologically, carcinoid tumors appear similar to other neuroendocrine tumors with nests of small uniform cells.

Bridge to Biochemistry
Serotonin is converted to 5-HIAA by monoamine oxidase.
Chapter Summary

- Congenital and mechanical disorders of the esophagus include tracheoesophageal fistula (associated with esophageal atresia and aspiration), esophageal webs (associated with iron deficiency anemia and increased risk of cancer), and achalasia (associated with increased risk of cancer). Achalasia is due to failure of the lower esophageal sphincter to relax with swallowing.

- Esophageal bleeding can be due to laceration at the gastroesophageal junction produced by severe vomiting (Mallory-Weiss syndrome), or esophageal varices that develop secondary to portal hypertension.

- Gastroesophageal reflux disease is esophageal irritation and inflammation due to reflux of gastric secretions into the esophagus. Barrett esophagus is metaplasia of the squamous esophageal mucosa to a more protective columnar type because of chronic exposure to gastric secretions.

- Esophageal carcinoma may be either squamous-cell carcinoma or adenocarcinoma. Squamous cell carcinoma is the most common form in the world and is associated with heavy smoking, heavy alcohol use, achalasia, and Plummer-Vinson syndrome. Adenocarcinoma involves the distal esophagus and usually arises in areas of Barrett esophagus.

- Pyloric stenosis is a congenital stenosis of the pylorus due to marked muscular hypertrophy of the pyloric sphincter, resulting in gastric outlet obstruction. Congenital diaphragmatic hernia is a congenital defect in the diaphragm, resulting in herniation of the abdominal organs into the thoracic cavity.

- Menetrier disease is a form of hypertrophic gastropathy with enlarged rugal folds that can produce decreased acid production, a protein-losing enteropathy, and increased risk of cancer. Zollinger-Ellison syndrome is a form of hypertrophic gastropathy with enlarged rugal folds that occurs secondary to gastrin stimulation by a pancreatic gastrinoma.

- Acute hemorrhagic gastritis is acute inflammation, erosion, and hemorrhage of the gastric mucosa due to a breakdown of the mucosal barrier and acid-induced injury. Gastric stress ulcers are multiple, small, round, superficial ulcers of the stomach and duodenum.

- Chronic gastritis is a chronic inflammation of the gastric mucosa resulting in eventual atrophy. Chronic gastritis is subdivided into a fundic type, which is related to autoantibodies to parietal cells and/or intrinsic factor, and an antral type, which is related to Helicobacter pylori gastritis.

- Peptic ulcers are ulcers of the distal stomach and proximal duodenum caused by gastric secretions (hydrochloric acid and pepsin) and impaired mucosal defenses. Duodenal peptic ulcers are more common than gastric ulcers.

- Gastric carcinomas tend to be asymptomatic until late in their course and may show a variety of histologic patterns.

- Volvulus is twisting of a segment of bowel on its vascular mesentery, resulting in intestinal obstruction and infarction. Intussusception is telescoping of a proximal segment of bowel into the distal segment. Incarcerated hernia is a segment of bowel that becomes imprisoned within a hernia. Hirschsprung disease is a congenital absence of ganglion cells in the rectum and sigmoid colon resulting in intestinal obstruction.

(Continued)
Chapter Summary (continued)

* Celiac sprue is a hypersensitivity to gluten, resulting in loss of small bowel villi and malabsorption. Tropical sprue is a malabsorptive disease of unknown etiology affecting travelers to tropical regions, such as the Caribbean and South America. Whipple disease is a rare infectious disease involving many organs, including small intestines, joints, lung, heart, liver, spleen, and CNS.

* Inflammatory bowel disease includes Crohn disease, ulcerative colitis, and colitis of indeterminate type. Crohn disease has “skip” lesions, has transmural involvement with formation of granulomas, and tends to form fistulas, abscesses, and sinuses. In contrast, ulcerative colitis is confined to the rectum and colon, has inflammation limited to the mucosa and submucosa with crypt abscess, is more likely to have extraintestinal manifestations, and can cause toxic megacolon.

* Ischemic bowel disease is the result of decreased blood flow and ischemia of the bowel secondary to atherosclerosis with thrombosis, thromboembolism, or reduced cardiac output from shock. Hemorrhoids are tortuous dilated submucosal veins caused by increased venous pressure. Angiodysplasia is arteriovenous malformation of the intestines. Melanosis coli is a black pigmentation of the colon that is common with laxative abuse. Pseudomembranous colitis is characterized by formation of inflammatory pseudomembranes in the intestine following infection by Clostridium difficile, and/or ischemic bowel disease.

* Meckel diverticulum is a congenital small bowel diverticulum that is a remnant of the vitelline duct. Colonic diverticulosis is a common condition among the elderly population and features acquired outpouchings of the bowel wall, characterized by herniation of the mucosa and submucosa through the muscularis propria.

* Adenomatous colonic polyps are benign neoplasms of the colonic mucosa that have the potential to progress to colonic adenocarcinoma. Familial adenomatous polyposis is a genetic condition in which patients develop thousands of colonic adenomatous polyps and have a virtually 100% chance of developing colon cancer by age 40 unless the affected colon is resected. Gardner syndrome is a variant of familial adenomatous polyposis with associated osteomas, fibromatosis, and epidermal inclusion cysts. Turcot syndrome is a rare variant of familial adenomatous polyposis associated with CNS gliomas. Hereditary nonpolyposis colorectal cancer has increased risks of colon, endometrial, and ovarian cancers, but it is not associated with multiple adenomatous polyps. Peutz-Jeghers syndrome has multiple hamartomatous polyps with increased risk of cancers of the lung, pancreas, breast, and uterus, but not colon.

* Colonic adenocarcinoma is the third most common cancer and a leading cause of cancer mortality in the United States. It tends to produce a polypoid mass when it involves the right side of the colon and a napkin ring lesion when it involves the left side. The Dukes system is used for staging colon cancer.

* Carcinoid tumors are neuroendocrine tumors that can involve the appendix and terminal ileum and may produce carcinoid syndrome with diarrhea, flushing, bronchospasms, fibrosis, and sometimes—carcinoid heart disease.
INFLAMMATION OF THE PANCREAS

1. Acute pancreatitis
   a. Definition: acute inflammation arising from injury to the exocrine portion of the pancreas
   b. Etiology
      i. Gallstones
      ii. Alcohol
      iii. Hypercalcemia
      iv. Drugs
      v. Shock
      vi. Infections
      vii. Trauma
      viii. Scorpion stings
   c. Mechanism: pancreatic acinar cell injury results in activation of pancreatic enzymes and enzymatic destruction of the pancreatic parenchyma
   d. Clinical presentation
      i. Stabbing epigastric abdominal pain radiating to the back
      ii. Shock
   e. Lab: elevation of serum amylase and lipase
   f. Gross
      i. Focal pancreatic hemorrhage and liquefaction
      ii. Chalky, white-yellow fat necrosis of adjacent adipose tissue
   g. Micro
      i. Liquefactive necrosis of pancreatic parenchyma
      ii. Acute inflammation
      iii. Enzymatic fat necrosis
      iv. Necrosis of blood vessels causes hemorrhage
   h. Complications
      i. May develop acute respiratory distress syndrome (ARDS) or disseminated intravascular coagulation (DIC)
      ii. Pseudocyst
      iii. Pancreatic calcifications
      iv. Hypocalcemia
   i. Prognosis: Severe cases have a 30% mortality rate
2. **Chronic pancreatitis**
   a. Definition: chronic inflammation, atrophy, and fibrosis of the pancreas secondary to repeated bouts of pancreatitis
   b. Middle-age male alcoholics
   c. Gross: firm, white, fibrotic pancreas
   d. Micro
      i. Extensive fibrosis and parenchymal atrophy
      ii. Chronic inflammation
   e. Presentation
      i. Abdominal pain
      ii. Pancreatic insufficiency and malabsorption
      iii. Pancreatic calcifications
      iv. Pseudocyst
      v. Secondary diabetes mellitus (late complication)

**Clinical Correlate**

Measurement of glycosylated hemoglobin (HbA1c) is an excellent measurement of long-term exposure to hyperglycemia.

**DIABETES MELLITUS**

1. Definition: chronic systemic disease characterized by insulin deficiency or peripheral resistance, resulting in hyperglycemia and nonenzymatic glycosylation of proteins
2. Diagnosis: fasting glucose >126 mg/dL on at least two separate occasions or a positive glucose tolerance test
3. **Insulin-dependent diabetes mellitus (IDDM)**
   a. Synonyms: type 1, juvenile onset diabetes, brittle diabetes
   b. Epidemiology
      i. Represents 10% of cases of diabetes
      ii. Affects children and adolescents usually younger than 20
   c. Risk factors
      i. Northern European ancestry
      ii. HLA-DR3, DR4, and DQ
   d. Pathogenesis
      i. Lack of insulin due to autoimmune destruction of β cells (type IV hypersensitivity reaction)
      ii. Absolutely dependent on insulin to prevent ketoacidosis and coma
   e. Etiology: thought to be caused by an autoimmune reaction triggered by an infection (Coxackie B virus) in a genetically susceptible individual
   f. Micro
      i. Lymphocytic inflammation of the islets of Langerhans (insulitis)
      ii. Loss of β cells
      iii. Fibrosis of the islets
   g. Presentation
      i. Polydipsia, polyuria, and polyphagia
      ii. Dehydration and electrolyte imbalance
      iii. Metabolic ketoacidosis
      iv. Coma and potentially death
   h. Treatment: insulin
4. **Non-insulin-dependent diabetes mellitus (NIDDM)**
   a. Synonyms: type 2, adult onset diabetes
   b. Epidemiology
      i. Represents 90% of cases of diabetes
      ii. Affects obese individuals both children and adults
      iii. Incidence increases with age.
      iv. Affects 10 million people in the United States (half are undiagnosed)
   c. Risk factors: obesity, increasing age, and genetic predisposition
   d. Pathogenesis
      i. Relatively reduced insulin secretion
      ii. *Peripher al insulin resistance*: reduced tissue sensitivity to insulin due to decreased numbers of insulin receptors on the cell membranes
   e. Micro
      i. Nonspecific changes
      ii. May have focal atrophy and amyloid deposition in islets (hyalinization)
   f. Presentation
      i. Frequently asymptomatic
      ii. Polydipsia, polyuria, and polyphagia
      iii. Hyperosmolar nonketotic diabetic coma
   g. Treatment
      i. Diet and weight loss
      ii. Oral antidiabetic drugs
      iii. Insulin

5. **Vascular pathology**
   a. Diabetes is a major risk factor for atherosclerosis
   b. Myocardial infarction (most common cause of death)
   c. Stroke (CVA)
   d. Peripheral vascular disease
      i. Atrophy of skin and loss of hair of lower extremities
      ii. Claudication
      iii. Nonhealing ulcers
      iv. Gangrene of lower extremities
   e. Microvascular disease
      i. Diffuse thickening of basement membranes
      ii. Hyaline arteriolosclerosis

6. **Diabetic nephropathy**
   a. Renal artery atherosclerosis
   b. Hyaline arteriolosclerosis of afferent and efferent arterioles
   c. Diffuse glomerulosclerosis
      i. Nephrotic syndrome
      ii. Increased mesangial matrix and mesangial proliferation
      iii. Thicknessed basement membranes

---

**Clinical Correlate**
Sulfonylureas enhance insulin secretion only in type 2 diabetes.
d. Nodular glomerulosclerosis (Kimmelstiel-Wilson disease)
   i. Nephrotic syndrome
   ii. Nodular PAS(+) deposits of mesangial matrix
   iii. Thickened basement membranes

Clinical Correlate
Diabetic nephropathy is the most common reason for renal transplantation in adults.

c. Pyelonephritis and necrotizing papillitis
f. Renal failure

7. Diabetic retinopathy
   a. Nonproliferative phase
      i. Microaneurysms
      ii. Retinal hemorrhages and exudates
   b. Proliferative phase: neovascularization
   c. Fibrosis phase: vitreous humor fibrosis and detachment of the retina
d. Increased rate of cataracts and glaucoma

8. Diabetic neuropathy
   a. Peripheral neuropathy
   b. Neurogenic bladder
   c. Sexual impotence

Figure 18-1. Nodular Glomerulosclerosis
PANCREATIC TUMORS

1. Islet cell tumors
   a. Insulinoma (β-cell tumor)
      i. Most common type of islet cell tumor
      ii. Tumor produces insulin
      iii. Hypoglycemia, sweating, hunger, confusion, insulin coma
      iv. Lab: elevated insulin and C-peptides
      v. Treatment: glucose

Table 18-1. Summary of Insulin-Related Pathophysiologic States

<table>
<thead>
<tr>
<th></th>
<th>Glucose</th>
<th>Insulin</th>
<th>C Peptide</th>
<th>Ketoacidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes</td>
<td>↑</td>
<td>↑, ↔</td>
<td>↑, ↔</td>
<td>—</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>+</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>—</td>
</tr>
<tr>
<td>Factitious hypoglycemia (self-injection of insulin)</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>—</td>
</tr>
</tbody>
</table>

b. Gastrinoma (G-cell tumor)
   i. Tumor produces gastrin
   ii. Zollinger-Ellison syndrome
      • Elevated serum gastrin
      • Gastric hyperacidity
      • Intractable peptic ulcers
   iii. May arise outside the pancreas
   iv. Associated with MEN I

c. Glucagonoma (α-cell tumor)
   i. Tumor produces glucagon
   ii. Hyperglycemia (diabetes), anemia, and skin rash

d. Somatostatinoma (S-cell tumor)
   i. Tumor produces somatostatin
   ii. Somatostatin inhibits
      • Insulin secretion → diabetes
      • Gastrin secretion → hypochlorhydria
      • Cholecystokinin secretion → gallstones and steatorrhea

e. VIPoma
   i. Tumor produces vasoactive intestinal peptide (VIP)
   ii. WDHA syndrome: watery diarrhea, hypokalemia, and achlorhydria

2. Pancreatic carcinoma
   a. Epidemiology
      i. Fifth most common cause of cancer death in the United States
      ii. Incidence is increasing.
Clinical Correlate

Trousseau Syndrome
Spontaneous venous thrombosis, which may resolve and recur in other areas (migratory thrombophlebitis), associated with a visceral malignancy due to the release of mucin from the tumor initiating the extrinsic pathway of coagulation.

Chapter Summary

* In acute hemorrhagic pancreatitis, pancreatic acinar cell injury results in activation of pancreatic enzymes and enzymatic destruction of the pancreatic parenchyma. Acute hemorrhagic pancreatitis can be seen in a variety of clinical settings, notably associated with gallstones or alcohol use. Chronic pancreatitis is a chronic inflammation of the pancreas with atrophy and fibrosis secondary to repeated bouts of pancreatitis.

* Diabetes mellitus is a chronic systemic disease characterized by insulin deficiency or peripheral resistance, resulting in hyperglycemia and non-enzymatic glycosylation of proteins.

* Insulin-dependent diabetes mellitus usually develops in children and adolescents and is related to lack of insulin secondary to autoimmune destruction of beta cells. Non-insulin-dependent diabetes mellitus is usually a disease of obese adults and is much more common than insulin-dependent diabetes mellitus.

* Both types of diabetes may lead to long-term complications including atherosclerosis, myocardial infarction, stroke, peripheral vascular disease, diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy.

* Pancreatic islet cell tumors may secrete insulin, gastrin, glucagon, somatostatin, or vasoactive intestinal peptide.

* Pancreatic carcinoma is the fifth most common cause of cancer death in the United States and has a very poor prognosis.
Gallbladder and Biliary Tract Pathology

GALLSTONES (CHOLELITHIASIS)

1. Cholesterol stones
   a. Composition: mostly cholesterol monohydrate
   b. Risk factors
      i. Female gender
      ii. Obesity
      iii. Pregnancy
      iv. Oral contraceptives and hormone replacement therapy (HRT)
      v. Incidence increases with age.
      vi. Genetics (Native American Pima and Navajo Indians)

2. Pigmented bilirubinate stones
   a. Composition: calcium salts and unconjugated bilirubin
   b. Risk factors
      i. Chronic hemolytic anemias
      ii. Cirrhosis
      iii. Bacteria
      iv. Parasites (Ascaris or Clonorchis [Opisthorchis] sinensis)

3. Clinical features of gallstones
   a. Presentation
      i. Frequently asymptomatic
      ii. Biliary colic: right upper quadrant pain due to impacted stones
   b. Diagnosis: ultrasound
   c. Complications
      i. Cholecystitis
      ii. Choledocholithiasis: calculi within the biliary tract
      iii. Biliary tract obstruction
      iv. Pancreatitis
      v. Cholangitis

Note
Formation of cholesterol stones involves the precipitation of cholesterol from supersaturated bile.
INFLAMMATORY CONDITIONS

1. Acute cholecystitis
   a. Definition: acute inflammation of the gallbladder, usually caused by cystic duct obstruction by gallstones
   b. Presentation
      i. Biliary colic
      ii. Right upper quadrant (RUQ) tenderness on palpation
      iii. Nausea and vomiting
      iv. Low-grade fever and leukocytosis
   c. Complications
      i. Gangrene of the gallbladder
      ii. Perforation and peritonitis
      iii. Fistula formation and gallstone ileus (small bowel obstruction by a large gallstone)

2. Chronic cholecystitis
   a. Definition: ongoing chronic inflammation of the gallbladder usually caused by gallstones
   b. Micro: chronic inflammation and Rokitansky-Aschoff sinuses
   c. Late complication: calcification of the gallbladder (“porcelain gallbladder”)

3. Ascending cholangitis
   a. Definition: bacterial infection of the bile ducts ascending up to the liver, usually associated with obstruction of bile flow
   b. Presentation: biliary colic, jaundice, high fever, and chills
   c. Organisms: gram-negative enteric bacteria

MISCELLANEOUS CONDITIONS

1. Cholesterolosis
   a. Definition: condition of accumulation of cholesterol-laden macrophages with the mucosa of the gallbladder wall
      i. Gross: yellow speckling of the red-tan mucosa (“strawberry gallbladder”)
      ii. Micro: collections of lipid-laden macrophages within the lamina propria

2. Hydrops of the gallbladder (mucocele): chronic obstruction of the cystic duct leads to the resorption of the normal gallbladder contents and enlargement of the gallbladder by the production of large amounts of clear fluid (hydrops) or mucous secretions (mucocele)

BILIARY TRACT CANCER

1. Gallbladder cancer
   a. Clinical presentation
      i. Frequently asymptomatic until late in the course
      ii. Cholecystitis
      iii. Enlarged palpable gallbladder
iv. Biliary tract obstruction (uncommon)
b. X-ray: may have a calcified “porcelain gallbladder”
c. Micro: adenocarcinoma
d. Prognosis: poor; 5-year survival ~1%

2. Bile duct cancer
   a. Bile duct carcinoma: carcinoma of the extrahepatic bile ducts
   b. Cholangiocarcinoma: carcinoma of the intrahepatic bile ducts
   c. Klatskin tumor: carcinoma of the bifurcation of the right and left hepatic bile ducts
   d. Risk factors
      i. Asia → Clonorchis (Opisthorchis) sinensis (liver fluke)
      ii. Primary sclerosing cholangitis
   e. Presentation: biliary tract obstruction
   f. Micro: adenocarcinoma arising from the bile duct epithelium
   g. Prognosis: poor

Chapter Summary

Gallstones can take the form of cholesterol stones or pigmented bilirubinate stones.

Cholesterol stones are composed of mostly cholesterol monohydrate and have as risk factors female gender, obesity, pregnancy, exogenous female hormones, increasing age, and genetics.

Pigmented bilirubinate stones are composed of calcium salts and unconjugated bilirubin and have as risk factors chronic hemolytic anemias, cirrhosis, bacteria, and parasites.

Gallstone disease is frequently asymptomatic, or may cause right upper quadrant pain due to impacted stones. Complications include cholecystitis, choledocholithiasis, biliary tract obstruction, and cholangitis.

Acute cholecystitis is an acute inflammation of the gallbladder that is usually caused by cystic duct obstruction by gallstones. Complications of acute cholecystitis include gangrene of the gallbladder, peritonitis, and gallstone ileus.

Chronic cholecystitis is ongoing chronic inflammation of the gallbladder that is usually caused by gallstones.

Ascending cholangitis is a bacterial infection of the bile ducts ascending up to the liver and is usually associated with obstruction of bile flow.

Cholesterosis is a clinically insignificant yellow-speckling of the gallbladder mucosa.

Hydrops of the gallbladder occurs when chronic obstruction of the cystic duct leads to the resorption of the normal gallbladder contents and enlargement of the gallbladder, with production of large amounts of clear fluid (hydrops) or mucous secretions (mucocoele).

Gallbladder cancer has a very poor prognosis because it is frequently asymptomatic until late in the course. Bile duct cancer also has a poor prognosis.
Liver Pathology

JAUNDICE

1. General
   a. Clinical jaundice occurs with bilirubin levels >2–3 mg/dL.
   b. Classic presentation: yellow skin (jaundice) and sclera (icterus)
   c. Causes of jaundice
      i. Overproduction of bilirubin
      ii. Defective hepatic bilirubin uptake
      iii. Defective conjugation
      iv. Defective excretion

Table 20-1. Unconjugated Versus Conjugated Bilirubinemia

<table>
<thead>
<tr>
<th>Unconjugated (Indirect) Bilirubinemia</th>
<th>Conjugated (Direct) Bilirubinemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased RBC turnover</td>
<td>Biliary tract obstruction</td>
</tr>
<tr>
<td>(hemolytic anemias)</td>
<td></td>
</tr>
<tr>
<td>Physiologic (newborn babies)</td>
<td>Biliary tract disease (PSC and PBC)</td>
</tr>
<tr>
<td>Hereditary (Gilbert and Crigler-Najjar syndromes)</td>
<td>Hereditary (Dubin-Johnson and Rotor syndromes)</td>
</tr>
<tr>
<td></td>
<td>Liver disease (cirrhosis and hepatitis)</td>
</tr>
</tbody>
</table>

2. Increased RBC turnover
   a. RBCs are the major source of bilirubin.
   b. Etiology
      i. Hemolytic anemia
      ii. Ineffective erythropoiesis (thalassemia, megaloblastic anemia, etc.)
   c. Lab: increased unconjugated bilirubin
   d. Chronic hemolytic anemia patients often develop pigmented bilirubinate gallstones.

3. Physiologic jaundice of the newborn
   a. Definition: transient unconjugated hyperbilirubinemia due to the immaturity of the liver
   b. Risk factors
      i. Prematurity
      ii. Hemolytic disease of the newborn (erythroblastosis fetalis)

Clinical Correlate

In infants, increased levels of unconjugated bilirubin (lipid-soluble) may cross the blood-brain barrier and deposit in the basal ganglia, causing irreversible brain damage (kernicterus).
c. Complication: kernicterus

d. Treatment: phototherapy

4. Hereditary hyperbilirubinemias
a. Gilbert syndrome
   i. Common benign inherited disorder
   ii. Unconjugated hyperbilirubinemia
   iii. Jaundice is related to stress (fasting, infection, etc.).
   iv. Mechanism: bilirubin glucuronosyltransferase (UGT) deficiency
   v. No clinical consequences

b. Crigler-Najjar syndrome
   i. Unconjugated hyperbilirubinemia
   ii. Type I: fatal because of kernicterus
   iii. Type II: jaundice
   iv. Mechanism: bilirubin glucuronosyltransferase (UGT) absence or deficiency

c. Dubin-Johnson syndrome
   i. Benign autosomal recessive disorder
   ii. Decreased bilirubin excretion due to a defect in the canalicular cationic transport protein
   iii. Conjugated hyperbilirubinemia
   iv. Gross: black pigmentation of the liver
   v. No clinical consequences

d. Rotor syndrome
   i. Autosomal recessive
   ii. Conjugated hyperbilirubinemia
   iii. Similar to Dubin-Johnson but without liver pigmentation
   iv. No clinical consequences

5. Biliary tract obstruction
a. Etiology
   i. Gallstones
   ii. Tumors (pancreatic, gallbladder, and bile duct)
   iii. Stricture
   iv. Parasites (liver flukes—_Clonorchis_ [Opisthorchis] sinensis)

b. Presentation
   i. Jaundice and icterus
   ii. Pruritus due to increased plasma levels of bile acids
   iii. Abdominal pain, fever, and chills
   iv. Dark urine (bilirubinuria)
   v. Pale clay-colored stools

c. Lab
   i. Elevated conjugated bilirubin
   ii. Elevated alkaline phosphatase and 5'-nucleotidase

6. Primary biliary cirrhosis (PBC)
   a. Definition: chronic liver disease of unknown etiology (autoimmune) characterized by inflammation and granulomatous destruction of intrahepatic bile ducts
b. Epidemiology: males:females = 1:10; age 30–65 years

c. Presentation
   i. Middle-aged women
   ii. Obstructive jaundice
   iii. Pruritus
   iv. Xanthomas, xanthelasmas, and elevated serum cholesterol
   v. Fatigue
   vi. Cirrhosis (late complication)

d. Lab
   i. Elevated conjugated bilirubin
   ii. Elevated alkaline phosphatase and 5'-nucleotidase
   iii. Antimitochondrial autoantibodies (AMA) are present in more than 90%

e. Most patients have another autoimmune disease (scleroderma, RA, or SLE)

f. Micro: lymphocytic and granulomatous destruction of interlobular bile ducts

7. Primary sclerosing cholangitis (PSC)

   a. Definition: chronic liver disease of unknown etiology characterized by segmental inflammation and fibrosing destruction of intrahepatic and extrahepatic bile ducts

   b. Epidemiology
      i. Males:females = 2:1, age 20–40 years
      ii. Majority are associated with ulcerative colitis

   c. Presentation: similar to PBC

   d. Micro
      i. Periductal chronic inflammation
      ii. Concentric fibrosis around bile ducts
      iii. Segmental stenosis of bile ducts

   e. Cholangiogram: “beaded appearance” of bile ducts

   f. Complications: biliary cirrhosis and cholangiocarcinoma

**CIRRHOSIS**

1. Definition: end-stage liver disease characterized by disruption of the liver architecture by bands of fibrosis that divide the liver into nodules of regenerating liver parenchyma

2. Etiology
   a. Alcohol
   b. Viral hepatitis
   c. Biliary tract disease
   d. Hemochromatosis
   e. Cryptogenic/idiopathic
   f. Wilson disease
   g. α1-antitrypsin deficiency

3. Gross
   a. Micronodular: nodules <3 mm
   b. Macronodular: nodules >3 mm
   c. Mixed micronodular and macronodular
d. At the end stage, most diseases result in a mixed pattern, and the etiology may not be distinguished based on the appearance.

4. Mechanism: fibrosis is produced by the Ito cell (hepatic stellate cells)

5. Consequences
   a. Portal hypertension
      i. Ascites
      ii. Splenomegaly/hypersplenism
      iii. Esophageal varices
      iv. Hemorrhoids
      v. Caput medusae
   b. Decreased detoxification
      i. Hepatic encephalopathy
      ii. Spider angiomas
      iii. Palmar erythema
      iv. Gynecomastia
   c. Decreased synthesis
      i. Hypoalbuminemia
      ii. Decreased clotting factors
   d. Hepatorenal syndrome

**VIRAL HEPATITIS**

1. Hepatitis viruses
   a. Clinical presentation
      i. Asymptomatic
      ii. Malaise and weakness
      iii. Nausea and anorexia
      iv. Jaundice
      v. Urine may be dark.
   b. Lab: markedly elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST)
   c. Diagnosis: serology

2. Acute viral hepatitis
   a. Definition: signs and symptoms <6 months
   b. Caused by any of the hepatitis viruses
   c. Micro
      i. Lobular disarray
      ii. Hepatocyte swelling (balloon cells)
      iii. Apoptotic hepatocytes (Councilman bodies)
      iv. Lymphocytes in portal tracts and in the lobule
      v. Hepatocyte regeneration
      vi. Cholestasis

**Clinical Correlate**

The prothrombin time (PT), not the partial thromboplastin time (P TT), is used to assess the coagulopathy due to liver disease.

**Clinical Correlate**

Viruses Other Than the Hepatitis Viruses That May Infect the Liver

- Epstein-Barr virus (EBV)—infectious mononucleosis
- Cytomegalovirus (CMV)
- Herpes
- Yellow fever
3. Chronic viral hepatitis
   a. Definition: signs and symptoms >6 months
   b. Caused by hepatitis viruses B, C, and D
   c. Micro
      i. Chronic persistent hepatitis: inflammation confined to portal tracts.
      ii. Chronic active hepatitis: Inflammation spills into the parenchyma, causing an interface hepatitis (piecemeal necrosis of limiting plate).
      iii. Hepatitis B often has "ground glass" hepatocytes (cytoplasmic HBsAg).

Table 20-2. The Hepatitis Viruses

<table>
<thead>
<tr>
<th>Common Virus Name</th>
<th>Hepatitis A (HAV)</th>
<th>Hepatitis B (HBV)</th>
<th>Hepatitis C (HCV)</th>
<th>Hepatitis D (HDV)</th>
<th>Hepatitis E (HEV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common disease name</td>
<td>&quot;Infectious&quot;</td>
<td>&quot;Serum&quot;</td>
<td>&quot;Post-transfusion&quot; or &quot;non-A, non-B&quot;</td>
<td>&quot;Delta&quot;</td>
<td>&quot;Enteric&quot;</td>
</tr>
<tr>
<td>Virus</td>
<td>Picornavirus naked capsid RNA</td>
<td>Hepadnavirus enveloped DNA</td>
<td>Flavivirus enveloped RNA</td>
<td>Defective enveloped circular RNA</td>
<td>Calicivirus naked capsid RNA</td>
</tr>
<tr>
<td>Transmission</td>
<td>Fecal-oral</td>
<td>Parenteral, sexual</td>
<td>Parenteral, sexual</td>
<td>Parenteral, sexual</td>
<td>Fecal-oral</td>
</tr>
<tr>
<td>Severity</td>
<td>Mild</td>
<td>Occasionally severe</td>
<td>Usually subclinical</td>
<td>Co-infection with HBV occasionally severe; super-infection with HBV often severe</td>
<td>Normal patients: mild; pregnant patients: severe</td>
</tr>
<tr>
<td>Chronicity or carrier state</td>
<td>No</td>
<td>Yes</td>
<td>Yes (high)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Clinical diseases</td>
<td>Acute hepatitis</td>
<td>• Acute hepatitis • Chronic hepatitis • Cirrhosis • Hepatocellular carcinoma (HCC)</td>
<td>• Acute hepatitis • Chronic hepatitis • Cirrhosis • HCC</td>
<td>• Acute hepatitis • Chronic hepatitis • Cirrhosis • HCC</td>
<td>Acute hepatitis</td>
</tr>
<tr>
<td>Laboratory diagnosis</td>
<td>Symptoms and anti-HAV IgM</td>
<td>Symptoms and serum levels of HBsAg, HBeAg, and anti-HBc IgM</td>
<td>Symptoms and anti-HCV ELISA</td>
<td>Anti-HDV ELISA</td>
<td></td>
</tr>
<tr>
<td>Prevention</td>
<td>Vaccine, hygiene</td>
<td>Vaccine</td>
<td></td>
<td></td>
<td>Hygiene</td>
</tr>
</tbody>
</table>
Table 20-3. Hepatitis B Terminology and Markers

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Name and Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>Hepatitis B virus, a hepatnavirus (enveloped, partially double-stranded DNA virus); Dane particle = infectious HBV</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Antigen found on surface of HBV; also found on spheres and filaments in patient’s blood; positive during acute disease; continued presence indicates carrier state</td>
</tr>
<tr>
<td>HBsAb</td>
<td>Antibody to HBsAg; provides immunity to hepatitis B</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Antigen associated with core of HBV</td>
</tr>
<tr>
<td>HBeAb</td>
<td>Antibody to HBeAg; positive during window phase; IgM HBeAb is an indicator of recent disease</td>
</tr>
<tr>
<td>HBeAg</td>
<td>A second, different allergenic determinant on the HBV core; important indicator of transmissibility</td>
</tr>
<tr>
<td>HBeAb</td>
<td>Antibody to e antigen; indicates low transmissibility</td>
</tr>
<tr>
<td>Delta agent</td>
<td>Small RNA virus with HBsAg envelope; defective virus that replicates only in HBV-infected cells</td>
</tr>
</tbody>
</table>

Table 20-4. Hepatitis A Serology

<table>
<thead>
<tr>
<th>Acute or recent infection</th>
<th>anti-HAV IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior infection or immunization</td>
<td>anti-HAV IgG</td>
</tr>
</tbody>
</table>

Table 20-5. Hepatitis B Serology

<table>
<thead>
<tr>
<th></th>
<th>HBsAg</th>
<th>HBeAg*</th>
<th>HBeAb IgM</th>
<th>HBeAb IgG</th>
<th>HBsAb IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute infection</td>
<td>+</td>
<td></td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Window period</td>
<td>-</td>
<td></td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Prior infection</td>
<td>-</td>
<td></td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Immunization</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

*HBeAg—Correlates with viral proliferation and infectivity.

AMEBIC LIVER ABSCESSES

1. Rare in the United States except for recent immigrants from Mexico, South America, India, etc.
2. Organism: Entamoeba histolytica
3. Gross: necrotic abscess filled with brown pastelike material ("anchovy paste")
4. Treatment: antibiotics ± surgical drainage
ALCOHOLIC LIVER DISEASE

1. Fatty change (steatosis)
   a. Reversible with abstinence
   b. Gross: enlarged, yellow, greasy liver
   c. Micro
      i. Centrilobular macrovesicular steatosis (reversible)
      ii. Eventual fibrosis around the central vein (irreversible)

2. Alcoholic hepatitis
   a. Acute illness usually following a heavy drinking binge
   b. Clinically variable
      i. No symptoms
      ii. RUQ pain, hepatomegaly, jaundice, malaise, and anorexia
      iii. Fulminant liver failure
   c. Micro
      i. Hepatocyte swelling (ballooning) and necrosis
      ii. Mallory bodies (cytokeratin intermediate filaments)
      iii. Neutrophils
      iv. Fatty change
      v. Eventual fibrosis around the central vein
   d. Prognosis
      i. Each episode has a 20% risk of death.
      ii. Repeated episodes increase the risk of developing cirrhosis.

3. Alcoholic cirrhosis
   a. Develops in 15% of alcoholics
   b. Micronodular cirrhosis
   c. Most common disease requiring liver transplantation in adults

---

Figure 20-1. Alcoholic Cirrhosis, Liver

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METABOLIC LIVER DISEASE

1. Wilson disease (hepatolenticular degeneration)
   a. Definition: genetic disorder of copper metabolism resulting in accumulation of toxic levels of copper in various organs
   b. Genetics
      i. Autosomal recessive (chromosome 13)
      ii. WD gene (ATP7B) codes for a hepatocyte canalicular copper-transporting ATPase
   c. Mechanism: decreased biliary excretion of copper
   d. Presents in childhood or adolescence with liver disease
   e. Distribution of disease
      i. Liver: fatty change, chronic hepatitis, and micronodular cirrhosis
      ii. Cornea: Kayser-Fleischer rings (copper deposition in Descemet membrane)
      iii. Brain: neurological and psychiatric manifestations, movement disorder
   f. Diagnosis
      i. Decreased serum ceruloplasmin levels
      ii. Increased tissue copper levels (liver biopsy)
      iii. Increased urinary copper excretion
   g. Treatment
      i. Copper chelators (D-penicillamine)
      ii. Liver transplantation is curative.

2. Hemochromatosis
   a. Definition: increased levels of iron, leading to tissue injury
   b. Hereditary (primary)
      i. Recessive disorder (HFE gene on chromosome 6p)
      ii. The most common mutation of the HFE gene is the C282Y mutation.
      iii. Mechanism: increased small-intestine absorption of iron
   c. Secondary (example: transfusions for chronic anemias)
   d. Epidemiology
      i. Males:females = 5:1
      ii. Common in people of Northern European descent
   e. Distribution of disease
      i. Liver: micronodular cirrhosis and HCC (200 times the normal risk ratio [RR])
      ii. Pancreas: secondary diabetes mellitus
      iii. Skin: hyperpigmentation ("bronzing")
      iv. Heart: congestive heart failure and cardiac arrhythmias
      v. Gonads: hypogonadism
   f. Diagnosis
      i. Markedly elevated serum iron and ferritin
      ii. Prussian blue stain and increased tissue iron levels (liver biopsy)
   g. Treatment: phlebotomy

3. α1-Antitrypsin deficiency
   a. Definition: autosomal recessive disorder characterized by production of defective α1-antitrypsin (α1-AT), which accumulates in hepatocytes and causes liver damage and low serum levels of α1-AT
b. Genetics
   i. α1-AT is produced by the Pi gene (chromosome 14)
   ii. More than 75 gene variants described
       • PiM: the normal, most common form (90%)
       • Most other variants also produce normal α1-AT levels.
       • PiS deficiency variant: mildly reduced levels
       • PiZ deficiency variant: markedly reduced levels
   iii. Homozygous PiZZ have severe reductions (15% of normal) in enzyme levels.

c. Distribution of disease
   i. Liver: micronodular cirrhosis and an increased risk of HCC
   ii. Lungs: panacinar emphysema

d. Micro: PAS positive, eosinophilic cytoplasmic globules within hepatocytes

e. Treatment
   i. Prevention of emphysema: no smoking!
   ii. Liver transplantation is curative.

4. Reye syndrome
   a. Rare, potentially fatal disease
   b. Occurs in young children with viral illness (varicella or influenza) treated with aspirin
   c. Mechanism: unknown; mitochondrial injury and dysfunction play an important role
   d. Distribution of disease
      i. Liver: fatty change (microvesicular steatosis)
      ii. Brain: cerebral edema/encephalopathy
   e. Prognosis
      i. Complete recovery (75%)
      ii. Coma, permanent neurologic deficits, and death
   f. Treatment: supportive

Figure 20-2. Reye Syndrome
5. Nonalcoholic fatty liver disease  
   a. Definition: a disease of lipids accumulating in hepatocytes that is not associated with heavy alcohol use  
   b. Occurs equally in men and women  
   c. Strongly associated with obesity, hyperinsulinemia, insulin resistance, and type 2 diabetes mellitus  
   d. Pathogenesis: lipid accumulation in hepatocytes that can progress to steatohepatitis (NASH—nonalcoholic steatohepatitis) and finally cirrhosis  
   e. Diagnosis of exclusion

HEMODYNAMIC LIVER DISEASES

1. Budd-Chiari syndrome (hepatic vein thrombosis)  
   a. Definition: occlusion of the hepatic vein by a thrombus, often resulting in death.  
   b. Etiology  
      i. Polycythemia vera  
      ii. Pregnancy  
      iii. Oral contraceptives  
      iv. Paroxysmal nocturnal hemoglobinuria  
      v. Hepatocellular carcinoma  
      vi. Idiopathic  
   c. Clinical: abdominal pain, hepatomegaly, ascites, and death  
   d. Micro: centrilobular congestion and necrosis

2. Chronic passive congestion of the liver  
   a. Definition: "backup of blood" into the liver, usually due to right-sided heart failure  
   b. Gross: nutmeg pattern of alternating dark (congested central areas) and light (portal tract areas) liver parenchyma  
   c. Micro: centrilobular congestion  
   d. Complications  
      i. Centrilobular necrosis: ischemic necrosis of centrilobular hepatocytes  
      ii. Long-standing congestion $\rightarrow$ centrilobular fibrosis $\rightarrow$ cardiac cirrhosis (sclerosis)

LIVER TUMORS

1. Hemangioma  
   a. Most common primary tumor of the liver  
   b. Benign vascular tumor  
   c. Gross: subcapsular, red, spongy mass  
   d. Often asymptomatic and detected incidentally

2. Hepatic adenoma (liver cell adenoma)  
   a. Young women  
   b. Related to oral contraceptive use  
   c. Subcapsular adenomas may rupture, causing an intraperitoneal hemorrhage  
   d. Micro: resembles normal liver except for the lack of portal tracts  
   e. May regress after oral contraceptives are discontinued
3. **Hepatocellular carcinoma (HCC)**
   a. Most common primary malignant tumor of the liver in adults
   b. Asia and Japan > United States
   c. Etiology: cirrhosis, hepatitis B and C viruses, alcohol, aflatoxin B1
   d. Tendency for hematogenous spread and invasion of portal and hepatic veins
   e. Tumor marker: α-fetoprotein (AFP)
   f. Fibrolamellar variant: younger age, fibrous bands, and better prognosis

4. **Metastatic tumors to the liver**
   a. Most common tumor found within the liver
   b. Common primary sites: colon, breast, and lung
   c. Tend to occur as multiple well-circumscribed masses

**Chapter Summary**

- Jaundice produces yellow skin and sclera and occurs with bilirubin levels >2-3 mg/dl.
- Increased red blood cell turnover, due to either hemolytic anemia or ineffective erythropoiesis, causes an unconjugated hyperbilirubinemia and may predispose for pigmented bilirubinate gallstones.
- Physiologic jaundice of the newborn is a transient unconjugated hyperbilirubinemia due to the immaturity of the liver.
- Gilbert syndrome and Crigler-Najjar syndrome are inherited causes of unconjugated hyperbilirubinemia due to bilirubin glucuronosyltransferase deficiency or absence. Gilbert disease is completely benign. Type I Crigler-Najjar syndrome is fatal in infancy secondary to kernicterus and type II Crigler-Najjar syndrome causes jaundice.
- Dubin-Johnson syndrome is a benign autosomal recessive disorder that causes conjugated hyperbilirubinemia secondary to decreased bilirubin excretion due to a defect in the canalicular transport protein. A distinctive feature of Dubin-Johnson syndrome is black pigmentation of the liver.Rotor syndrome is similar to Dubin-Johnson syndrome but does not have the liver pigmentation.
- Biliary tract obstruction can be due to gallstones, tumors, stricture, or parasite, and can present with jaundice, pruritus, abdominal pain, bilirubinuria, and pale stools.
- Primary biliary cirrhosis is a chronic liver disease of probable autoimmune etiology that is characterized by inflammation and granulomatous destruction of intrahepatic bile ducts.
- Primary sclerosing cholangitis is a chronic liver disease of unknown etiology characterized by segmental inflammation and fibrosing destruction of intrahepatic bile ducts.
- Cirrhosis is an end-stage liver disease due to many etiologies characterized by disruption of the liver architecture by bands of fibrosis that divide the liver into nodules of regenerating liver parenchyma. Complications of cirrhosis include portal hypertension, ascites, hypersplenism, esophageal varices, hemorhoids, caput medusae, hepatic encephalopathy, spider angioma, palmar erythema, gynecomasia, hypoalbuminemia, decreased clotting factors, and hepatorenal syndrome.

(Continued)
Chapter Summary (continued)

* Acute viral hepatitis can be due to any of the hepatitis viruses. Chronic viral hepatitis can be caused by hepatitis viruses B, C, and D. Hepatitis viruses vary in the nature of the virus and the manner in which they are spread. Hepatitis A virus is spread by the fecal-oral route and usually causes mild acute hepatitis. Hepatitis B virus is spread parenterally and by sexual contact and may cause acute hepatitis, chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Hepatitis C is spread by the parenteral and sexual routes and may cause acute hepatitis, chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Hepatitis D is a defective virus that requires hepatitis B as a coinfection or superinfection to produce severe disease, which may take the form of acute hepatitis, chronic hepatitis, or cirrhosis. Hepatitis E virus is spread by the fecal-oral route and causes acute hepatitis that may be severe in infected pregnant women.

* Amoebic liver abscess is due to infection with Entamoeba histolytica and requires antibiotics and surgical drainage for therapy.

* Alcoholic liver disease can produce steatosis, alcoholic hepatitis, or alcoholic cirrhosis.

* Wilson disease is a genetic disorder of copper metabolism resulting in accumulation of toxic levels of copper leading to liver disease, Kayser-Fleischer corneal rings, and neurologic and psychiatric manifestations.

* Hemochromatosis is characterized by increased levels of iron that can deposit into tissues, leading to cirrhosis, hepatocellular carcinoma, diabetes mellitus, bronze skin, congestive heart failure, cardiac arrhythmias, and hypogonadism.

* Alpha-1-antitrypsin deficiency is an autosomal recessive disorder characterized by production of defective alpha-1-antitrypsin, which accumulates in hepatocytes and causes liver damage and low serum levels of alpha-1-antitrypsin.

* Reye syndrome is a potentially fatal disease that occurs in young children with viral illnesses treated with aspirin. It can cause liver steatosis and cerebral edema.

* Nonalcoholic fatty liver disease is highly associated with obesity and type 2 diabetes mellitus leading to hepatic lipid accumulation, nonsteatosishepatitis, and can progress to cirrhosis in 10-30% of patients.

* Budd-Chiari syndrome is occlusion of the hepatic vein by a thrombus, often resulting in death.

* Chronic passive congestion of the liver is a "backup of blood" into the liver, usually due to right-sided heart failure, and may, in long-standing cases, lead to cirrhosis (sclerosis).

* Benign tumors of the liver include hemangiomas and hepatic adenomas. Malignant tumors include hepatocellular carcinoma, cholangiocarcinoma, angiosarcoma, and metastatic tumors.
Central Nervous System Pathology

INFECTIONS

1. Acute meningitis
   a. Acute aseptic (viral) meningitis
      i. Leptomeningeal inflammation due to viruses (enterovirus most frequent)
      ii. Lymphocytic infiltration of leptomeninges and superficial cortex
      iii. Fever, signs of meningeal irritation, depressed consciousness
      iv. Low mortality
   b. Acute purulent meningitis
      i. Purulent leptomeningeal inflammation due to bacteria
         • Neonates: group B streptococci, Escherichia coli
         • Infants and children: Haemophilus influenzae
         • Adolescents and young adults: Neisseria meningitidis
         • Elderly: Streptococcus pneumoniae and Listeria monocytogenes
      ii. Neutrophilic infiltration of the leptomeninges, extending variably to cortex
      iii. Opaque leptomeninges
      iv. Diffuse cerebral edema: risk of fatal herniations
      v. Headache, fever, nuchal rigidity, cloudy sensorium, coma, and death
      vi. Sequelae due to organization of purulent exudate and fibrosis
         • Hydrocephalus
         • Cranial nerve impairment (neural deafness)

2. Mycobacterial meningoencephalitis
   a. Can be caused by Mycobacterium tuberculosis or atypical mycobacteria
   b. Usually involves the basal surface of the brain
   c. Characteristic tuberculomas within the brain and dura mater
   d. Frequent in AIDS patients, particularly by Mycobacterium avium-intracellulare (MAI)
Table 21-1. CSF Parameters in Different Forms of Meningitis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cells/µL</th>
<th>Glucose (µg/dL)</th>
<th>Proteins (mg/dL)</th>
<th>Pressure (mm H₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal values</td>
<td>&lt;5 lymphocytes</td>
<td>45–85 (50–70%</td>
<td>15–45</td>
<td>70–180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>glycemia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purulent (bacterial)</td>
<td>Up to 90,000</td>
<td>Decreased (&lt;45)</td>
<td>Increased (&gt;50)</td>
<td>Markedly elevated</td>
</tr>
<tr>
<td>neutrophils</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Aseptic (viral)</td>
<td>100–1,000 most</td>
<td>Normal</td>
<td>Increased (&gt;50)</td>
<td>Slightly elevated</td>
</tr>
<tr>
<td>lymphocytes</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Granulomatous (mycobacterial/fungal)</td>
<td>100–1,000 most</td>
<td>Decreased (&lt;45)</td>
<td>Increased (&gt;50)</td>
<td>Moderately elevated</td>
</tr>
<tr>
<td>lymphocytes</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

3. Viral encephalitides
   a. Common features: perivascular cuffs, microglial nodules, neuron loss, and neurophagia
   b. Clinical manifestations: variable (mental status change, fever, and headache, often progressing to coma)
   c. Specific forms
      i. *Arthropod-borne*: St. Louis, California, Eastern and Western equine, Venezuelan encephalitides
      ii. *Herpes simplex type 1*: characteristic hemorrhagic necrosis of temporal lobes
      iii. *Rabies*: characteristic Negri bodies in hippocampal and Purkinje neurons
      iv. *HIV*
         • Cerebral involvement is frequent and leads to AIDS-dementia complex.
         • Dementia and other neurological abnormalities
         • Histopathology: microglial nodules and diagnostic multinucleated giant cells
         • Spinal involvement leads to *vasculopathy*: similar to vitamin B₁₂ deficiency–associated subacute combined degeneration
   v. *Progressive multifocal leukoencephalopathy* (PML)
      • Related to *JC virus* (a polyomavirus)
      • JC virus causes PML in immunocompromised patients (especially AIDS)
      • Histopathology: demyelination, lymphohistiocytic, and astrogliosis
      • Astrocytes acquire bizarre shapes.
      • Oligodendrocytes in active lesions contain viral intranuclear inclusions.

4. Fungal meningoencephalitides
   a. *Candida, Aspergillus, Cryptococcus,* and *Mucor* species most frequent agents
   b. *Aspergillus and Mucor* have a marked tropism for blood vessels: *vasculitis, rupture* of blood vessels, and hemorrhage
   c. *Cryptococcus* causes diffuse meningoencephalitis: invasion of the brain through Virchow-Robin space—continuation of the subarachnoid space around blood vessels entering the neuropil, and *soap bubble lesions*

5. Toxoplasmosis
   a. Frequent in AIDS patients
   b. Cerebral abscess with central necrosis and chronic inflammation
   c. MRI/CT scan: characteristic *ring-enhancing lesion*
6. Cerebral abscess
   a. Hematogenous dissemination or direct spread from contiguous foci
   b. Predisposing conditions
      i. Acute bacterial endocarditis, cyanotic heart disease (right-to-left shunt), and chronic pulmonary abscesses
      ii. Mastoiditis, paranasal sinusitis, acute otitis, open fracture, previous neurosurgery
   c. CT/MRI appearance: ring-enhancing lesion
   d. Clinical manifestations
      i. Signs of increased intracranial pressure (headache, vomiting, and papilledema)
      ii. Focal neurological deficits (vary depending on site of lesion)

7. Subacute sclerosing panencephalitis
   a. Rare complication of measles (rubeola) virus infection
   b. Persistent immune-resistant measles virus causes a slow-virus encephalitis
   c. Typical scenario is a child who had measles before age 2 and then 6 to 15 years later develops progressive mental deterioration with seizures.
   d. May be fatal in 1 to 2 years once it develops

8. Creutzfeldt-Jakob disease (CJD)
   a. Definition: the most common human transmissible spongiform encephalopathy due to a prion (a protein with the capacity to be an infectious agent) that can change the conformation of normal prion protein(s), leading to rapidly progressive dementia, memory loss, personality changes, and hallucinations
   b. Caused by a prion protein (PrP)
      i. PrP is a 30-kD protein normally present in neurons.
      ii. Encoded by a single-exon gene on chromosome 20
      iii. Its normal conformation is an α-helix: PrP\(^{\alpha}\).
      iv. In disease states, PrP\(^{\alpha}\) changes to a β-pleated sheet conformation: PrP\(^{\beta}\).
      v. Low spontaneous change results in sporadic cases of CJD.
      vi. Mutations of PrP result in hereditary cases of CJD
      vii. PrP\(^{\beta}\) facilitates conformational change of other PrP\(^{\alpha}\) molecules into PrP\(^{\beta}\).
      viii. PrP\(^{\beta}\) is responsible for cerebral pathologic changes.
   c. Results in spongiform change
      i. Fine vacuolization of the neuropil in the gray matter (especially cortex)
      ii. Due to large membrane-bound vacuoles within neuronal processes
      iii. Associated with neuronal loss and astrogliosis
      iv. Kuru plaques are deposits of amyloid of altered PrP protein.
   d. What are the clinical manifestations of spongiform encephalopathies?
      i. CJD: 85% cases are sporadic; 15% are familial.
      ii. Middle-age to elderly patients
      iii. Rapidly progressive dementia
      iv. Memory loss with startle myoclonus or other involuntary movements
      v. Typical EEG changes
      vi. Death within 6–12 months
Table 21-2. Prion Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Infectious Agent</th>
<th>Host</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuru</td>
<td>Prion</td>
<td>Human</td>
<td>Subacute spongiform encephalopathy (SSE); Fore Tribe in New Guinea; consuming infected brains</td>
</tr>
<tr>
<td>Creutzfeldt-Jakob disease</td>
<td>Prion</td>
<td>Human</td>
<td>SSE; Genetic predisposition</td>
</tr>
<tr>
<td>Gerstmann-Straussler</td>
<td>Prion</td>
<td>Human</td>
<td>SSE</td>
</tr>
<tr>
<td>Fatal familial insomnia</td>
<td>Prion</td>
<td>Human</td>
<td>SSE</td>
</tr>
<tr>
<td>Scrapie</td>
<td>Prion</td>
<td>Sheep</td>
<td>SSE—scraping their wool off on fences</td>
</tr>
</tbody>
</table>

Bridge to Anatomy

The brain is highly dependent on a constant supply of oxygen and glucose from the cerebral arteries, which have collateral blood flow at the circle of Willis.

CEREBROVASCULAR DISEASE

1. Etiology
   a. Third most frequent cause of death in industrialized countries
   b. Leading cause of serious disability in the United States
   c. Risk factors similar to coronary artery disease

2. Clinicopathological forms
   a. Global cerebral ischemia (diffuse ischemic encephalopathy)
      i. Fall in blood flow to the brain (shock, cardiac arrest, and hypotensive episodes)
      ii. Damage to regions of selective vulnerability: Purkinje neurons, hippocampus CA1 (Sommer sector), and pyramidal neurons of cortex
      iii. Infarcts in watershed areas
      iv. Cortical laminar necrosis
          • Diffuse ischemic necrosis of neocortex
          • May lead to brain death
   b. Transient ischemic attack (TIA): reversible, symptoms last less than 24 h; due to small platelet thrombi or atheroemboli
   c. Stroke
      i. Infarction (85% of all stroke cases)
      ii. Hemorrhage (15% of all stroke cases)
   d. Infarction
      i. Infarction causes 85% of all stroke cases.
      ii. Thrombotic occlusion
          • Due to atherosclerosis of the cerebral arteries
          • Leads to anemic (white) infarct
      iii. Embolic occlusion
          • Often due to thromboemboli from cardiac chambers
          • Less frequently due to atheroemboli
          • Leads to hemorrhagic infarct
      iv. Small-vessel disease
          • Related to hypertension, resulting in hyaline arteriolosclerosis
          • Leads to lacunar infarcts or lacunae
      v. Pathology (i.e., morphological features of brain infarcts)
<table>
<thead>
<tr>
<th>Time</th>
<th>Gross Changes</th>
<th>Microscopic Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–12 h</td>
<td>No changes</td>
<td>Minimal or no changes</td>
</tr>
<tr>
<td>12–24 h</td>
<td>Minimal changes</td>
<td>Red (hypereosinophilic) neurons with pyknotic nuclei</td>
</tr>
<tr>
<td>24–48 h</td>
<td>Indistinct gray-white matter junction</td>
<td>Neutrophilic infiltration</td>
</tr>
<tr>
<td>2–10 d</td>
<td>Friable tissue with marked edema</td>
<td>Histiocytic infiltration; neurons disappear</td>
</tr>
<tr>
<td>2–3 wk</td>
<td>Tissue liquefies</td>
<td>Liquefactive necrosis; histiocytes filled with products of myelin breakdown</td>
</tr>
<tr>
<td>3 wk–mo</td>
<td>Fluid-filled cavity demarcated by gliotic scar</td>
<td>Fluid-filled cavity; reactive astrocytes and lipid-laden macrophages</td>
</tr>
<tr>
<td>Years</td>
<td>Old cyst surrounded by gliotic scar</td>
<td>Astrogliosis surrounding a cyst</td>
</tr>
</tbody>
</table>

*Note: Hemorrhagic infarct leads to erythrocyte degradation and hemosiderin deposition.*

vi. Clinical manifestations depend on affected arterial distribution.

c. Hemorrhage
   i. Causes 15% of strokes
   ii. *Intracerebral* (intraparenchymal) hemorrhage
      - Hypertension: most frequent predisposing condition; involves basal ganglia, cerebellum, pons, and centrum semiovale
      - Other causes: vascular malformations, especially *arteriovenous malformations* (AVMs), cerebral amyloid angiopathy, neoplasms, vasculitides, abnormal hemostasis, hematological malignancies, infections, and diabetes mellitus
      - Symptoms: severe headache, frequent nausea/vomiting, steady progression of symptoms over 15–20 minutes, and coma
iii. **Epidural hemorrhage**  
- Virtually always traumatic  
- Usually associated with skull fracture  
- Tear of dural arteries, most frequently *middle meningeal artery*  
- Leads to cerebral herniation (usually subfalcine) if not promptly evacuated  
- Lucid interval before loss of consciousness ("*talk and die syndrome*")

![Epidural Hematoma](commons.wikimedia.org)  
*Figure 21-1. Epidural Hematoma*

iv. **Subdural hemorrhage**  
- Usually traumatic in older individuals  
- Caused by rupture of *bridging veins* (from cerebral convexities to sagittal sinus)  
- Predisposing conditions: brain atrophy (due to simply aging) and abnormal hemostasis  
- Headache, drowsiness, focal neurological deficits, sometimes dementia  
- Recurs frequently

![Subdural Hematoma](commons.wikimedia.org)  
*Figure 21-2. Subdural Hematoma*
v. **Subarachnoid hemorrhage**
   - Most frequent cause: ruptured berry aneurysm
   - Less frequent causes: extension of an intracerebral or subdural hematoma, vascular malformations, trauma, abnormal hemostasis, and tumors
   - Sudden ("*thunderclap*") headache, nuchal rigidity, neurological deficits on one side, and stupor

f. **Berry aneurysms**
   i. Definition: thin-walled saccular outpouchings, consisting of intima and adventitia only
   ii. Most frequent cause of subarachnoid hemorrhage
   iii. Most frequent sites: anterior circle of Willis at branching points
   iv. Pathogenesis: congenital focal weakness of artery; not identifiable at birth
   v. Associated disorders: Marfan syndrome, Ehlers-Danlos type 4, and adult polycystic kidney disease
   vi. Hypertension and cigarette smoking predispose to formation
   vii. Rupture is precipitated by sudden increase in blood pressure.
   viii. Prognosis after rupture: 1/3 die, 1/3 recover, and 1/3 rebleed

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**CNS TRAUMA**

1. Cranial cavity and brain
   a. **Concussion**
      i. Definition: mild traumatic brain injury with a transient loss of brain function
      ii. Change in the momentum of the head (impact against a rigid surface)
      iii. Loss of consciousness and reflexes, temporary respiratory arrest, and amnesia for the event
      iv. Pathogenesis uncertain
      v. Parenchymal injuries may or may not be evident at autopsy.

   b. **Contusions**
      i. Definition: a bruise of the brain tissue
      ii. Sites of injury: crests of orbital gyri in frontal and temporal poles
      iii. *Coup* (site of injury) and *contre-coup* (site diametrically opposite)
      iv. Coup and contre-coup develop when the head is mobile at the time of impact
      v. *Acute*: hemorrhage of brain tissue in a wedge-shaped area
      vi. *Subacute*: necrosis and liquefaction of brain
      vii. *Remote*: depressed area of cortex with yellow discoloration ("*plaque jaune*")

   c. **Diffuse axonal injury**
      i. Definition: damage to axons at nodes of Ranvier with impairment of axoplasmic flow
      ii. *Histopathology*: axonal swellings appreciable in the white matter
      iii. It is *diffuse*, but predilection for
         - Corpus callosum, periventricular white matter, and hippocampus
         - Cerebral and cerebellar peduncles
      iv. Coma after trauma without evidence of direct parenchymal injuries
v. Poor prognosis, related to duration of coma
vi. Injury to the white matter due to acceleration/deceleration

2. Spinal cord
   a. Injuries are usually traumatic, due to vertebral displacement.
   b. Symptomatology depends on interruption of ascending and descending tracts.
   c. Lesions to thoracic segments or below: paraplegia
   d. Lesions to cervical segments: tetraplegia
   e. Lesions above C4: respiratory arrest due to paralysis of diaphragm

3. Cerebral herniations
   a. Subfalcine (cingulate gyrus)
      i. Definition: cingulate gyrus is displaced underneath the falx to the opposite side
   b. Transtentorial (uncal)
      i. Definition: uncus of the temporal lobe is displaced over the free edge of the tentorium
      ii. Compression of the third nerve
         • Papillary dilatation on the same side
         • Infarct in dependent territory
      iii. Advanced stages: Duret hemorrhage within the central pons and midbrain
   c. Cerebellar tonsillar
      i. Definition: displacement of cerebellar tonsils through the foramen magnum
      ii. Compression of medulla: cardiorespiratory arrest

DEVELOPMENTAL ABNORMALITIES

1. Neural tube defects
   a. Most common developmental CNS abnormalities
   b. Results from defective closure of the neural tube
   c. Occurs at the two extremities of the neuraxis
   d. Folate deficiency involved in pathogenesis
   e. Anencephaly
      i. Absence of cranial vault
      ii. Incompatible with life—babies die soon after birth
   f. Neural tube defects of the spinal cord
      i. Spina bifida occulta: bony defect of the vertebral arch
      ii. Meningocele: bony defect with outpouching of meninges
      iii. Meningomyelocele: defective formation of the bony arch with cystic outpouching
         of meninges, spinal cord, and spinal roots
      iv. Myelocle: defective bony arch with complete exposure of spinal cord
      v. Significant defects lead to paraplegia and urinary incontinence from birth

2. Arnold-Chiari malformations
   a. Type 1
      i. Common, but mostly asymptomatic
ii. Definition: downward displacement of cerebellar tonsils and the medulla through the foramen magnum

b. Type 2
   i. Most often symptomatic
   ii. Faulty craniospinal junction, resulting in small posterior fossa, with
       - Abnormal development of the cerebellar vermis and medulla leading to downward displacement
       - Compression of the fourth ventricle
       - Obstructive hydrocephalus
       - Frequent lumbar meningomyelecele
   iii. Frequent association with syringomyelia

3. Syringomyelia
   a. Ependymal-lined, CSF-filled channel parallel to and connected with central canal in the spinal cord (Hydromyelia: central canal is simply dilated)
   b. Ninety percent of cases associated with Arnold-Chiari type 2
   c. Remaining cases: post-traumatic or associated with intraspinal tumors
   d. Syrinx (the cyst) enlarges progressively and destroys the spinal parenchyma.
   e. Symptomatology: paralysis and loss of sensory functions

4. Perinatal brain injury
   a. Definition: injury to the brain during prenatal or immediately postnatal period
   b. Most common cause of cerebral palsy
   c. Most frequent in premature babies
   d. Germinal matrix hemorrhage: localized in the germinal matrix due to its fragile vessels
   e. Periventricular leukomalacia
      i. Infarcts in watershed areas (periventricular white matter in the fetus)
      f. Multicystic encephalopathy: multiple brain infarcts occurring early in pregnancy

5. Dandy-Walker malformation
   a. Non-communicating hydrocephalus with dilation of the fourth ventricle and hypoplasia of the cerebellar vermis

Demyelinating Disorders

1. Multiple sclerosis
   a. Definition: chronic relapsing-remitting disorder of probable autoimmune origin characterized by recurrent episodes of demyelination in the brain (including optic nerves) and spinal cord, which results in progressive neurological deficits
   b. Epidemiology
      i. Overall prevalence: 1/1,000
      ii. Prevalence higher in northern countries
      iii. Persons who emigrate after age 15 from areas of high prevalence to areas of low prevalence maintain original risk.
      iv. Women have double the risk of men
      v. Clinical onset in the third or fourth decade
c. Etiopathogenesis (the cause and development of a disease or abnormal condition)
   i. Multifactorial
   ii. Genetic factors
      • Familial propensity
      • Concordance rate in twins: 25% in monozygotic, 2% in dizygotic
      • Strong association with HLA-DR2
   iii. Immune factors
      • Oligoclonal CD4 lymphocytic infiltration
      • Experimental allergic encephalitis (EAE) obtained by injection of myelin basic protein (MBP)
      • T_{H1} cytokines (IF-γ and TNF) facilitate; T_{H2} cytokines (IL-4 and IL-10 retard EAE
   iv. Infectious agents (suspected, not proven): mumps, rubella, herpes simplex, measles, and JC virus

d. Pathology
   i. Acute lesions: well-circumscribed plaques, with loss of myelin
      • Gross: well circumscribed, bilateral distribution frequently periventricular with same color as gray matter
      • Histology: chronic inflammation with phagocytosis of myelin by macrophages; axons are initially preserved
   ii. Chronic lesions: no inflammation, with axons showing remyelination
   iii. Remyelination is defective because myelin sheaths are thinner with shorter internodes.

e. Pathophysiology
   i. Acute attack: nerve conduction is entirely blocked, acute neurological deficit
   ii. Chronic plaque: slower nerve conduction, allowing for partial recovery
   iii. Recurrent attacks: progressive neurological deterioration

f. Clinical course
   i. 85% of cases: relapsing-remitting course
   ii. Minority: primary progressive (slow deterioration) or progressive-relapsing (slow progression punctuated by acute exacerbations) course
   iii. Recovery from each episode of demyelination occurs in weeks or months.

g. Symptomatology
   i. Blurred vision or loss of vision in one eye (optic nerve involvement)
   ii. Diplopia and vertigo (brain stem involvement)
   iii. Loss of sensation or weakness in one leg (spinal cord involvement)
   iv. Hemiparesis or loss of sensation in half of the body (cerebral-white matter involvement)

v. Many other symptoms, sometimes of neuropsychiatric nature

h. Treatment
   i. Acute attack: high-dose steroids facilitate recovery
   ii. Chronic treatment slows progression of disease
   iii. Interferon-β
   iv. Copolymer 1 (Copaxone)
2. Central pontine myelinolysis (CPM)
   a. Definition: focal demyelination of central area of basis pontis
   b. Patients at risk: severely malnourished, alcoholics, with liver disease
   c. Probably derives from rapid correction of hyponatremia
   d. Very often fatal

DEGENERATIVE AND DEMENTING DISORDERS

1. Parkinson disease and syndrome
   a. Definition
      i. Loss of dopaminergic neurons in the substantia nigra
      ii. Tremor, rigidity, and akinesia
      iii. Parkinson disease (PD) is the idiopathic form.
      iv. Parkinson syndrome (PS) is secondary to known injuries to the substantia nigra (SN) (e.g., infections, vascular conditions, toxic insults).
   b. Epidemiology
      i. Common disease: 2% of the population
      ii. PD arises in the fifth to eighth decade of life.
      iii. No genetic-familial, sex, or race predisposition
   c. Etiopathogenesis
      i. Loss of dopaminergic neurons is unexplained in PD.
      ii. Theories emphasize oxidative stress.
      iii. Accidental exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes death of dopaminergic neurons in SN.
      iv. MPTP is a by-product of illicit synthesis of meperidine (Demerol) analogue.
   d. Pathology
      i. Gross: pallor of SN
      ii. Histology: loss of pigmented (dopaminergic) neurons in SN
         • Lewy bodies: intracytoplasmic round eosinophilic inclusions that contain α-synuclein; EM shows filaments most likely of cytoskeletal origin
      iii. Secondary degeneration of dopaminergic axons in the striatum
   e. Pathophysiology
      i. Loss of extrapyramidal nigra-striatal pathway
      ii. Inhibition of movement of proximal muscles and disruption of fine regulation of distal muscles
      iii. The pathophysiologic basis of PD-associated dementia is not clear.
   f. Clinical manifestations
      i. Slowing of all voluntary movements
      ii. "Tremor at rest that disappears during movement
      iii. Expressionless face
      iv. Rigidity of limbs and trunk and inability to initiate voluntary movement
      v. Increased incidence (20–40% of patients) of dementia and depression
   g. Treatment and prognosis: levodopa treatment of choice usually combined with other drugs
2. Huntington disease (HD)
   a. Definition: autosomal dominant disorder characterized pathologically by degeneration of GABA-ergic neurons of caudate nucleus and clinically by chorea and dementia
   b. Epidemiology
      i. HD affects those of northwestern European descent.
      ii. No cases are known due to new mutations.
      iii. Incidence in high-prevalence regions is 1/12,000–20,000.
   c. Etiopathogenesis
      i. HD gene is located on chromosome 4 coding for a protein called Huntingtin.
      ii. Mutations are due to expansion of an unstable trinucleotide repeat.
      iii. HD shows features of anticipation and genomic imprinting
   d. Pathology
      i. Gross: atrophy of the caudate nucleus with secondary ventricular dilatation
      ii. Histology: loss of small neurons in the caudate nucleus followed by the larger neurons
      iii. Pathophysiology: loss of caudate nucleus GABA-ergic neurons removes inhibitory influences on extrapyramidal circuits, thus leading to chorea
   e. Clinical manifestations
      i. The disease manifests between age 20 and 40 years.
      ii. Chorea: sudden, unexpected, and purposeless contractions of proximal muscles
      iii. Changes in personality, marked tendency for suicide, and dementia
   f. Diagnosis: genetic diagnosis possible but controversial
   g. Treatment: antipsychotic drugs (e.g., haloperidol)

<table>
<thead>
<tr>
<th>Table 21-4. The Dementias</th>
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<tbody>
<tr>
<td><strong>Frequent Causes</strong></td>
</tr>
<tr>
<td>Alzheimer disease</td>
</tr>
<tr>
<td>Lewy body dementia</td>
</tr>
<tr>
<td>Vascular dementia</td>
</tr>
<tr>
<td>Mixed Alzheimer and vascular</td>
</tr>
</tbody>
</table>

3. Alzheimer disease (AD)
   a. Epidemiology
      i. 60% of all cases of dementia
      ii. Incidence: 2% at 65 years, doubles every 5 years
      iii. Risk factors: aging, significant head trauma, and familiarity; aluminum: epi-phenomenon, not a risk factor
      iv. Protective factors: high level of education, smoking
b. Etiopathogenesis
   i. Genetic factors
      • 5–10% of AD cases are hereditary, early onset, and transmitted as an autosomal dominant trait.

Table 21-5. Genetics of AD

**Mutations known to cause AD:**

- Amyloid precursor protein (APP) gene (chromosome 21)
  *Virtually all Down syndrome patients are destined to develop AD in their forties. Down patients have triple copies of the APP gene.*

- Presenilin-1 gene (chromosome 14): majority of hereditary AD cases
  *Mutations of presenilin-2 gene (chromosome 1)*
  *AD caused by all of the above mutations is early in onset.*

- Apolipoprotein E gene:
  *There are 3 allelic forms of this gene, ε2, ε3, and ε4*
  *The allele ε4 of apolipoprotein E (ApoE) increases the risk for AD:*
    - ε4 allele is overrepresented in AD patients.
    - ε2 is underrepresented; it confers relative protection.
  *AD associated with ε4 ApoE allele is late in onset.*

c. Pathology
   i. Accumulation of abnormal proteins intra- and extracellularly
   
ii. Abnormal proteins
      • Aβ amyloid: 42-residue peptide from a normal transmembrane protein, the amyloid precursor protein (APP)
      • Abnormal tau (a microtubule-associated protein)

   iii. **Neuritic plaques (NP):** core of Aβ amyloid surrounded by dystrophic neuritic/dendritic processes and associated with microglia and astrocytes

   iv. **Neurofibrillary tangles (NFT):** intraneuronal aggregates of insoluble cytoskeletal elements, mainly composed of abnormally phosphorylated tau forming paired helical filaments (PHF)

   v. Cerebral amyloid angiopathy (CAA): accumulation of Aβ amyloid within the media of small and medium-size intracortical and leptomeningeal arteries. CAA may occur by itself and cause intracerebral hemorrhage.

   vi. Additional changes
      • Granulovascular degeneration (GVD) and Hirano bodies (HBs)
      • Develop in the hippocampus and are less significant diagnostically

   vii. Lesions involve neocortex, hippocampus, and several subcortical nuclei, including forebrain cholinergic nuclei (i.e., basal nucleus of Meynert).
      • Affected areas are involved in learning and memory.
      • The earliest and most severely affected are hippocampus and temporal lobe.
      • Small number of NP-NFT also form in intellectually normal aging persons.

   viii. Macroscopic changes: atrophy of affected regions
      • Brains are smaller (atrophic), with thinner gyri and wider sulci.
      • Hippocampi and temporal lobes are markedly atrophic.
d. Clinical manifestations
   i. Insidious onset beginning usually in the seventh or eighth decade
   ii. Progressive memory impairment, especially related to recent events
   iii. Alterations in mood and behavior
   iv. Progressive disorientation
   v. Aphasias (loss of language skills) and apraxia (loss of learned motor skills)
   vi. Within 5–10 years, patients become mute and bedridden.

e. Treatment
   i. No effective treatment available
   ii. Mild improvement with inhibitors of acetylcholinesterase (e.g., tacrine)

4. Lewy body dementia
   a. Definition: a progressive brain disease associated with the formation of Lewy bodies in neurons involving neocortex and subcortical nuclei. Etiopathogenesis: obscure, no known risk factors and is the second leading cause of degenerative dementia in the elderly

   b. Pathology
      i. The histopathological hallmark is Lewy body (see Parkinson disease).
      ii. Neuron loss accompanies Lewy body formation.
      iii. Sites involved
         • Neocortex, especially the limbic system and cingulate gyrus
         • Subcortical nuclei: basal nucleus of Meynert, amygdala, and substantia nigra

   c. Pathophysiology
      i. Involvement of neocortex and substantia nigra responsible for cognitive deterioration and parkinsonism.

   d. Clinical manifestations: memory loss, parkinsonism, and visual hallucinations

e. Treatment: possible benefit from cholinesterase inhibitors

5. Amyotrophic lateral sclerosis
   a. Definition: degeneration and loss of upper and/or lower motor neurons

   b. Usually manifests in middle age

c. Loss of upper motor neurons
   i. Hyperreflexia
   ii. Spasticity

d. Loss of lower motor neurons
   i. Weakness
   ii. Atrophy
   iii. Fasciculations

e. In some cases, involvement of cranial nerve nuclei

f. Clinical diagnosis supported by biopsy of muscles

g. Etiopathogenesis is obscure, but
   i. 5–10% of cases are hereditary
   ii. A small number due to mutation of the gene encoding zinc-copper superoxide dismutase on chromosome 21
6. Friedreich ataxia
   a. Definition: an autosomal recessive disorder leading to degeneration of nerve tissue in the spinal cord, especially those sensory neurons connected to the cerebellum affecting muscle movement of the arms and legs
   b. Autosomal recessive disorder with onset in early childhood
   c. Due to expansion of an unstable triplet nucleotide repeat (GAA repeats in the first intron) in the frataxin gene on chromosome 9
      i. The frataxin protein is essential for mitochondrial function by helping in mitochondrial iron regulation, and in the absence of frataxin, mitochondrial iron builds up, leading to free radical damage and mitochondrial dysfunction.
   d. Degeneration involves the following groups of neurons:
      i. Dorsal root ganglia
      ii. Clarke column (origin of spinocerebellar tract)
      iii. Neurons of posterior column of spinal cord
      iv. Cranial nerve nuclei of VII, X, and XII
      v. Dentate nucleus and Purkinje cells of cerebellum
      vi. Betz neurons of primary motor cortex
   e. Clinical manifestations: gait ataxia, dysarthria, hand clumsiness, loss of sense of position, impaired vibratory sensation, and loss of tendon reflexes. Patients become wheelchair bound by age 5 years.

7. Wilson disease
   a. Autosomal recessive genetic abnormality of the Wilson disease protein leads to defective synthesis of ceruloplasmin and copper accumulation in liver and brain.
   b. Some patients develop cirrhosis as children or teenagers, while others present with neuropsychiatric symptoms and ataxia (due to basal ganglia involvement) in their 20's and 30's.
   c. Other problems that may occur include Kayser-Fleisher (golden-brown) rings in Descemet membrane of the eye, renal tubular acidosis, cardiomyopathy, and hormonal disturbances.

8. Acute intermittent porphyria
   a. Autosomal dominant defect in porphyrin metabolism with deficient uroporphyrinogen synthase
   b. Porphobilinogen and aminolevulinic acid increase
   c. Urine is initially colorless but on exposure to light turns dark red.
   d. Patients may develop recurrent severe abdominal pain, psychosis, neuropathy, and dementia.

9. Vitamin B12 deficiency
   a. In addition to megaloblastic anemia, vitamin B12 deficiency causes demyelination of the spinal cord posterior columns and lateral corticospinal tracts (subacute combined degeneration of the spinal tract).
   b. Vitamin B12 deficiency also causes dementia and peripheral neuropathy.

10. Alcohol abuse
    a. Generalized cortical and cerebellar atrophy
    b. Wernicke-Korsakoff syndrome
       i. Usually related to thiamine deficiency
       ii. Hemorrhages in mamillary bodies and walls of third and fourth ventricles
iii. Neuronal loss and gliosis
iv. Wernicke encephalopathy has reversible confusion, ataxia, and nystagmus.
v. Korsakoff psychosis is more severe and has irreversible anterograde and retrograde amnesia.
c. Central pontine myelinolysis

**CNS TUMORS**

1. Epidemiology
   a. Half of all brain and spinal cord tumors are metastatic.
   b. Most frequent primary CNS tumors: meningiomas and glioblastoma multiforme
   c. Primary malignant CNS tumors account for 2–3% of all cancer deaths in the United States.

2. Clinical manifestations
   a. Headache, often worse at night or early morning
   b. Seizures, with tumors involving cerebral cortex
   c. Mental changes (e.g., deficits in memory, concentration, reasoning, etc.)
   d. Focal neurological symptoms, related to involvement of specific brain regions
   e. Symptoms related to increased intracranial pressure
      i. Presence of a space-occupying mass within the cranial cavity
      ii. Blockage of CSF flow
      iii. Edema around the tumor (peritumoral edema)

3. Special features of brain tumors
   a. The concept of benign versus malignant neoplasm must be revised; consider
      i. Malignant CNS tumors do not metastasize outside the cranial cavity.
      ii. Clinical consequences depend on infiltrative behavior and location.

<table>
<thead>
<tr>
<th>Table 21-6. Differences Between Primary and Metastatic Tumors</th>
</tr>
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<tbody>
<tr>
<td><strong>Primary</strong></td>
</tr>
<tr>
<td>Poorly circumscribed</td>
</tr>
<tr>
<td>Usually single</td>
</tr>
<tr>
<td>Location varies according to specific type</td>
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</table>

**Note**

Glioblastoma multiforme has a tendency to cross the midline by involving the corpus callosum ("butterfly glioma").

4. Astrocytomas
   a. Definition: originate from astrocytes and exhibit
      i. Fibrillary background
      ii. Immunoreactivity for glial fibrillary acidic protein (GFAP)
      iii. Diffuse (ill-demarcated) pattern of growth
   b. Grading is important for both prognosis and treatment. Most frequent systems in the United States and Europe: 
      Daumas-Duport and WHO
   c. Both systems identify four grades based on nuclear atypia (pleomorphism), mitoses, necrosis, and vascular endothelial hyperplasia (VEH) due to increased production of vascular endothelial growth factor.
i. Grade 1 pilocytic astrocytomas are well-differentiated, arise throughout the neuraxis, and are common in children and in young adults.
- Definition: benign astrocytic tumor of children and young adults
- Locations: posterior fossa (cerebellum) and diencephalon
- Often presents as a cystic lesion with a mural nodule
- Histology: spindly neoplastic astrocytes with long bipolar processes; tumors rich in Rosenthal fibers, thick corkscrew-like eosinophilic structures, which derive from hypertrophic processes of astrocytes
- Favorable prognosis for posterior fossa tumors

ii. Grade 2 fibrillary astrocytomas arise in the cerebral hemisphere of young to middle-aged adults and the brain stem of children.

iii. Grade 3 astrocytomas are anaplastic astrocytomas.

iv. Grade 4 astrocytomas are called glioblastoma multiforme (GBM).
- GBM is the most common CNS primary malignancy in adults.
- Histology: marked nuclear atypia, mitoses, necrosis, and VEH
- Characteristic histopathological feature: areas of necrosis surrounded by rows of neoplastic cells (pseudopalisading necrosis)
- Spreads through CSF; VEH is often florid, giving rise to glomeruloid formations

v. Most common location: white matter, commonly in the centrum semiovale

vi. Well-differentiated: affect younger patients and grow slowly

vii. Anaplastic astrocytomas and GBM: aggressive, affect older patients

5. Oligodendroglioma
   a. Definition: glioma of oligodendroglial origin
   b. Occurs in 30- to 50-year-old patients
   c. Location: white matter of cerebral hemispheres adjacent to neocortex
   d. Often manifests with seizures
   e. Characteristic histopathology
      i. Neoplastic cells are similar to oligodendroglia.
      ii. Pronounced perinuclear halo: "fried-egg" appearance
      iii. Prominent capillary network in a chicken-wire pattern
   f. Slow-growing tumors that allow long survival (average 5–10 years)
   g. Recur after surgery and degenerate into high-grade gliomas over time

6. Ependymoma
   a. Definition: glioma of ependymal origin
   b. Location
      i. Children: fourth ventricle
      ii. Adults: lateral ventricle or spinal canal
   c. Gross appearance: circumscribed tumors with papillary architecture
   d. Histology: neoplastic cells resemble ependymal cells. Characteristic features:
      i. Ependymal rosettes: cells organized around a lumen
      ii. Perivascular pseudorosettes: cells arranged around small vessels
   e. Often presents with obstructive hydrocephalus, when present in the fourth ventricle
   f. Tend to recur after surgery and acquire more aggressive behavior
7. Meningioma
   a. Definition: a tumor that originates from meningothelial cells of the arachnoid
   b. Tumors of adulthood (women > men), rare in children
   c. Gross: attached to the dura, pushes underlying brain without invasion
   d. Microscopic
      i. Spindle-shaped cells with indistinct borders (syncytioid)
      ii. Cells arranged in whorls or fascicles
      iii. Psammoma bodies frequent
   e. May develop at any meningeal site. Most frequent are dural convexities
   f. Generally, good prognosis
   g. Tumors in some locations may not be amenable to complete resection.

8. Primitive neuroectodermal tumors (PNET)
   a. Definition: highly undifferentiated tumors; originate from a primordial neuroglial precursor
   b. Variably named, depending on location in the brain
   c. Most frequent PNETs: medulloblastoma and retinoblastoma
   d. All PNETs share the following features:
      i. Develop in children
      ii. Histology: blue, small, round cell tumors, with pseudorosettes
      iii. Highly aggressive but responsive to radiation therapy
   e. Medulloblastoma arises in the cerebellar vermis (midline location)
      i. Grows rapidly and spreads through CSF
      ii. Resection and radiation therapy allow 5-year survival of 75%.

9. Schwannoma
   a. Definition: a tumor that originates from Schwann cells of cranial or spinal nerves
   b. Most frequent location: eighth cranial nerve, cerebellopontine angle (CPA)
      i. Manifests characteristically with loss of hearing and tinnitus
   c. Histology
      i. Spindly cells arranged in hypercellular Antoni A areas, alternating with hypocellular Antoni B areas
      ii. Verocay bodies: parallel rows of neoplastic Schwann cells
   d. Neoplastic cells are immunoreactive for a protein called S-100 (S-100 tumor antigen is 100% soluble in ammonium sulfate at neutral pH).
   e. Good prognosis after surgical resection

10. Craniopharyngioma
    a. Definition: a tumor that arises from rests of odontogenic epithelium within the suprasellar/diencephalic region
    b. Patients affected are usually children or young adults
    c. Contains deposits of calcium evident on x-rays
    d. Histology resembles adamantinoma (rare low-grade primary bone tumor of unknown histological origin), the most common tumor of the tooth.
    e. Benign but tends to recur after resection
Chapter Summary

* Acute aseptic (viral, most commonly enterovirus) meningitis causes a lymphocytic infiltration of the leptomeninges with clinical features of fever, meningeal irritation, depressed consciousness, and low mortality. Acute purulent meningitis (Escherichia coli and group B streptococcus in neonates; Haemophilus influenzae in infants and children; Neisseria meningitidis in adolescents and young adults; Streptococcus pneumoniae and Listeria monocytogenes in elderly persons) causes a neutrophilic infiltration of the leptomeninges with clinical features of diffuse cerebral edema with risk of fatal herniation, headache, fever, nuchal rigidity, cloudy sensorium, coma, late hydrocephalus, and late neural deafness or other cranial nerve impairment. Mycobacterial (either M. tuberculosis or atypical Mycobacteria such as MAC, particularly in AIDS patients) meningoencephalitis causes tuberculosis of the basal surface of the brain and dura mater.

* Viral encephalitides in general show perivascular cuffs, microglial nodules, and neuronophagia microscopically, and clinically cause mental status changes, fever, headache, and often progression to coma. Specific types include arthropod-borne (St. Louis, various equine, and Venezuelan encephalitides), herpes simplex type 1 (predilection for hemorrhagic necrosis of temporal lobes with viral inclusions), rubies (kuru bodies in hippocampus and Purkinje neurons), and HIV (AIDS-dementia complex with microglial nodules and multinucleated giant cells, vascular myeloapthy of spinal cord). Progressive multifocal leukoencephalopathy can be considered a subtype of viral encephalitis related to JC virus infection in immunocompromised patients that microscopically produces demyelination, bizarre astrocytes, and oligodendrocytes with intranuclear inclusions.

* Fungal meningoencephalitis can be due to Candida, Aspergillus (vasculitis with hemorrhage), Mucor (vasculitis with hemorrhage), and Cryptococcus (invasion of brain through Virchow-Robin spaces with formation of "soap bubble lesions"). Toxoplasmosis occurs in AIDS patients and causes cerebral abscesses/lobar necrosis that may be seen on MR/CT as ring-enhancing lesions. Cerebral abscess due to bacteria can complicate a variety of medical conditions (acute bacterial endocarditis, chronic pulmonary abscess, cysticercus granuloma with right-to-left shunt, mastoiditis, sinusitis, otitis, open fracture, prior neurosurgery) and causes increased intracranial pressure, focal neurologic deficits, and a ring-enhancing lesion on CT/MRI.

* Subacute sclerosing panencephalitis is a potentially fatal slow virus encephalitis that can follow measles infection.

* Creutzfeldt-Jakob disease is caused by a conformational change in a prion protein that leads to spongiform vacuolar degeneration of neurons with kuru plaques in the neuropil, rapid progressive dementia, memory loss, and involuntary movements; death within 6 to 12 months.

* Cerebrovascular disease is the third most frequent cause of death in industrialized countries and can occur in several histopathological forms, including global cerebral ischemia (overall drop in blood flow/oxygenation of brain that can, if severe, cause brain death; most vulnerable sites are Purkinje neurons, hippocampus CA1, and pyramidal neurons of cortex), transient ischemic attack (severe focal neurologic symptoms due to small platelet thrombi or atherothrombosis), infarction (85% of strokes), and hemorrhage (15% of strokes).

(Continued)
Chapter Summary (continued)

* Infarctions can be due to atherosclerosis with superimposed thrombosis (anemic white infarct), thromboemboli (hemorrhagic red infarct), or small vessel disease (tiny lacunar infarcts). Infarcted brain tissue undergoes liquefactive necrosis (most prominent at 2–3 weeks) to produce eventual cyst formation. Common neurovascular syndromes after stroke include the anterior cerebral artery syndrome (weakness and sensory loss in contralateral leg, transient aphasia, abulia), the middle cerebral artery syndrome (contralateral hemiplegia of face and arm with gaze palsy, contralateral sensory loss, and sometimes aphasia), the posterior cerebral artery syndrome (contralateral homanopia or total cortical blindness, alexia (inability to read), thalamic syndrome, and dementia (secondary to recurrent infarcts or small vessel disease).

* Hemorrhage causes 15% of strokes and occurs in several forms, including epidural hemorrhage (traumatic, often involves middle meningeal artery in dura, can cause subfalcine or other cerebral herniation, "talk and die syndrome"), subdural hemorrhage (traumatic, rupture of bridging veins, risk factors of cerebral atrophy and abnormal hemostasis, various neurologic symptoms, often recurrent), subarachnoid hemorrhage (ruptured berry aneurysm or other causes, "thunderclap" headache, nuchal rigidity, neurologic deficits, stupor), and intracerebral hemorrhage (hypertension, vascular malformation, or less commonly, many other predisposing conditions: basal ganglia, cerebellum, pons, or centrum ovale, severe headache with rapid progression of symptoms, often coma).

* Berry aneurysms of the circle of Willis (risk factors include hypertension, cigarette smoking, Marfan syndrome, Ehlers-Danlos type 4, and adult polycystic kidney disease) are the most frequent cause of subarachnoid hemorrhage (1/3 die, 1/3 recover, and 1/3 re-bleed with risk of death).

* CNS trauma to the cranial cavity and brain can take several forms, including concussion (transient loss of consciousness after impact against a rigid surface), contusions (brain bruises, sometimes in a coup and contre-coup pattern, can cause local infarction), and diffuse axonal injury (sudden acceleration/deceleration stretches and "pops" axons, producing little gross injury, but coma can occur, which can be permanent). CNS trauma to the spinal cord is usually due to vertebral displacement, and can cause paraplegia (thoracic segments or below), tetraplegia (cervical segments), and paralysis of the diaphragm (above C4).

* Cerebral herniations can take several forms, including subfalcine (cingulate gyrus goes under falx and can compress the anterior cerebral artery), transtentorial (temporal lobe uncus goes under the tentorium, can compress the third nerve, and cause Duran hemorrhage in brain stem), and cerebellar tonsillar (goes through the foramen magnum to compress the medulla causing cardiorespiratory arrest).

* Neural tube defects (risk factor: folate deficiency) are the most common developmental CNS abnormalities and can take several forms, including anencephaly (no cranial vault, death in infancy), spina bifida occulta (bony defect of the vertebral arch), meningocele (bony defect with outpouching of meninges), meningocelele (with outpouching of meninges, spinal cord, and spinal roots), and myelomeningocele (complete exposure of spinal cord). Paraplegia and urinary incontinence may complicate the more severe spinal cord defects.

* Arnold-Chiari malformation type I (common, often asymptomatic) is a downward displacement of the cerebellar tonsils. Type 2 (often symptomatic) has a small posterior fossa, downward displacement of cerebellar vermis and medulla, compressed fourth ventricle with obstructive hydrocephalus, and frequent lumbar meningocelele and syringomyelia (CSF-filled channel near central canal; most often related to Arnold-Chiari type 2).
Chapter Summary (continued)

* Perinatal brain injury (risk factor: prematurity) can cause cerebral palsy, germinal matrix hemorrhage, periventricular leukomalacia, and multicystic encephalopathy. Dandy-Walker malformation is a cause of noncommunicating hydrocephalus characterized by cerebellar vermis hypoplasia and enlarged fourth ventricle.

* Multiple sclerosis is a chronic relapsing-remitting disorder of probable autoimmune origin characterized by recurrent episodes of demyelination (causing "plaques") and defective remyelination in the brain (including optic nerves) and spinal cord, which results in progressive (but variable in time and from person to person) neurological deficits (visual changes, sensation changes, motor changes, neuropsychiatric disturbances). Central pontine myelolysis is a rare, potentially fatal, focal demyelination of the brain points possibly related to over-rapid correction of hyponatremia in malnourished patients and alcoholics.

* Parkinson disease is one of the degenerative and demyelinating disorders of the brain and features loss of substantia nigra dopaminergic neurons with Lewy body formation, tremor, rigidity, and akinesia. Huntington disease is an autosomal dominant disorder that presents in young to middle-aged adulthood characterized pathologically by degeneration of CA1 pyramidal neurons of the caudate nucleus and clinically by chorea and dementia.

* Alzheimer disease (30% of all cases of dementia) has increasing incidence with older age, is characterized by gross and microscopic brain abnormalities (atrophy, brain with particular involvement of the hippocampus and temporal lobes, neuritic plaques, neurofibrillary tangles, and cerebral amyloid angiopathy), and clinically manifests with insidious onset, progressive memory impairment, mood alterations, disorientation, aphasia, apraxia, and progression to a bedridden state with eventual death. Dementia with Lewy bodies causes cognitive deterioration coupled with parkinsonism.

* Amyotrophic lateral sclerosis causes eventual generalized paralysis with earlier findings related to both upper motor neuron (hyperreflexia, fasciculations) and lower motor neuron (weakness, atrophy) loss. Friedreich ataxia is an autosomal recessive disorder related to an unstable triplet nucleotide repeat that causes progressive degeneration in the cerebellum, brain stem, and spinal cord, clinically producing gait ataxia leading to a wheelchair-bound state by age 5. Wilson disease is an abnormality of copper metabolism that can cause cirrhosis, neuropsychiatric symptoms, and ataxia. Acute intermittent porphyria is a disorder of porphyrin metabolism that can cause abdominal pain, psychosis, and dementia. Vitamin B12 deficiency can cause anemia, subacute combined degeneration of the spinal cord, dementia, and peripheral neuropathy. Alcohol abuse can cause cortical and cerebellar atrophy, Wernicke-Korsakoff syndrome, and central pontine myelinolysis.

* CNS tumors can be secondary to metastases (half of cases) or primary, and in general, can produce headache, seizures, mental changes, focal neurologic symptoms, and increased intracranial pressure. Primary CNS tumors include astrocytomas (most common malignant primary tumor of the brain; subtype pilocytic (grade 1), fibrillary (grade 2) is well-differentiated, anaplastic (grade 3), and aggressive glioblastomas multiforme (grade 4)), astrocytomas involving cerebellum or diaphragm of children and young adults and having a particularly good prognosis), oligodendrogliomas (middle-aged adults, cerebral hemispheres, "fried-egg" cells embedded in chicken-wire capillary pattern, slow growing, may eventually become high grade), ependymoma (fourth ventricle in children, lateral ventricle or spinal cord in adults, papillary tumors with ependymal rosettes and perivascular pseudorosettes, may cause hydrocephalus), meningiomas (most common benign tumor, form balls attached to meninges, whitened cells, psammoma bodies, usually good prognosis), primitive neuroectodermal tumors (aggressive but therapy-responsive small B-cell tumors of children including medulloblastoma and retinoblastoma), schwannomas (benign eighth nerve tumors of cerebellopontine angle that can cause hearing loss and tinnitus), and craniopharyngiomas (suprasellar/diencephalic tumors of children or young adults that histologically resemble the tooth tumor adamantinoma and arise from rests of odontogenic epithelium).
Hematopoetic Pathology—White Blood Cell Disorders & Lymphoid and Myeloid Neoplasms

REACTIVE CHANGES IN WHITE BLOOD CELLS

1. Leukocytosis
   a. Increased neutrophils (neutrophilia)
      i. Increased bone marrow production is seen with acute inflammation associated
         with pyogenic bacterial infection or tissue necrosis.
      ii. Increased release from bone marrow storage pool may be caused by corticosteroids,
          stress, or endotoxin.
      iii. Increased bands ("left shift") in peripheral blood is characteristic.
      iv. Reactive changes include Döhle bodies (aggregates of rough endoplasmic
          reticulum [RER]), toxic granulations (prominent granules), and cytoplasmic
          vacuoles of neutrophils.
   b. Increased eosinophils (eosinophilia) are seen with
      i. Allergies and asthma (type I hypersensitivity reaction)
      ii. Parasites
      iii. Drugs (especially in hospitals)
      iv. Certain skin diseases and cancers (adenocarcinomas, Hodgkin disease)
   c. Increased monocytes (monocytosis) are seen with
      i. Certain chronic diseases, such as some collagen vascular diseases and inflam-
         matory bowel disease (IBD)
      ii. Certain infections, especially TB
   d. Increased lymphocytes (lymphocytosis) are seen with
      i. Acute (viral) diseases
      ii. Chronic inflammatory processes
      iii. Infectious mononucleosis (IM) is an example of a viral disease causing lym-
           phocytosis.
      iv. Most common cause is Epstein-Barr virus (EBV) (a herpesvirus) but less
          commonly due to other viruses (heterophile-negative IM is most likely due to
          cytomegalovirus [CMV]).
   v. Sequence of events
      • EBV invades B-lymphocytes via CD21 (CR2) receptors.
      • Cytotoxic (CD8) T-lymphocytes respond against invaded B cells and form
        atypical lymphocytes (Dowrey cells), which are enlarged lymphocytes that
        have abundant cytoplasm that is condensed peripherally ("ballet dancer"
        appearance); they are similar in appearance to monocytes, hence the name
        "mononucleosis."
   vi. Antibody production: heterophil antibodies (antibodies against other species
       such as red cells of sheep and horses) are the basis of the Paul-Bunnell reaction
       used as the monospot test (may be negative first week, so need to repeat test).

Note
Increased leukocyte alkaline phosphatase (LAP) is useful to differentiate benign reactions
from neoplastic chronic myelocytic leukemia (CML)
(which has decreased LAP).
vii. Clinical infectious mononcytosis
   • Age groups include adolescents and young adults ("kissing disease")
   • Symptoms (classic triad): fever, sore throat (see gray-white membrane on tonsils), and lymphadenitis (posterior auricular nodes); fourth sign is hepatosplenomegaly
   • Mono is an acute, self-limited disease that usually resolves in 4–6 weeks.

viii. Complications include hepatic dysfunction, splenic rupture, and rash if treated with ampicillin.

e. Increased basophils are seen with
   i. Chronic myeloproliferative disorders such as polycythemia vera

2. Leukopenia
   a. Decreased neutrophils are seen with
      i. Decreased production: aplastic anemia, chemotherapy
      ii. Increased destruction: infections, autoimmune disease (systemic lupus erythematosus)
      iii. Activation of neutrophil adhesion molecules on endothelium; endotoxins in septic shock
   b. Decreased eosinophils are seen with
      i. Increased cortisol (causes sequestration of eosinophils in lymph nodes): Cushing syndrome, exogenous corticosteroids
   c. Decreased lymphocytes are seen with
      i. Immunodeficiency syndromes: HIV, DiGeorge syndrome (T-cell deficiency), severe combined immunodeficiency (B- and T-cell deficiency)
      ii. Immune destruction: systemic lupus erythematosus
      iii. Corticosteroids
      iv. Radiation (lymphocytes are the most sensitive cells to radiation)
         • Atypical lymphocytes are found in the peripheral blood and T-cell areas of lymph nodes (paracortex).

![Diagram of a lymph node with labels for the germinal center of follicle, cortex, paracortex, medulla, afferent lymphatic, and efferent lymphatic.](Figure 22-1. Lymph Node)
3. **Lymphadenopathy**
   a. Definition: Lymph node enlargement due to reactive conditions, or neoplasia
      i. Acute nonspecific lymphadenitis
      ii. Tender enlargement of lymph nodes
      iii. Local involvement is seen with bacterial lymphadenitis
         * Histology: may see neutrophils within the lymph node
         * Note: cat-scratch fever (due to *A. felis*) causes stellate microabscesses
      iv. Generalized involvement of lymph nodes is seen with viral infections (see reactive T-cell immunoblast in lymph nodes and peripheral blood).
   b. Chronic nonspecific lymphadenitis
      i. Nontender enlargement of lymph nodes
      ii. Follicular hyperplasia involves B lymphocytes and may be seen with rheumatoid arthritis, toxoplasmosis, and early HIV infections.
      iii. Paracortical lymphoid hyperplasia involves T cells and may be seen with viruses, drugs (Dilantin), and systemic lupus erythematosus (SLE).
      iv. Sinus histiocytosis involves macrophages and, in most cases, is nonspecific. An example is lymph nodes draining cancers.
   d. Neoplasia
      i. Nontender enlargement of lymph nodes
      ii. Most common tumor to involve lymph nodes is metastatic cancer, initially seen under the lymph node capsule (e.g., breast, lung, malignant melanoma, stomach and colon carcinoma).
      iii. Malignant lymphoma and infiltration by leukemias are another important cause for lymphadenopathy.

**LYMPHOID NEOPLASMS**

1. General definitions, characteristics, and classifications
   a. Acute leukemias
      i. Peripheral blood has decreased mature forms and increased immature forms called blasts, which have immature chromatin with nucleoli.
      ii. Bone marrow has increased immature cells (blasts); the diagnostic criteria is >30% blasts in the bone marrow.
      iii. Acute symptoms are secondary to marrow failure, which can produce decreased RBCs (causing anemia and fatigue), decreased WBCs (permitting infections and fever), and decreased platelets (inducing bleeding).
   b. Lymphoid neoplasia classifications
      i. The *Revised European-American classification of Lymphomas* (REAL)
         * Precursor B-cell neoplasms (immature B cells)
         * Peripheral B-cell neoplasms (mature B cells)
         * Precursor T-cell neoplasms (immature T cells)
         * Peripheral T-cell neoplasms (mature T cells)
Clinical Correlate

ALL is associated with infiltration of the CNS and testes (sanctuary sites). Prophylactic radiation and/or chemotherapy to the CNS is recommended because malignant cells in brain are protected from chemotherapy by the blood–brain barrier.

PRECURSOR B- AND T-CELL NEOPLASMS

1. Acute lymphoblastic leukemia (ALL)
   a. Lymphoblasts are positive for terminal deoxynucleotidyl transferase (TdT) (which is determined by using a nuclear stain), PAS, hyperploidy (greater than 50 chromosomes), polyoidy (e.g., t(12;21), t(4;11) and t(9;22)), and acid phosphatase.
   b. The immunologic classification of ALL (at present preferred)
      i. B-cell lineage; classification is based on presence or absence of cytoplasmic or surface markers
         • Surface immunoglobulin (sIg) present: mature B-ALL
         • Cytoplasmic μ present: pre-B-ALL
         • Almost always express pan B-cell molecules – CD19 and CD 10
         • Early pre-B-ALL is the most common type of ALL and is seen primarily in children.
         • The rapid onset of symptoms is due to marrow involvement and pancytopenia.
      ii. T-cell lineage (T-ALL) is associated with mediastinal mass in young (adolescent) adult male (think "T" = thymus = mediastinal)

2. Lymphoblastic lymphoma
   a. The majority of cases are T cells and are aggressive and rapidly progressive.
   b. Clinical: young males with mediastinal mass (think thymus)
   c. The leukemic phase of lymphoblastic lymphoma is similar to T-ALL.
   d. Most cells express CD1+, CD2+, CD5+ and CD7+.

PERIPHERAL B-CELL NEOPLASMS

1. Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL)
   a. CLL is very similar to SLL, which is also called well-differentiated lymphocytic lymphoma (WDL)
      i. Patients present with blood findings = CLL, whereas patients who present with lymph node findings = SLL
      ii. Note: lymph node involvement is also common (50%) with CLL
   b. Small lymphocytic lymphoma (SLL)
      i. SLL is a proliferation of small B-lymphocytes, which have B-cell markers and one T-cell marker (CD5), like B-CLL.
   c. Classification of CLL
      i. B-CLL (95% of cases) have B-cell markers, such as CD19 and CD20.
         • One T-cell marker is also present: CD5
         • Also important is that the cells are CD23 positive and CD10 negative.
      ii. T-CLL (5% of cases) have T-cell markers.
   d. Histology of affected lymph nodes reveals only diffuse pattern (not nodular), but proliferation centers may also be present.
   e. Peripheral blood findings
      i. Increased numbers of normal-appearing lymphocytes
      ii. Numerous smudge cells ("parachute cells") are present; smudge cells result from the fact that the neoplastic lymphocytes are unusually fragile.
   f. Bone marrow findings: numerous normal-appearing neoplastic lymphocytes
g. Clinical characteristics of CLL
   i. CLL is the most indolent of all the leukemias.
   ii. Mean age at time of diagnosis is 60 years of age.
   iii. The malignant cells are nonfunctional → patients develop hypogammaglobulinemia → increased risk of infections
   iv. CLL is associated with warm autoimmune hemolytic anemia (AIHA) (10% of cases), which will cause spherocytes to be observed in peripheral blood.
   v. CLL rarely transforms into a worse disease, such as prolymphocytic leukemia or large cell lymphoma (Richter syndrome).

2. Hairy cell leukemia
   a. Definition: a rare B-cell neoplasm indolent disease of middle-aged Caucasian men
   b. Lymphocytes have “hairlike” cytoplasmic projections (“dry tap” with bone marrow aspiration)
   c. Diagnostic stain: positive tartrate-resistant acid phosphatase (TRAP)
   d. Physical exams a markedly enlarged spleen (splenomegaly) due to infiltrate of red pulp by malignant cells
   e. Treatment with 2-chlorodeoxyadenosine (2-CDA), which inhibits adenosine deaminase (ADA) and increases levels of toxic deoxyadenosine

3. Follicular lymphomas
   a. Definition: a well-differentiated B-cell lymphoma with follicular architecture
   b. The most common form of non-Hodgkin lymphoma (NHL) in the United States
   c. All follicular lymphomas are derived from B lymphocytes.
   d. Characteristic translocation is t(14;18).
      i. Chromosome 14 has immunoglobulin heavy-chain genes.
      ii. Chromosome 18 has bcl-2 (activation of bcl-2 inhibits apoptosis by blocking the bax channel).
   e. Clinical features
      i. Commonly present with disseminated disease (more advanced stage)
      ii. Has a better prognosis than diffuse lymphomas
      iii. Doesn’t respond to therapy (unlike the more aggressive diffuse lymphomas)
      iv. Up to half of cases will progress to a diffuse large-cell NHL

4. Diffuse large B-cell lymphoma
   a. Definition: a high grade large B-cell lymphoma with a diffuse growth pattern
   b. Common features
      i. Aggressive, rapidly proliferating tumor
      ii. May respond to therapy
   c. Special subtypes
      i. Immunodeficiency-associated B-cell lymphomas (these are often infected with EBV)
      ii. Body-cavity large B-cell lymphomas (some of these are associated with human herpes virus [HHV]-8)

5. Small noncleaved lymphoma (Burkitt lymphoma)
   a. Definition: a high grade B-cell lymphoma composed of intermediate-sized lymphoid cells with a “starry-sky” appearance due to numerous reactive tingible-body macrophages (phagocytosis of apoptotic tumor cells)
b. Characteristic t(8;14) translocation
   i. Chromosome 14 has immunoglobulin heavy-chain genes.
   ii. Chromosome 8 has oncogene c-myc.

c. African type is the endemic form.
   i. Involvement of mandible or maxilla is characteristic.
   ii. Associated with EBV

d. American type is the nonendemic form.
   i. Commonly involves the abdomen (such as bowel, retroperitoneum, or ovaries)
   ii. High incidence in AIDS patients

e. Endemic and sporadic forms of Burkitt lymphoma largely occurs primarily in children and young adults.

6. Mantle cell lymphoma (MCL)
   a. Definition: the tumor cells arise from mantle zone B lymphocytes (positive for CD19, CD20, and CD5; negative for CD23).
   b. Synonym: intermediate differentiated lymphocytic lymphoma
   c. Characteristic translocation t(11;14)
      i. Chromosome 11 has bcl-1 (cyclin D)
      ii. Chromosome 14 has immunoglobulin heavy-chain genes.

7. Marginal zone lymphoma (MALToma)
   a. Definition: a diverse group of B-cell neoplasms that arise within lymph nodes, spleen, or extranodal tissues
   b. Associated with mucosa-associated lymphoid tissue: MALTomas
   c. Begins as reactive polyclonal reaction and may be associated with previous autoimmune disorders or infectious disease (e.g., Sjögren disease, Hashimoto thyroiditis, Helicobacter gastritis)
   d. Remains localized for long periods of time

8. Multiple myeloma
   a. Definition: a malignant neoplasm of plasma cells
   b. Multiple myeloma is the most common primary tumor arising in the bone marrow of adults.
   c. Lab
      i. Increased serum protein with normal serum albumin
      ii. M spike: monoclonal immunoglobulin spike
         • Most common is IgG (60%)
         • Next most common is IgA (20%)
      iii. Bence-Jones proteins are light chains that are small and can be filtered into urine.
   d. Histology
      i. Bone marrow has increased numbers of plasma cells (>20% is characteristic).
      ii. Peripheral blood may show rouleaux formation ("stack of coins").
   e. Multiple lytic bone lesions due to the osteoclastic activating factor (OAF)
      i. Lytic bone lesions cause hypercalcemia, bone pain, and increased risk of fracture.
   f. Complications
      i. Increased risk of infection, the most common cause of death
      ii. Renal disease, such as myeloma nephrosis
iii. Primary amyloidosis (10% of patients) due to amyloid light (AL) chains
iv. Increased amounts of IL-6 are associated with a poorer prognosis because
survival of myeloma cells is dependent on IL-6.

9. Plasmacytoma
a. Definition: a solitary myeloma either within bone or soft tissue
b. Within bone: precursor lesions to later develop into myeloma
c. Outside bone (extramedullary): usually found within the upper respiratory tract
   and are not precursor lesions for myeloma

10. Monoclonal gammopathy of undetermined significance (MGUS)
a. Old name was benign monoclonal gammopathy.
b. M protein is found in 1–7% of asymptomatic individuals over the age of 50 (the
   incidence increases with increasing age).
c. Prognosis: the annual risk of developing a plasma cell dyscrasia, usually multiple
   myeloma, is 1–2% per year. MGUS may also evolve into Waldenström macroglobulinemia,
   primary amyloidosis, B-cell lymphoma, or chronic lymphocytic leukemia

11. Lymphoplasmacytic lymphoma (Waldenström macroglobulinemia)
a. Definition: small lymphocytic lymphoma with plasmacytic differentiation
b. Waldenström macroglobulinemia (WM) is a cross between multiple myeloma and
   small lymphocytic lymphoma (SLL).
   i. Like myeloma, WM has an M spike (IgM).
   ii. Like SLL (unlike myeloma), the neoplastic cells infiltrate many organs, such as
       lymph nodes, spleen, and bone marrow.
   iii. Unlike multiple myeloma (MM), there are no lytic bone lesions and serum
        calcium levels do not increase.
c. Russell bodies (cytoplasmic immunoglobulin) and Dutcher bodies (intranuclear
   immunoglobulin) may be present.
d. May have hyperviscosity syndrome (because IgM is a large pentamer)
   i. Visual abnormalities due to vascular dilatations and hemorrhages in the retina
   ii. Neurologic symptoms include headaches and confusion.
   iii. Bleeding and cryoglobulinemia due to abnormal globulins, which precipitate
        at low temperature and may cause Raynaud phenomenon

PERIPHERAL T-CELL AND NATURAL KILLER CELL NEOPLASMS

1. Peripheral T-cell lymphoma, unspecified
a. This is a "wastebasket" diagnostic category

2. Adult T-cell leukemia/lymphoma (ATLL)
a. ATLL is a malignant T-cell disorder (CD4-T cells) due to HTLV-I infection that is
   found in Japan and the Caribbean.
b. Clinical symptoms: skin lesions, hypercalcemia, enlarged lymph nodes, liver, and
   spleen
c. Micro: hyperlobated "4-leaf clover" lymphocytes in the peripheral blood

3. Mycosis fungoides (MF) and Sézary syndrome (SS)
a. MF is a malignant T-cell disorder (post-thymic CD4 cells) but has a better prog-
   nosis than ATLL.
b. Clinical: generalized pruritic erythematous rash (no hypercalcemia)
c. Sequence of skin changes (stages): inflammatory eczematous → plaque stage → tumor nodule stage
d. Micro reveals atypical PAS-positive lymphs in epidermis (epidermotropism); aggregates of these cells are called Pautrier microabscesses
e. Cerebriform Sézary cells in peripheral blood; Sézary syndrome (which is also associated with a generalized exfoliative skin rash)

LYMPHOMA

1. Hodgkin (HL) versus non-Hodgkin lymphomas (NHL)
   a. Characteristics of HL that are different from NHL
      i. Clinically, HL may present similar to infection (with fever)
      ii. Spread is contiguous to adjacent node groups (unlike non-Hodgkin lymphomas)
      iii. Classification is based on inflammatory response and not malignant cell
      iv. No leukemic state
      v. Extranodal spread uncommon

2. Hodgkin lymphoma
   a. The malignant cells are the diagnostic Reed-Sternberg (RS) cells intermixed with reactive inflammatory cells.
      i. Definition: The RS cell is a large malignant tumor cell that has a bilobed nucleus with a prominent large inclusion-like nucleolus in each lobe.
      ii. RS cells are positive for CD15 (Leu-M1) and CD30 (Ki-1).
      iii. Except for lymphocyte predominate HL, in which the malignant cells stain for B-cell markers and have negative CD15 and CD30
   b. Classification of HL
      i. LR (lymphocyte-rich) type; a rare form, which is composed of mainly of reactive lymphocytes and is associated with EBV (40% of cases)
      ii. LP (lymphocyte predominant) type; has lympho-histiocytic variants (L&H cells; called "popcorn cells") and are negative for CD15 and CD30
      iii. Mixed cellularity; has eosinophils and plasma cells (increased number of eosinophils is related to IL-5 secretion)
      iv. Lymphocyte depleted (LD); has few lymphocytes, and there are many RS cells
   c. Clinical characteristics
      i. Bimodal age group distribution (late 20s and >50)
      ii. Usually patients present with painless enlargement of lymph nodes.
      iii. B-cell symptoms: fever (that comes and goes = Pel-Ebstein fever), weight loss, night sweats
      iv. Bad prognosis is directly proportional to the number of RS cells present.
      v. Survivors of chemotherapy and radiotherapy have increased risk for secondary non-Hodgkin lymphoma or acute leukemia.
MYELOID NEOPLASMS

1. Acute myelogenous leukemia
   a. Myeloblasts may have intracytoplasmic rods (stain red) called Auer rods.
      i. Auer rods are abnormal lysosomes (primary granules) that are pathognomonic of myeloblasts and not found in ALL.
      ii. Auer rods also stain positive with myeloperoxidase (MPO) or Sudan-black B stain.
      iii. Auer rods are most commonly found in M3 AML.
   b. The tissue form of AML is called granulocytic sarcoma (chloroma).
   c. French-American-British (FAB) classification of AML.
      i. M0: undifferentiated
      ii. M1: myeloblastic leukemia without maturation
      iii. M2: myeloblastic leukemia with maturation (some promyelocytes)
      iv. M3: hypergranular (microgranular) promyelocytic leukemia
         • Micro: numerous cytoplasmic granules and numerous Auer rods
         • May develop disseminated intravascular coagulation (DIC) due to release of thromboplastin substances in granules (especially when therapy kills the leukemic cells)
         • Characteristic translocation: t(15;17)
         • 15 has the polymorphonuclear leukocyte (PML) gene, whereas 17 has the retinoic acid receptor α gene (RAR-α).
         • This translocation forms an abnormal retinoic acid receptor; therefore, therapy is with all-trans-retinoic acid.
      v. M4: myelomonocytic leukemia has both myeloblasts and monoblasts
      vi. M5: monocytic leukemia (may have gingival infiltrates)
      vii. M6: erythroleukemia (Di Guglielmo disease); as abnormal erythroid precursors (binucleate and megaloblastic changes)
      viii. M7: acute megakaryocytic leukemia; associated with acute myelofibrosis due to release of platelet-derived growth factor (PDGF)

2. Myelodysplastic syndromes (MDS)
   a. The classification of myelodysplastic syndromes is based on the number of blasts in the marrow.
   b. Dysplastic changes include Pelger-Huet cells ("aviator glasses" nuclei), ring sideroblasts, nuclear budding, and "pawn ball" megakaryocytes.
   c. MDS patients have an increased risk of developing acute leukemia (preleukemias).

3. Myeloproliferative syndromes (MPS)
   a. General
      i. Definition: MPSs are clonal neoplastic proliferations of multipotent myeloid stem cells
      ii. Bone marrow is usually markedly hypercellular (hence the name myeloproliferative)
         • All cell lines are increased in number (erythroid, myeloid, and megakaryocytes).
         • Cannot tell the MPSs apart by the histologic appearance of the bone marrow
b. Chronic myelogenous leukemia (CML)
   i. Clonal proliferation of pluripotent granulocytic precursor stem cells
   ii. A unique characteristic is the chromosomal translocation
       - *Philadelphia (Ph) chromosome, which has t(9;22)*
       - 9 has c-abl (an oncogene), while 22 has bcr (breakpoint cluster region)
       - This translocation forms a new protein P210 that has tyrosine kinase activity.

![Diagram showing translocation of chromosomal segments between chromosomes 9 and 22]

**Figure 22-2. Translocation of Chromosomal Segments Between Chromosomes 9 and 22**

iii. Insidious onset (i.e., chronic) and massive splenomegaly
iv. Micro; hypercellular bone marrow with all cell lines increased in number
v. Peripheral leukocytosis including
   - Markedly increased numbers of neutrophils (and bands and metamyelocytes)
   - Increased eosinophils and basophils (like the other MPSs)
vi. Decreased leukocyte alkaline phosphatase (LAP) activity is diagnostic compared with leukemoid reaction, which has increased LAP.
vii. Treatment
   - Imatinib mesylate blocks the P210 tyrosine kinase protein produced by the translocation.
   - Bone marrow transplant
viii. Prognosis
   - Slow progression (half develop accelerated phase <5 years)
   - Then blast crisis (very bad prognosis; doesn't respond to chemotherapy): 2/3 myeloid blasts and 1/3 lymphoid blasts

c. Polycythemia vera (P. vera)
   i. Characteristic findings
      - Increased erythroid precursors with increased red cell mass (primary)
      - Increased hematocrit
      - Increased blood viscosity
ii. Decreased erythropoietin (EPO), but RBCs have increased sensitivity to EPO and overproliferate
iii. Increased basophils and increased eosinophils (like all of the MPSes)
iv. Histamine release from basophils causes intense pruritus and gastric ulcers (bleeding may cause iron deficiency).
v. Increased LAP
vi. Clinical characteristics: plethora (redness) and cyanosis (blue)
vii. Complications
   - Increased blood viscosity can cause deep vein thromboses and infarcts.
   - High cell turnover can cause hyperuricemia, resulting in gout.
   - P. vera may develop into a "spent phase" with myelofibrosis.
   - Increased risk for acute leukemia
d. Essential thrombocythemia (ET)
i. Increased megakaryocytes (and other cell lines) in bone marrow
ii. Peripheral blood smear
   - Increased number of platelets (>1,000,000), some with abnormal shapes
   - Also increased numbers of leukocytes
iii. Clinical signs include excessive bleeding and occlusion of small vessels.
e. Myelofibrosis (MF) with myeloid metaplasia
i. Etiology is unknown (agnogenic).
ii. Bone marrow aspiration may be a "dry tap."
iii. Biopsy specimen shows hypocellular marrow with fibrosis (increased reticulin).
   - Fibroblasts are polyclonal proliferation (not neoplastic).
   - Fibrosis is secondary to factors released from megakaryocytes, such as platelet-derived growth factor (PDGF).
iv. Enlarged spleen due to extramedullary hematopoiesis (myeloid metaplasia)
v. Peripheral smear
   - Leukoerythroblastosis (immature white cells and nucleated red cells)
   - Teardrop RBCs
vi. High cell turnover causes hyperuricemia and gout.

Note
The spleen is the most common site for extramedullary hematopoiesis.

Figure 22-3. Natural History of the Myeloproliferative Syndromes
SPLEEN DISORDERS

1. Enlarged spleen (splenomegaly)
   a. Vascular congestion: portal hypertension
   b. Reactive hyperplasia of white pulp: autoimmune disorders, infectious mononucleosis, malaria
   c. Infiltrative diseases: metastatic non-Hodgkin lymphoma, primary amyloidosis, leukemias
   d. Accumulated macrophages in red pulp: Gaucher disease (macrophages have fibrillary appearance due to accumulation of glucocerebrosides); Niemann-Pick disease (macrophages have a soap bubble appearance due to accumulation of sphingomyelin); extravascular hemolysis
   e. Extramedullary hematopoiesis in splenic sinusoids

2. Splenic dysfunction
   a. Loss of ability to remove damaged red cells leads to Howell-Jolly bodies in peripheral red blood cells
   b. Predisposition to infections (sepsis, peritonitis), particularly due to Streptococcus, Haemophilus, and Salmonella

MISCELLANEOUS DISEASES AND DISEASES OF THE SPLEEN

1. Langherhan cell histioctosis
   a. Proliferation of Langherhan histocytes (from epidermis)
      i. Birbeck granules (look like tennis rackets) on EM
      ii. CD1 positive
   b. Three clinical presentations:
      i. Letterer-Siwe disease is a malignant histiocytosis seen in children and infants younger than 2 years that causes diffuse rash, multiple organ involvement, cystic defects in bones, and 50% mortality rate.
      ii. Hand-Schüller-Christian disease is a malignant histiocytosis that mainly affects children, has an intermediate prognosis, and causes fever, rash, cystic skull defects, and diabetes insipidus (due to involvement of the posterior pituitary).
      iii. Eosinophilic granuloma is a benign histiocytosis that occurs in adolescents and young adults, and causes bone pain and fractures secondary to unifocal lytic lesions in skull, ribs, or femurs.

2. Mast cell diseases
   a. Mast cells have metachromatic granules that stain with toluidine blue; mast cell diseases are associated with general pruritus and swelling of tissues secondary to histamine release.
   b. Types of mast cell diseases
      i. Solitary mastocytoma occurs in infants and is characterized by localized mast cell hyperplasia with release of mediators.
      ii. Urticaria pigmentosum is a skin disease with increased dermal mast cells that causes multiple oval, red-brown macules that heal with hyperpigmentation; dermatographism (skin stroked with a sharp object becomes edematous); and severe pruritus.
      iii. In systemic mastocytosis there are mast cell infiltrations in multiple organs, and patients can have splenomegaly, decreased marrow production of other cell lines, histamine release with food or other triggers, and increased risk of developing a myeloproliferative disorder, leukemia, or lymphoma.
Chapter Summary

* Leukocytosis and leukopenia are common reactions patterns of white cells, determining whether the leukocytosis is related to neutrophilia, eosinophilia, monocytosis, or lymphocytosis may be helpful in narrowing the diagnostic possibilities.

* Infectious mononucleosis is a common viral disease typically lasting 4 to 6 weeks that can cause lymphocytosis, fever, sore throat, lymphadenitis, and hepatosplenomegaly.

* Acute nonspecific lymphadenitis tends to cause tender lymph nodes and can be seen with bacterial or viral infections. Chronic nonspecific lymphadenitis tends to cause non-tender lymph nodes and can be seen with chronic inflammatory conditions, viral infections, medications, and in nodes draining cancers.

* Acute leukemias are characterized by more than 30% blasts in the bone marrow, which may also be identified in the peripheral blood. Clinically, acute leukemias cause symptoms related to marrow failure, such as anemia, fatigue, increased infections, fever, and bleeding.

* Non-Hodgkin lymphomas are classified by a variety of schemes, including the REAL (most current) classification, the Working Formulation, and the Rappaport classification.

* Acute lymphoblastic leukemia (ALL) is a leukemia of precursor lymphoid cells that may be of either B-cell or T-cell lineage. The early pre-B ALL is usually seen in children and is the most common type of ALL. T-ALL typically causes a mediastinal mass in adolescent or young adult men. A similar presentation to T-ALL is seen in lymphoblastic lymphoma, which is usually of T-cell lineage.

* Chronic lymphocytic leukemia and small lymphocytic lymphoma are very similar diseases that differ in whether they present with blood findings or lymph node findings. Both conditions are proliferations of small B cells that characteristically have B-cell markers with one T-cell marker (CD5). These are indolent diseases of the elderly.

* Hairy cell leukemia is an indolent disease of older men with characteristic lymphocytes with "hair-like" cytoplasmic projections that stain positive for TRAP.

* Follicular lymphomas are the most common form of non-Hodgkin lymphoma in the United States and are all derived from B cells. They tend to present with diffuse disease and have a better prognosis than diffuse lymphomas.

* Diffuse large B-cell lymphoma is an aggressive, rapidly proliferating tumor that may be present at extranodal sites and may be associated with EBV or HHV-8 infection.

* Small noncleaved lymphoma (Burkitt lymphoma) occurs in African type with jaw involvement and American type with involvement of the abdomen. Burkitt lymphoma has a characteristic "starry-sky" microscopic appearance and is related to a characteristic (8;14) translocation.

* Mantle cell lymphoma arises from mantle zone B lymphocytes and has a characteristic t(11;14) translocation.

* Marginal zone lymphomas often involve mucosa-associated lymphoid tissue and appear to often begin as reactive polyclonal disorders.

* Multiple myeloma is a tumor of plasma cells that is the most common primary tumor arising in the bone marrow of adults and can be associated with production of a monoclonal immunoglobulin spike (M protein) in serum or urine. Monoclonal gammopathy of undetermined significance is the term used when an M protein is found in an asymptomatic individual.

(Continued)
Chapter Summary (continued)

* Lymphoplasmacytic lymphoma (Waldenström macroglobulinemia) is a cross between multiple myeloma and small lymphocytic lymphoma with M spike, but with neoplastic cells that tend to infiltrate many organs and do not cause lytic bone lesions.

* Adult T-cell leukemia/lymphoma is a malignant T-cell disorder due to HTLV-1 infection that is found in Japan and the Caribbean.

* Mycosis fungoides is a malignant T-cell disorder with a predilection for involving skin. The term Sezary syndrome is used if the abnormal lymphocytes are found in the blood and a generalized skin rash is present.

* In Hodgkin disease, the malignant cell is the Reed-Sternberg cell, which is positive for CD15 and CD30. Hodgkin disease is classified into lymphocyte predominant, mixed cellularity, lymphocyte depletion, and nodular sclerosing types. Hodgkin disease has a bimodal age group distribution (late 20s and >50) and usually presents with painless enlargement of lymph nodes.

* Acute myelogenous leukemia is a proliferation of nonlymphoid leukemic cells within bone marrow. The French-American-British classification of AML divides the condition into eight subtypes based on the degree and type of maturation of myeloid cells that is seen.

* Myelodysplastic syndromes are proliferations of dysplastic myeloid precursors and are associated with an increased risk of developing acute leukemias.

* Myeloproliferative syndromes are clonal neoplastic proliferations of multipotent myeloid stem cells usually seen in a setting of markedly hypercellular marrow with increases in multiple cell lines including erythroid, myeloid, and megakaryocytic.

* When neutrophils, eosinophils, and basophils predominate, the condition is called chronic myelogenous leukemia and is characterized by presence of the Philadelphia chromosome, insidious onset, and massive splenomegaly.

* When erythroid precursors predominate, the condition is called polycythemia vera and clinically produces increased hematocrit with complications of hyperviscosity and risk of progression to acute leukemia.

* When megakaryocyte proliferation dominates the marrow, the condition is called essential thrombocythemia and may produce excessive bleeding and occlusion of small vessels.

* The last of the myeloproliferative syndromes is myelofibrosis with myeloid metaplasia, which is characterized by a hypocellular marrow with fibrosis accompanied by an enlarged spleen secondary to extramedullary hematopoiesis.

* Langerhans cell histiocytosis has several clinical forms and can behave in a malignant or benign fashion.

* Splenomegaly can have many causes; splenic dysfunction manifests with erythrocyte abnormalities and predisposition for serious infections.
Female Genital Pathology

VULVA

1. Condyloma acuminatum
   a. Definition: verrucous, wartlike lesions
   b. May occur on the vulva, perineum, vagina, and cervix
   c. Associated with human papillomavirus (HPV) serotypes 6 and 11
   d. Micro
      i. Koilocytosis
      ii. Acanthosis, hyperkeratosis, and parakeratosis

2. Papillary hidradenoma
   a. Definition: benign tumor of modified apocrine sweat glands of the labia majora or interlabial folds
   b. Occur along the milk line and may ulcerate, mimicking carcinoma
   c. Histologically similar to an intraductal papilloma of the breast

3. Extramammary Paget disease of the vulva
   a. Usually involves labia majora
   b. Girce erythematous, crusted rash
   c. Micro: intraepidermal malignant cells with pagetoid spread
   d. Not usually associated with underlying tumor

4. Squamous cell carcinoma
   a. Most common malignancy
   b. Most common risk factors are HPV 16 infection, cigarette use, and immunodeficiencies, including AIDS.

5. Melanoma
   a. Can occur on vulva
   b. Melanoma cells look similar to Paget cells but do not stain with PAS.

6. Bartholin gland abscess
   a. Neisseria gonorrhoeae is most common pathogen

7. Lichen sclerosis
   a. Epidermal thinning and dermal changes cause pale skin in postmenopausal women.
   b. Small risk of progression to squamous cell carcinoma

8. Lichen simplex chronicus
   a. Squamous cell hyperplasia and dermal scarring due to chronic scratchitch cycle cause white plaques.
   b. Small risk of progression to squamous cell carcinoma
**Clinical Correlate**

Historically, DES was used in high-risk pregnancies from 1940 to 1970. Subsequently, vaginal adenosis and clear cell carcinoma began to be discovered in the female offspring. Vaginal adenosis is a benign condition that is thought to be a precursor of clear cell carcinoma.

### VAGINA

1. **Vaginal adenosis and clear cell adenocarcinoma**
   a. Rare
   b. Increased risk in females exposed to diethylstilbestrol (DES) in utero

2. **Embryonal rhabdomyosarcoma (sarcoma botryoides)**
   a. Infants and young children (age <4)
   b. Gross: polypoid, "grapelike," soft tissue mass protruding from the vagina
   c. Micro
      i. Spindle-shaped tumor cells with rare cross-striations
      ii. Cambium layer: tendency of tumor to grow beneath the vaginal epithelium
      iii. Tumor cells are positive for desmin.

3. **Vaginal squamous cell carcinoma**
   a. Primary forms are usually related to HPV infection.
   b. Secondary forms are more common and are usually due to extension from a cervical cancer.

4. **Rhabdomyoma**
   a. Benign skeletal muscle tumor

5. **Gartner duct cyst**
   a. Cyst of lateral wall of vagina
   b. Due to persistence of a mesonephric (Wolffian) duct remnant

6. **Rokitansky-Kuster-Hauser syndrome**
   a. Congenital absence of upper part of vagina and uterus
   b. Presents with primary amenorrhea

### CERVIX

1. **Pelvic inflammatory disease (PID)**
   a. Definition: ascending infection (sexually transmitted disease [STD]) from the cervix to the endometrium, fallopian tubes, and pelvic cavity
   b. Organisms: gonorrhea and/or chlamydia
   c. Distribution of disease
      i. Endometrium: endometritis
      ii. Fallopian tubes: salpingitis
      iii. Pelvic cavity: peritonitis and pelvic abscesses
      iv. Fitz-Hugh–Curtis syndrome (perihepatitis) characterized by “violin-string” adhesions between the fallopian tube and liver capsule
   d. Clinical presentation
      i. Vaginal discharge (cervicitis)
      ii. Vaginal bleeding and midline abdominal pain (endometritis)
      iii. Bilateral lower abdominal and pelvic pain (salpingitis)
      iv. Abdominal tenderness and peritoneal signs (peritonitis)
      v. Pleuritic right upper quadrant pain (perihepatitis)
e. Complications
   i. Tubo-ovarian abscess
   ii. Tubal scarring increases risk of infertility and ectopic tubal pregnancies.
   iii. Intestinal obstruction secondary to fibrous adhesions

Table 23-1. Malignant Tumors of the Lower Female Genital Tract in the United States

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Endometrial cancer</td>
<td>1. Ovarian cancer</td>
</tr>
<tr>
<td>2. Ovarian cancer</td>
<td>2. Endometrial cancer</td>
</tr>
</tbody>
</table>

2. Cervical carcinoma
   a. Epidemiology
      i. Third most common malignant tumor of the lower female genital tract in United States
      ii. Peak incidence in middle age (above 40 years)
      iii. Most commonly squamous cell carcinoma, but can also be adenocarcinoma or small cell neuroendocrine carcinoma
   b. Risk factors
      i. Early age of first intercourse
      ii. Multiple sexual partners
      iii. Multiple pregnancies
      iv. Oral contraceptive use
      v. Smoking
      vi. STDs
      vii. Immunosuppression
   c. HPV
      i. High risk types 16, 18, 31, and 33
      ii. Viral oncogenes E6 (binds to p53) and E7 (binds to Rb)
   d. Precursor lesion: cervical intraepithelial neoplasia (CIN)
      i. Increasing in incidence
      ii. Occurs commonly at the squamocolumnar junction (transformation zone)
      iii. Progression
         • CIN I (mild dysplasia)—low grade SIL (squamous intraepithelial lesion)
         • CIN II (moderate dysplasia)—high grade SIL
         • CIN III (severe dysplasia)—high grade SIL
         • CIS (carcinoma in situ)
         • Invasive squamous-cell carcinoma
   e. Clinical presentation
      i. Asymptomatic
      ii. Postcoital vaginal bleeding
      iii. Dyspareunia
      iv. Malodorous discharge

Clinical Correlate
Tubal ectopic pregnancies usually occur in the ampulla of the fallopian tube. Tubal rupture results in severe, acute lower abdominal pain.
f. Diagnosis
   i. Papanicolaou (Pap) test: early detection
   ii. Colposcopy with biopsy

3. Cervicitis
   a. Acute and chronic cervicitis are common and usually nonspecific inflammatory conditions.
   b. Important specific causes of acute cervicitis include *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, *Candida*, and herpes simplex II.
   c. A specific severe form of chronic cervicitis (follicular cervicitis) can be due to *Chlamydia trachomatis*, and can cause neonatal conjunctivitis and pneumonia in infants delivered vaginally through an infected cervix.

4. Cervical polyps
   a. Common non-neoplastic polyps that can be covered with columnar or stratified squamous epithelium

**UTERUS**

1. Endometritis
   a. Acute endometritis
      i. Ascending infection from the cervix
      ii. Associated with pregnancy or abortions
   b. Chronic endometritis
      i. Associated with PID and intrauterine devices (IUDs)
      ii. Micro: plasma cells in the endometrium

2. Endometriosis
   a. Definition: presence of endometrial glands and stroma outside the uterus
   b. Most commonly affects women of reproductive age
   c. Common sites
      i. Ovary
      ii. Ovarian and uterine ligaments
      iii. Pouch of Douglas
      iv. Serosa of bowel and urinary bladder
      v. Peritoneal cavity
   d. Gross
      i. Red-brown serosal nodules ("powder burns")
      ii. Endometrioma: ovarian "chocolate" (hemolyzed blood) cyst
   e. Clinical presentation
      i. Chronic pelvic pain
      ii. Dysmenorrhea and dyspareunia
      iii. Rectal pain and constipation
      iv. Infertility

3. Leiomyoma (fibroids)
   a. Definition: a benign smooth muscle tumor of the myometrium
   b. Most common tumor of the female genital tract

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**Clinical Correlate**

Adenomyosis is the presence of endometrial glands and stroma within the myometrium of the uterus.
c. High incidence in African Americans
d. Responsive to estrogen
e. Gross
   i. Well-circumscribed, rubbery, white-tan masses
   ii. Whorl-like trabeculated appearance on cut section
   iii. Commonly multiple
f. Locations: subserosal, intramural, and submucosal
g. Clinical presentation
   i. Menorrhagia
   ii. Abdominal mass
   iii. Pelvic pain, back pain, or suprapubic discomfort
   iv. Infertility and spontaneous abortion
h. Malignant variant: leiomyosarcoma

4. Endometrial carcinoma

   a. Epidemiology
      i. Most common malignant tumor of the lower female genital tract
      ii. Most commonly affects postmenopausal women
   b. Clinical presentation: postmenopausal vaginal bleeding
   c. Risk factors
      i. Early menarche and late menopause
      ii. Nulliparity
      iii. Hypertension and diabetes
      iv. Obesity
      v. Chronic anovulation
      vi. Estrogen-producing ovarian tumors (granulosa cell tumors)
      vii. Estrogen replacement therapy (ERT) and tamoxifen
      viii. Endometrial hyperplasia (complex atypical hyperplasia)
      ix. Lynch syndrome: colon, endometrial, and ovarian cancers
d. Gross
   i. Tan polypoid endometrial mass
   ii. Invasion of myometrium is prognostically important.
   e. Micro: endometroid adenocarcinoma (most common type)

5. Less common types of uterine malignancy

   a. Leiomyosarcoma is a malignant smooth muscle tumor.
   b. Malignant mixed müllerian tumors contain both malignant stromal cells and endometrial adenocarcinoma.

6. Adenomyosis

   a. Invagination of the deeper layers of the endometrium into the myometrium causes menorrhagia and dysmenorrhea.
OVARY

1. Polycystic ovarian disease (Stein-Leventhal syndrome)
   a. Definition: an endocrine disorder showing signs of androgen excess (clinical or biochemical), oligoovulation and/or anovulation, polycystic ovaries, and other endocrine disorders are excluded
   b. Clinical presentation
      i. Young females of reproductive age
      ii. Oligomenorrhea or secondary amenorrhea
      iii. Hirsutism
      iv. Infertility
      v. Obesity
   c. Unknown etiology
   d. Lab
      i. Elevated luteinizing hormone (LH)
      ii. Low follicle-stimulating hormone (FSH)
      iii. Elevated testosterone
   e. Gross: bilaterally enlarged ovaries with multiple cysts
   f. Micro: multiple follicle cysts
   g. Treatment: oral contraceptives or Provera

2. Epithelial ovarian tumors
   a. Arise from the ovarian surface epithelium
   b. Most common form of ovarian tumor
   c. Cystadenoma
      i. Most common benign ovarian tumor
      ii. Gross: unicocular, smooth-lined cyst
      iii. Micro: simple serous or mucinous lining
   d. Borderline tumors (tumors of low malignant potential)
   e. Cystadenocarcinoma
      i. Most common malignant ovarian tumor
      ii. Gross
         • Complex multiloculated cyst
         • Nodular and solid areas
      iii. Micro
         • Stratified serous or mucinous lining with tufting
         • Papillary structures with psammoma bodies
         • Stromal invasion
      iv. Hereditary risk factors
         • BRCA-1: breast and ovarian cancers
         • Lynch syndrome
      v. Tumor marker: CA 125
      vi. Commonly spreads by seeding the peritoneal cavity
      vii. Often detected at a late stage with a poor prognosis
3. Ovarian germ cell tumors
   a. Teratoma (dermoid cyst)
      i. Vast majority (>95%) are benign
      ii. Commonly occur in the early reproductive years
      iii. Elements from all three germ cell layers are present.
          • Ectoderm: skin, hair, adnexa, and neural tissue
          • Mesoderm: bone and cartilage
          • Endoderm: thyroid and bronchial tissue
      iv. Gross: ovarian cyst containing hair, teeth, and greasy material
      v. Struma ovarii: preponderance of thyroid tissue
      vi. Immature teratoma: histologically immature tissue
      vii. Complications
          • Torsion
          • Rupture
          • Malignant transformation (1%): usually squamous cell carcinoma (SCC)
   b. Dysgerminoma
      i. Malignant germ cell tumor
      ii. Common in young adults
      iii. Risk factors: Turner syndrome and pseudohermaphrodites
      iv. Gross and microscopic features are similar to seminomas
      v. Radiosensitive
      vi. Good prognosis
   c. Yolk sac tumor (endodermal sinus tumor)
   d. Choriocarcinoma

4. Ovarian sex cord–stromal tumors
   a. Ovarian fibroma
      i. Most common stromal tumor
      ii. Gross: firm, white masses
      iii. Meigs syndrome: fibroma + ascites + pleural effusion
   b. Granulosa cell tumor
      i. Potentially malignant
      ii. Estrogen-producing tumor
      iii. The clinical presentation depends on age:
          • Prepuberal → precocious puberty
          • Reproductive age → irregular menses
          • Postmenopausal → vaginal bleeding
      iv. Gross: yellow-white mass
      v. Micro
          • Polygonal tumor cells
          • Formation of follicle-like structures (Call-Exner bodies)
      vi. Complications: endometrial hyperplasia and cancer
   c. Sertoli-Leydig cell tumor (androblastoma)
      i. Androgen-producing tumor
ii. Clinical presentation: virilization
iii. Complication: risk of female psuedohermaphrodite

5. Metastatic tumors to the ovary
   a. Primary sites
      i. Breast cancer
      ii. Colon cancer
      iii. Endometrial cancer
      iv. Gastric "signet-ring cell" cancer (Krukenberg tumor)

Table 23-2. Origins of Common Ovarian Neoplasms

<table>
<thead>
<tr>
<th>Age group affected</th>
<th>Surface Epithelial Cells (Surface epithelial-stromal cell tumors)</th>
<th>Germ Cell</th>
<th>Sex Cord-Stroma</th>
<th>Metastasis to Ovaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall frequency</td>
<td>65–70%</td>
<td>15–20%</td>
<td>5–10%</td>
<td>5%</td>
</tr>
<tr>
<td>Percentage of malignant ovarian tumors</td>
<td>90%</td>
<td>3–5%</td>
<td>2–3%</td>
<td>5%</td>
</tr>
<tr>
<td>Types</td>
<td>Serous tumor</td>
<td>Teratoma</td>
<td>Fibroma</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>Mucinous tumor</td>
<td>Dysgerminoma</td>
<td>Granulosa-theca</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endometrioid tumor</td>
<td>Endodermal sinus tumor</td>
<td>cell tumor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clear cell tumor</td>
<td>Choriocarcinoma</td>
<td>Sertoli-Leydig cell tumor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brenner tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cystadenofigroma</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GESTATIONAL TROPHOBLASTIC DISEASE AND PLACENTAL DISEASE

1. Hydatidiform mole (molar pregnancy)
   a. Definition: tumor of placental trophoblastic tissue
      i. Complete mole: results from fertilization of an ovum that lost all its chromosomal material
         • All chromosomal material is derived from sperm.
         • 90% of the time, the molar karyotype is 46,XX.
         • 10% of the time, the molar karyotype includes a Y chromosome.
         • The embryo does not develop.
      ii. Partial mole: results from fertilization of an ovum that has not lost its chromosomal material by two sperms, one 23,X and one 23,Y
         • This results in a trilopoid cell 69, XXY (23,X [maternal] + 23,X [one sperm] + 23,Y [the other sperm])
         • The embryo may develop for a few weeks.
   b. Incidence
      i. United States: 1 per 1,000 pregnancies
      ii. Asia > United States
      iii. Increased risk in women ages <15 and >40
c. Clinical presentation
   i. Excessive uterine enlargement → "size greater than dates"
   ii. Vaginal bleeding
   iii. Passage of edematous, grapelike soft tissue
   iv. Elevated *beta human chorionic gonadotropin* (β-HCG)

d. Micro
   i. Edematous chorionic villi
   ii. Trophoblast proliferation
   iii. Fetal tissue (only in partial mole)

e. Diagnosis: ultrasound

f. Treatment: endometrial curettage and follow β-HCG levels

**Table 23-3. Properties of a Partial Mole Versus Those of a Complete Mole**

<table>
<thead>
<tr>
<th></th>
<th>Partial Mole</th>
<th>Complete Mole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ploidy</td>
<td>Triploid</td>
<td>Diploid</td>
</tr>
<tr>
<td>Number of chromosomes</td>
<td>69</td>
<td>46 (All paternal)</td>
</tr>
<tr>
<td>β-HCG</td>
<td>Elevated (+)</td>
<td>Elevated (+++)</td>
</tr>
<tr>
<td>Chorionic villi</td>
<td>Some are hydropic</td>
<td>All are hydropic</td>
</tr>
<tr>
<td>Trophoblast proliferation</td>
<td>Focal</td>
<td>Marked</td>
</tr>
<tr>
<td>Fetal tissue</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Invasive mole</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>Rare</td>
<td>2%</td>
</tr>
</tbody>
</table>

2. **Invasive mole**: a mole that invades the myometrium of the uterine wall

3. **Choriocarcinoma**
   a. Malignant germ cell tumor derived from the trophoblast
   b. Gross: necrotic and hemorrhagic mass
   c. Micro: proliferation of cytotrophoblasts, intermediate trophoblasts, and syncytiotrophoblasts
   d. Hematogenous spread to lungs, brain, liver, etc.
   e. Responsive to chemotherapy

4. **Ectopic pregnancy**
   a. Fetus implants outside normal location, most often in the fallopian tube, and less often in the ovaries or abdominal cavity.
   b. Fetus almost never survives.
   c. Mother is at risk of potentially fatal intra-abdominal hemorrhage.
   d. Risk factors include scarring of fallopian tubes from pelvic inflammatory disease, endometriosis, and decreased tubal motility.

5. **Enlarged placentas**
   a. More common with maternal diabetes mellitus, Rh hemolytic disease, and congenital syphilis
6. Succenturiate lobes
   a. Accessory lobes of the placenta that may cause hemorrhage if they are torn away from the main part of the placenta during delivery

7. Placental abruption
   a. Partial premature separation of the placenta away from the endometrium with resulting hemorrhage and clot formation
   b. Risk factors include hypertension, cigarette use, cocaine, and older maternal age.

8. Placenta previa
   a. Placenta overlies cervical os.
   b. Vaginal delivery can cause the placenta to tear, with potentially fatal maternal or fetal hemorrhage.

9. Placenta accreta
   a. Placenta implants directly on the myometrium rather than on endometrium.
   b. Hysterectomy is required after delivery to remove the rest of the placenta.

10. Fraternal twins
    a. Always have 2 amnions and 2 chorions; placental discs are usually separate, but can grow together to appear to be a single placental disc

11. Identical twins
    a. Variable pattern in the number of membranes and discs due to variations in the specific point in embryonic development at which the twins separated
    b. Twin-twin transfusion syndrome can occur if there is only one placental disc and one twin's placental vessels connect to the other twin's placental vessels.
    c. Conjoined twins are always identical twins with one amnion, one chorion, and one disc.
Chapter Summary

* Lesions of the vulva include condyloma acuminatum, papillary hyperplasia, extramammary Paget disease, squamous cell carcinoma, melanoma, Bartholin gland abscess, lichen sclerosis, and lichen simplex chronicus.

* Lesions of the vagina include vaginal adenosis, clear cell adenocarcinoma, embryonal rhabdomyosarcoma, squamous cell carcinoma, rhabdomyosarcoma, Gardner duct cyst, and Rokitansky-Kuster-Hauser syndrome.

* Pelvic inflammatory disease is an ascending infection that is often due to gonorrhea and/or Chlamydia, from the cervix to the endometrium, fallopian tubes, and pelvic cavity. Pelvic inflammatory disease is an important cause of pelvic and even peritoneal inflammation, abscess formation, and scarring.

* Cervical carcinoma is the third most common malignant tumor of the female genital tract and typically arises from HPV-types 16, 18, 31, and 33. Cervical polyps and cysts can also affect the cervix.

* Acute endometritis is usually due to an ascending infection of the cervix, sometimes associated with pregnancy or abortions. Chronic endometritis is associated with PID and intrauterine devices.

* Endometriosis is the presence of endometrial glands and stroma outside the uterus, and may cause red-brown nodules or cysts in a wide variety of sites.

* Leiomyomas are benign smooth muscle tumors that are the most common tumors of the female tract.

* Endometrial adenocarcinoma is the most common malignant tumor of the female genital tract and usually presents as postmenopausal bleeding. Less common tumors of the uterus include leiomyosarcoma and malignant mixed mullerian tumors.

* Polycystic ovarian disease is a cause of infertility and hirsutism in young women.

* Ovarian tumors are subclassified as epithelial, germ-cell, or sex cord origin. Epithelial ovarian tumors include cystadenoma, borderline tumors, and cystadenocarcinoma. Ovarian germ-cell tumors include teratoma, dysgerminoma, yolk sac tumor, and choriocarcinoma. Ovarian sex cord-stromal tumors include ovarian fibroma, granulosa cell tumor, and Sertoli-Leydig cell tumor. The ovaries are also a site of metastatic disease, with common primary sites including breast, colon, endometrium, and stomach.

* Gestational trophoblastic disease includes benign and malignant tumors derived from trophoblast, including hydatidiform mole, invasive mole, and choriocarcinoma.

* Abnormalities of the placenta include ectopic pregnancy, enlarged placenta, succenturiate lobes, placental abruption, placenta previa, placenta accreta, and twin placenta.
Table 24-1. Anatomic Correlation to Common Breast Lesions

<table>
<thead>
<tr>
<th>Normal</th>
<th>Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal duct</td>
<td>Cyst</td>
</tr>
<tr>
<td>Lobular unit</td>
<td>Sclerosing adenosis</td>
</tr>
<tr>
<td></td>
<td>Small duct papilloma</td>
</tr>
<tr>
<td></td>
<td>Hyperplasia</td>
</tr>
<tr>
<td></td>
<td>Atypical hyperplasia</td>
</tr>
<tr>
<td></td>
<td>Carcinoma</td>
</tr>
<tr>
<td>Lobular stroma</td>
<td>Fibroadenoma</td>
</tr>
<tr>
<td></td>
<td>Phyllodes tumor</td>
</tr>
</tbody>
</table>

Nipple and areola:

Large ducts and lactiferous sinuses
- Duct ectasia
- Recurrent subareolar abscess
- Solitary ductal papilloma
- Paget disease

Interlobular stroma
- Fat necrosis
- Lipoma
- Fibrous tumor
- PASH
- Fibromatosis
- Sarcoma

**MASTITIS**

1. Acute mastitis
   a. Definition: acute inflammation of the breast, commonly during lactation
   b. Organism: *Staphylococcus aureus* (most common)

2. Fat necrosis
   a. Definition: fat necrosis often related to trauma or prior surgery
   b. May produce a palpable mass or lesion on mammography

**Note**

Most Common Causes of Breast Lumps
- Fibrocystic changes
- Normal breast, no disease
- Cancer
FIBROCYSTIC CHANGES

1. Definition: a collection of benign breast tissue changes with nonproliferative components and proliferative components that increase the risk of breast cancer
2. Old name: fibrocystic disease
3. Age 20–50 years
4. Extremely common
5. May produce a palpable mass or nodularity
6. Most often involves the upper outer quadrant

Table 24-2. Nonproliferative Versus Proliferative Fibrocystic Changes

<table>
<thead>
<tr>
<th>Nonproliferative</th>
<th>Proliferative Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis</td>
<td>Ductal hyperplasia ± atypia</td>
</tr>
<tr>
<td>Cysts (blue-domed)</td>
<td>Sclerosing adenosis</td>
</tr>
<tr>
<td>Apocrine metaplasia</td>
<td>Small duct papillomas</td>
</tr>
<tr>
<td>Microcalcifications</td>
<td></td>
</tr>
</tbody>
</table>

Table 24-3. Relative Risk of Developing Breast Cancer with Fibrocystic Change

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>Fibrocystic Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>No increase</td>
<td>Fibrosis, cysts, apocrine metaplasia, adenosis</td>
</tr>
<tr>
<td>1.5–2x</td>
<td>Sclerosing adenosis, ductal hyperplasia, papillomas</td>
</tr>
<tr>
<td>4–5x</td>
<td>Atypical ductal or lobular hyperplasia</td>
</tr>
</tbody>
</table>

Table 24-4. Features That Distinguish Fibrocystic Change from Breast Cancer

<table>
<thead>
<tr>
<th>Fibrocystic Change</th>
<th>Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Often bilateral</td>
<td>Often unilateral</td>
</tr>
<tr>
<td>May have multiple nodules</td>
<td>Usually single</td>
</tr>
<tr>
<td>Menstrual variation</td>
<td>No menstrual variation</td>
</tr>
<tr>
<td>Cyclic pain and engorgement</td>
<td>No cyclic pain or engorgement</td>
</tr>
<tr>
<td>May regress during pregnancy</td>
<td>Does not regress during pregnancy</td>
</tr>
</tbody>
</table>

BENIGN NEOPLASMS

1. Fibroadenoma
   a. Most common benign breast tumor in women <35 years old
   b. Presentation: palpable, round, movable, rubbery mass
   c. Gross: well-circumscribed, tan, rubbery mass with small, cleftlike spaces
   d. Micro: proliferation of benign stroma; ducts, and lobules
2. Phyllodes tumor (cystosarcoma phyllodes)
   a. Fibroadenoma variant usually involves an older patient population (50s)
   b. Micro: increased cellularity, stromal overgrowth, and irregular margins
   c. May locally recur or rarely metastasize
3. Intraductal papilloma
   a. Commonly presents as a bloody nipple discharge
   b. Micro: benign papillary growth within lactiferous ducts or sinuses

MALIGNANT NEOPLASMS

1. Carcinoma of the breast
   a. Epidemiology
      i. Most common cancer in females (1 in 9 women in the U.S.)
      ii. Second most common cause of cancer death
      iii. United States > Japan
      iv. Incidence is increasing
   b. Risk factors
      i. Incidence increases with age
      ii. First-degree relative with breast cancer
      iii. Hereditary (5-10% of breast cancers)
         • BRCA1 (error-free repair of DNA double strand breaks) chromosome 17q21
         • BRCA2 (error-free repair of DNA double strand breaks) chromosome 13q12-13
         • P53 germ-line mutation: Li-Fraumeni syndrome
      iv. Prior breast cancer
      v. Long length of reproductive life
      vi. Nulliparity
      vii. Obesity
      viii. Exogenous estrogens
      ix. Proliferative fibrocystic changes, especially atypical hyperplasia
   c. Clinical presentation
      i. Mammographic calcifications or architectural distortion
      ii. Physical exam: solitary painless mass
      iii. Nipple retraction or skin dimpling
      iv. Fixation to the chest wall
      v. Most common in upper outer quadrant
   d. Gross: stellate, white-tan, gritty mass

2. Histologic variants
   a. Preinvasive lesions
      i. Ductal carcinoma in situ (DCIS)
      ii. Lobular carcinoma in situ (LCIS)
      iii. Paget disease of the nipple (see Other Breast Conditions below)
   b. Invasive (infiltrating) ductal carcinoma
      i. Most common (>50%)
ii. Micro: tumor cells form ducts within a desmoplastic stroma

c. Invasive (infiltrating) lobular carcinoma
   i. Some 5–10% of cases
   ii. Micro: small, bland tumor cells form a single-file pattern
   iii. High incidence of multifocal and bilateral disease

d. Mucinous (colloid) carcinoma
   i. Micro: clusters of bland tumor cells float within pools of mucin
   ii. Better prognosis

e. Tubular carcinoma: rarely metastasizes and excellent prognosis

f. Medullary carcinoma
   i. Micro
      • Pleomorphic tumor cells form syncytial groups
      • Surrounded by a dense lymphocytic host response
   ii. Better prognosis

g. Inflammatory carcinoma
   i. Red, warm, edematous skin
   ii. Peau d’orange: thickened skin resembles an orange peel
   iii. Extensive dermal lymphatic edema

3. Prognosis
   a. Axillary lymph node status
   b. Size of tumor
   c. Histological type and grade of tumor
   d. ER/PR receptor status
   e. Overexpression of c-erbB2 (HER2/neu) – more aggressive than other types of breast cancer
   f. Flow cytometry S-phase and DNA ploidy

4. Treatment
   a. Local disease
      i. Mastectomy or lumpectomy with radiation
      ii. Axillary dissection
   b. Metastatic disease
      i. Tamoxifen
      ii. Chemotherapy

OTHER BREAST CONDITIONS

1. Paget disease of the nipple
   a. Ulceration, oozing, crusting, and fissuring of the nipple and areola
   b. Micro
      i. Intraepidermal spread of tumor cells (Paget cells)
      ii. Tumor cells occur singly or in groups.
      iii. Often have a clear halo surrounding the nucleus
   c. Commonly associated with an underlying invasive or in situ ductal carcinoma
2. Gynecomastia
   a. Unilateral or bilateral benign breast enlargement in a male patient
   b. Usually the result of altered androgen-estrogen balance that favors estrogen effect
   c. Ductal epithelial hyperplasia, ductal elongation and branching, proliferation of periductal fibroblasts, and an increase in vascularity are seen in the involved tissue.

Figure 24-1. Paget Cells
Chapter Summary

* Acute mastitis commonly occurs during lactation and is usually due to *Staphylococcus aureus*.

* Fibrocystic change is an extremely common condition of women 20 to 50 years of age that can produce fibrosis, cyst formation, apocrine metaplasia, microcalcifications, ductal hyperplasia with or without atypia, sclerosing adenosis, and small duct papillomas.

* Fibroadenoma is the most common benign breast tumor of women younger than 35 years of age, and produces a palpable, rubbery, movable mass.

* Cystosarcoma phylloides is a large tumor involving both stroma and glands that behaves malignantly in 10–20% of cases.

* Carcinoma of the breast is the most common cancer in women, with a 1 in 9 incidence in the United States. Clinical features can include calcifications or architectural distortion visible by mammography, solitary painless mass, nipple retraction or skin dimpling, and fixation to the chest wall. Preinvasive lesions that may progress to breast cancer include ductal carcinoma *in situ* and lobular carcinoma *in situ*. Invasive cancer occurs in several histologic variants, including ductal carcinoma, lobular carcinoma, mucinous carcinoma, tubular carcinoma, medullary carcinoma, and inflammatory carcinoma.

* Paget disease of the nipple is an intraepidermal spread of tumor cells that is commonly associated with an underlying invasive or *in situ* ductal carcinoma.

* Gynecomastia is a benign breast enlargement in a male, usually resulting from an increased estrogen to androgen ratio.
Male Pathology

PENIS

1. Malformations
   a. Epispadias: urethral opening on the dorsal surface of the penis
   b. Hypospadias: urethral opening on the ventral surface of the penis
   c. Both malformations may be associated with undescended testes.
   d. Both malformations have an increased risk of urinary tract infections (UTIs) and infertility.

2. Balanitis/balanoposthitis
   a. Definition: inflammation of the glans penis
   b. Causes: poor hygiene and lack of circumcision

3. Peyronie disease: Penile fibromatosi resulting in curvature of the penis

4. Condyloma acuminatum
   a. Warty, cauliflower-like growth
   b. Human papilloma virus (HPV) serotypes 6 and 11

5. Squamous cell carcinoma (SCC)
   a. Uncommon in the United States
   b. Increased risk in uncircumcised males
   c. Human papilloma virus (HPV) serotypes 16 and 18
   d. Precursors: Bowen disease, Bowenoid papulosis, erythroplasia of Queyrat (may be regarded as synonymous with penile Bowen disease or as representative of one end of a spectrum of in situ penile carcinoma)

6. Priapism
   a. Persistent painful erection that can be caused by sickle cell anemia (causes blood clumping in penis), trauma, and drugs (e.g., trazodone)

7. Erectile dysfunction
   a. Causes of impotence include psychological factors, decreased testosterone, vascular insufficiency (most common cause over age 50), neurologic disease (multiple sclerosis, diabetic neuropathy, radical prostatectomy), some medications (leuprolide, methylpap, psychotropic medications), hypothyroidism, prolactinoma, and penile disorders

TESTES

1. Varicocele
   a. Dilated vein within the spermatic cord
   b. May cause infertility
2. **Hydrocele**: fluid within the tunica vaginalis
3. **Spermatocele**: dilated efferent duct in the epididymus containing sperm
4. **Epididymitis**
   a. Acute epididymitis
      i. Age <35: *Neisseria gonorrhoeae* and *Chlamydia trachomatis*
      ii. Age >35: *Escherichia coli* and *Pseudomonas*
   b. Chronic epididymitis: TB
5. **Orchitis**: viral—mumps
6. **Testicular torsion**
   a. Twisting of the spermatic cord
   b. May be associated with physical activity or trauma
   c. Painful hemorrhagic infarction leading to gangrene
7. **Cryptorchidism**
   a. Failure of one or both testes to descend
      i. Testes are most commonly found in inguinal canal.
      ii. Increased risk for developing seminoma
8. **Male infertility**
   a. Decreased sperm count due to primary testicular dysfunction can be due to either Leydig cell dysfunction or seminiferous tubule dysfunction.
   b. Decreased sperm count due to secondary hypogonadism can be due to pituitary and hypothalamic dysfunction.
   c. Inability of sperm to exit the body in sufficient numbers may be due to obstruction of the vas deferens or disordered ejaculation.

**TESTICULAR CANCER**

1. **Clinical presentation**
   a. Firm, painless testicular mass
   b. Nonseminomatous tumors may present with widespread metastasis.
2. **Risk factors**
   a. Cryptorchidism: (5–10 times increased risk!)
   b. Testicular dysgenesis (testicular feminization and Klinefelter syndrome)
   c. Caucasians > African Americans
   d. Family history
3. **Diagnosis**
   a. Ultrasound: hypoechoic intratesticular mass
   b. Tumor marker studies
   c. Radical orchiectomy
   d. Staging: CXR and abdominal and/or chest CT scan
Figure 25-1. Germ-Cell Malignancies

Table 25-1. Seminomas Versus Nonseminomatous Germ-Cell Tumors

<table>
<thead>
<tr>
<th>Seminomas</th>
<th>Nonseminomatous Germ-Cell Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminoma</td>
<td>Embryonal, yolk sac, choriocarcinoma, teratoma</td>
</tr>
<tr>
<td>Radiosensitive</td>
<td>Not radiosensitive</td>
</tr>
<tr>
<td>Chemosensitive</td>
<td>Chemosensitive</td>
</tr>
<tr>
<td>Late metastasis</td>
<td>Early metastases to retroperitoneal lymph nodes</td>
</tr>
<tr>
<td>Excellent prognosis</td>
<td>More aggressive</td>
</tr>
</tbody>
</table>

4. Germ-cell tumors

a. Seminoma
i. Most common germ-cell tumor in adults age 15–35 years
ii. Gross: large, gray-tan, bulky masses
iii. Micro—
   • Polygonal germ cells with clear cytoplasm and round nuclei
   • Arranged in lobules, which are separated by fibrous septae
   • Lymphocytes, granuloma, and giant cells may be seen.
iv. Tumor marker: placental alkaline phosphatase (PLAP)
v. Treatment: chemo- and radiosensitive
vi. Prognosis: excellent; early stage 95% cure
vii. Variant: spermatocytic seminoma—older men, excellent prognosis
b. Embryonal carcinoma
   i. Age 20–40 years
   ii. Gross: bulky masses with hemorrhage and necrosis
   iii. Micro: large primitive cells
   iv. Tumor markers: nonspecific, may have alpha-fetoprotein (AFP) and/or beta human chorionic gonadotropin (β-hCG)
   v. More aggressive than seminoma

c. Choriocarcinoma
   i. Highly malignant with widespread metastasis
   ii. Gross: often small primaries with extensive hemorrhage and necrosis
   iii. Micro: proliferation of syncytiotrophoblasts and cytotrophoblasts
   iv. Tumor marker: β-hCG
   v. Hematogenous spread to lungs and liver

d. Yolk sac tumor (endodermal sinus tumor)
   i. Most common germ-cell tumor in children
   ii. Good prognosis in children
   iii. In adults, it is often mixed with other components.
   iv. Micro: Schiller-Duval bodies—a mesodermal core with a central capillary, all lined by flattened layers of both visceral and parietal cells resembling a glomerulus-like structure
   v. Tumor marker: alpha-fetoprotein (AFP)

e. Teratoma
   i. Majority (99%) are malignant
   ii. Gross: often cystic masses that may contain cartilage and bone
   iii. Micro: contains ectodermal, endodermal, and mesodermal tissue in a haphazard arrangement
   iv. Immature elements and malignant transformation are often seen.

f. Mixed germ-cell tumors
   i. As many as 60% of germ-cell tumors are mixed and contain more than one component!
   ii. Teratocarcinoma: teratoma + embryonal carcinoma

5. Sex cord–stromal tumors
   a. Leydig cell tumors
      i. May produce androgens and estrogens
      ii. Age 20–60 years
      iii. Presentation
          • Painless testicular mass
          • Adults → gynecomastia
          • Children → precocious puberty
      iv. Prognosis
          • Benign tumors (90%) have an excellent prognosis.
          • Malignant (10%)

b. Sertoli cell tumors: rare
6. **Testicular lymphoma**
   a. Most common testicular tumor in men over age 50 years
   b. Non-Hodgkin lymphoma, diffuse large-cell type

7. **Scleral squamous cell carcinoma** (SCC) is associated with exposure to soot (chimney sweeps)

### PROSTATE

1. **Benign prostatic hypertrophy (BPH)**
   a. Synonyms: nodular hyperplasia, glandular and stromal hyperplasia
   b. Definition: glandular and stromal hyperplasia resulting in prostate enlargement
   c. Epidemiology
      i. Extremely common
      ii. Incidence increases with age (age 60 years = 70%, age 70 years = 80%)
      iii. Not premalignant
   d. Pathogenesis: androgens (dihydrotestosterone) play an important role
   e. Gross
      i. Enlarged prostate with well-demarcated nodules in the transition and central (periurethral zones)
      ii. Often results in slitlike compression of the prostatic urethra
   f. Presentation
      i. Decreased caliber and force of stream
      ii. Trouble starting (hesitancy) and stopping the stream
      iii. Postvoid dribbling, urinary retention, incontinence
      iv. Urgency, frequency, nocturia, dysuria
   g. Prostatic specific antigen (PSA) may be elevated but is usually <10 ng/ml
   h. Treatment
      i. Transurethral resection of prostate (TURP)
      ii. Finasteride (Proscar): 5-alpha reductase inhibitor
      iii. Terazosin, prazosin: selective alpha-1 receptor blockers

2. **Prostate adenocarcinoma**
   a. Epidemiology
      i. Most common cancer in men in the United States
      ii. Second most common cause of cancer death in men
      iii. Incidence increases with age
      iv. Highest rate in African Americans
   b. Gross
      i. Ill-defined, firm, yellow mass
      ii. Commonly arises in the posterior aspect of the peripheral zone

**Note**
The term BPH more accurately represents hyperplasia than hypertrophy, although you may see either term used.

**Bridge to Anatomy**
Hyperplasia → transitional/periurethral zones
Carcinoma → peripheral zone
c. Presentation
   i. Often clinically silent
   ii. May present with lower back pain secondary to metastasis
   iii. Advanced localized disease may present with urinary tract obstruction or UTIs (uncommon).

d. Detection
   i. Digital rectal exam (induration)
   ii. Serum PSA levels
   iii. Transrectal ultrasound and biopsy

e. Micro
   i. Adenocarcinoma
   ii. Gleason grading system

f. Metastasis
   i. Commonly goes to the obturator and pelvic lymph nodes
   ii. Osteoblastic bone metastasis to the lumbar spine
   iii. Alkaline phosphatase elevated with metastasis

g. Treatment
   i. Local disease: prostatectomy and/or external beam radiation
   ii. Metastatic disease
      • Orchiectomy
      • Estrogens or androgen receptor blockade (flutamide or leuprolide)
   iii. Monitor with PSA levels

3. Prostatitis
   a. **Acute prostatitis** is usually due to intraprostatic reflux of urine containing *Escherichia*, *Pseudomonas*, or *Klebsiella* pathogens.

   b. **Chronic prostatitis** may develop following recurrent acute prostatitis, and bacterial pathogens may not be detectable.

   c. Clinical findings can include fever (acute prostatitis), pain (lower back, perineal, or suprapubic), painful prostate on rectal exam, and dysuria (sometimes with hematuria).
Chapter Summary

* Malformations of the penis related to aberrant opening of the urethra include epispadias (opening on dorsal surface) and hypospadias (opening on ventral surface). Balanitis is inflammation of the glans penis, often related to poor hygiene and lack of circumcision. Peyronie disease is penile fibromatosis resulting in curvature of the penis. Condyloma acuminatum is a warty growth related to HPV infection. Squamous cell carcinoma of the penis is uncommon in the United States but can be related to HPV infection. Priapism is a persistent painful erection. Erectile dysfunction has many causes.

* Varicocele is a dilated vein within the spermatic cord. Hydrocele is fluid within the tunica vaginalis. Spermatocele is a dilated efferent duct in the epididymis containing sperm.

* Acute epididymitis is usually caused by Neisseria gonorrhoeae and/or Chlamydia trachomatis. Chronic epididymitis is usually caused by tuberculosis. Oorhitis or testicular inflammation can be caused by mumps.

* Testicular torsion is a twisting of the spermatic cord that may cause painful hemorrhagic infarction leading to gangrene.

* Testicular cancers tend to cause firm, painless masses, and occur in a wide variety of subtypes. Seminoma is a chemotherapy- and radiation therapy-sensitive cancer of young adult men that causes bulky testicular masses. Spermatocytic seminoma is a variant affecting older men. Cryptorchidism is a failure of descent of one or both testes, and is associated with an increased risk of developing seminoma. Male infertility has many causes.

* Embryonal carcinoma also affects young men and behaves more aggressively than seminoma. Choriocarcinoma is a highly malignant testicular carcinoma. Yolk sac tumor is the most common germ-cell tumor in children, in whom it has a better prognosis than in adults. Teratoma in testes (as opposed to in ovaries) is almost always malignant and aggressive. Mixed germ-cell tumors are common and usually behave aggressively.

* Most sex cord tumors of the testes are Leydig cell tumors, of which 10% are malignant. Testicular lymphoma is the most common testicular tumor in men over age 50 years.

* Benign prostatic hypertrophy (nodular hyperplasia) is an extremely common condition of older men that may alter the function of the urinary tract by compressing the urethra.

* Prostate cancer is the most common cancer in men in the United States and commonly arises in the posterior aspect of the peripheral zone of the prostate. It is often clinically silent, but may be detected by digital rectal exam, serum PSA levels, and transrectal ultrasound and biopsy.

* Prostatitis can be acute or chronic, and causes tenderness of the prostate on rectal examination.
THYROID GLAND

1. Multinodular goiter (nontoxic goiter)
   a. Definition: goiter refers to enlargement of the thyroid
   b. Presentation
      i. Females > males
      ii. Multinodular goiter is frequently asymptomatic, and the patient is typically euthyroid.
      iii. Goiter (enlarged, nodular thyroid gland)
      iv. Plummer syndrome: development of hyperthyroidism (toxic multinodular goiter) late in the course
   c. Gross: enlarged thyroid gland with multiple colloid nodules
   d. Microscopic
      i. Nodules of varying sizes composed of colloid follicles
      ii. Calcification, hemorrhage, cystic degeneration, and fibrosis
   e. Lab: normal T4, T3, and TSH

HYPERTHYROIDISM

1. General features of hyperthyroidism
   a. Definition: the mean metabolic rate of all cells is increased due to increased T4 or T3
   b. Clinical features include:
      i. Tachycardia and palpitations
      ii. Nervousness and diaphoresis
      iii. Heat intolerance
      iv. Weakness and tremors
      v. Diarrhea
      vi. Weight loss despite a good appetite
   c. Lab
      i. Elevated free T4
      ii. 1st hyperthyroidism: decreased TSH
      iii. 2nd and 3rd hyperthyroidism: elevated TSH

2. Graves disease
   a. Definition: autoimmune disease characterized by production of IgG autoantibodies to the TSH receptor
   b. Clinical features

Clinical Correlate

The most sensitive test in thyroid diseases is TSI. If the TSH is normal, then the patient is euthyroid.

Note

Long-acting thyroid stimulator (LATS): original name for the autoantibodies of Graves disease

Thyroid-stimulating immunoglobulin (TSI): current name for the autoantibodies of Graves disease
i. Females > males; age 20–40
ii. Hyperthyroidism
iii. Diffuse goiter
iv. Ophthalmopathy: exophthalmus
v. Dermopathy: pretibial myxedema
c. Micro: hyperplastic follicles with scalloped colloid

3. Other causes of hyperthyroidism
   a. Toxic multinodular goiter
   b. Toxic adenoma: functioning adenoma producing thyroid hormone
   c. Hashimoto and subacute thyroiditis (transient hyperthyroidism)

HYPOTHYROIDISM

1. General features of hypothyroidism
   a. Definition: the mean metabolic rate of all cells is decreased due to decreased T4 or T3
   b. Clinical features include:
      i. Fatigue and lethargy
      ii. Sensitivity to cold temperatures
      iii. Decreased cardiac output
      iv. Myxedema: accumulation of proteoglycans and water
         • Facial and periorbital edema
         • Peripheral edema of the hands and feet
         • Deep voice
         • Macroglossia
      v. Constipation
     vi. Anovulatory cycles
   c. Lab
      i. Decreased free T4
      ii. 1st hypothyroidism: elevated TSH
      iii. 2nd and 3rd hypothyroidism: decreased TSH

2. Iatrogenic hypothyroidism
   a. Most common cause of hypothyroidism in the United States
   b. Secondary to thyroidectomy or radioactive iodine treatment
   c. Treatment: thyroid hormone replacement

3. Congenital hypothyroidism (cretinism)
   a. Etiology
      i. Endemic regions: iodine deficiency during intrauterine and neonatal life
      ii. Nonendemic regions: thyroid dysgenesis
   b. Presentation
      i. Failure to thrive
      ii. Stunted bone growth and dwarfism
      iii. Spasticity and motor incoordination
      iv. Mental retardation
      v. Goiter is present in endemic cretinism.
4. Endemic goiter
   a. Uncommon in the United States
   b. Etiology: dietary deficiency of iodine

THYROIDITIS

1. Hashimoto thyroiditis
   a. Definition: chronic autoimmune disease characterized by immune destruction of the thyroid gland and hypothyroidism
   b. Most common noniatrogenic/nonidiopathic cause of hypothyroidism in the United States
   c. Clinical presentation
      i. Females > males; age 40–65 years
      ii. Painless goiter
      iii. Hypothyroidism
      iv. Initial inflammation may cause transient hyperthyroidism (hashitoxicosis).
   d. Gross: pale, enlarged thyroid gland
   e. Micro
      i. Lymphocytic inflammation with germinal centers
      ii. Epithelial “Hurthle cell” changes
   f. May be associated with other autoimmune diseases (SLE, RA, SS (Sjögren syndrome), etc.)
   g. Complication: increased risk of non-Hodgkin B-cell lymphoma

2. Subacute thyroiditis
   a. Synonyms: de Quervain thyroiditis, granulomatous thyroiditis
   b. Clinical features
      i. Second most common form of thyroiditis
      ii. Females > males; age 30–50 years
      iii. Preceded by a viral illness
      iv. Tender, firm, enlarged thyroid gland
      v. May have transient hyperthyroidism
   c. Micro: granulomatous thyroiditis
   d. Prognosis: typically the disease follows a self-limited course

3. Riedel thyroiditis
   a. Definition: rare disease of unknown etiology characterized by destruction of the thyroid gland by dense fibrosis and fibrosis of surrounding structures (trachea and esophagus)
   b. Clinical features
      i. Females > males; middle age
      ii. Irregular, hard thyroid that is adherent to adjacent structures
      iii. May mimic carcinoma and present with stridor, dyspnea, or dysphagia
   c. Micro
      i. Dense fibrous replacement of the thyroid gland
      ii. Chronic inflammation
   d. Associated with retroperitoneal and mediastinal fibrosis
Clinical Correlate

Thyroid tumors tend to be cold nodules on thyroid iodine 131 scans.

THYROID NEOPLASIA

1. Adenomas
   a. Follicular adenomas are the most common.
   b. Clinical features
      i. Usually painless, solitary nodules
      ii. “Cold nodule” on thyroid scans
      iii. May be functional and cause hyperthyroidism (toxic adenoma)

2. Papillary carcinoma
   a. Epidemiology
      i. Account for 80% of malignant thyroid tumors
      ii. Females > males; age 20–50 years
      iii. Risk factor: radiation exposure
   b. Micro
      i. The tumor typically exhibits a papillary pattern.
      ii. Occasional psammoma bodies
      iii. Characteristic nuclear features
         • Clear “Orphan Annie eye” nuclei
         • Nuclear grooves
         • Intranuclear cytoplasmic inclusions
   c. Lymphatic spread to cervical nodes is common.
   d. Treatment
      i. Resection is curative in most cases.
      ii. Radiotherapy with iodine 131 is effective for metastases.
   e. Prognosis: excellent; 20-year survival = 90% due to slow growth and metastasis to regional cervical lymph nodes

3. Follicular carcinoma
   a. Accounts for 15% of malignant thyroid tumors
   b. Females > males; age 40–60 years
   c. Hematogenous metastasis to the bones or lungs is common.

4. Medullary carcinoma
   a. Accounts for 5% of malignant thyroid tumors
   b. Arises from C cells (parafollicular cells) and secretes calcitonin
   c. Micro: nests of polygonal cells in an amyloid stroma
   d. Minority (25%) are associated with MEN II and MEN III syndromes

5. Anaplastic carcinoma
   a. Presentation
      i. Females > males; age >60 years
      ii. Firm, enlarging, bulky mass
      iii. Dyspnea and dysphagia
      iv. Tendency for early widespread metastasis and invasion of the trachea and esophagus
   b. Micro: undifferentiated, anaplastic, and pleomorphic cells
   c. Prognosis: very aggressive and rapidly fatal
PARATHYROID GLANDS

1. Primary hyperparathyroidism
   a. Etiology
      i. Parathyroid adenoma (80%)
         • Adenomas are the most common cause of primary hyperparathyroidism.
         • Adenomas may be associated with MEN I.
      ii. Parathyroid hyperplasia (15%)
          • Diffuse enlargement of all four glands
          • The enlarged glands are usually composed of chief cells.
      iii. Parathyroid carcinoma (very rare)
      iv. Paraneoplastic syndrome: lung and renal cell carcinomas
   b. Pathogenesis: excess production of parathyroid hormone (PTH) leads to hypercalcemia
   c. Clinical features
      i. Lab: elevated serum calcium and PTH
      ii. Often asymptomatic
      iii. Kidney stones
      iv. Osteoporosis and osteitis fibrosa cystica
      v. Metastatic calcifications
      vi. Neurologic changes

2. Secondary hyperparathyroidism
   a. Etiology
      i. Chronic renal failure
      ii. Vitamin D deficiency
      iii. Malabsorption
   b. Pathogenesis: caused by any disease that results in hypocalcemia, leading to increased secretion of PTH by the parathyroid glands

3. Hypoparathyroidism
   a. Etiology
      i. Surgical removal of glands during thyroidectomy
      ii. DiGeorge syndrome
      iii. Idiopathic
   b. Clinical features
      i. Lab: hypocalcemia
      ii. Neuromuscular excitability and tetany: Chvostek (twitching of the ipsilateral facial muscles after tapping the muscles, suggestive of neuromuscular excitability caused by hypocalcemia) and Trousseau (inflating a sphygmomanometer cuff above systolic blood pressure for several minutes so that if hypocalcemia is present, then muscular contractions, including flection of the wrist and metacarpophalangeal joints, hyperextension of the fingers, and flexion of the thumb on the palm occur, suggesting neuromuscular excitability) signs
      iii. Psychiatric disturbances
      iv. Cardiac conduction defects (ECG: prolonged QT interval)
   c. Treatment: vitamin D and calcium
Clinical Correlate

Pituitary adenomas may be associated with MEN I.

PITUITARY GLAND, HYPOTHALAMUS, AND PINEAL GLAND

1. Pituitary adenomas
   a. Prolactinoma
      i. Most common type of pituitary adenoma
      ii. Lactotroph cells secrete prolactin, which results in hyperprolactinemia
      iii. Clinical features include:
          • Galactorrhea, amenorrhea, and infertility
          • Decreased libido and impotence
   b. Growth-hormone–producing adenoma
      i. Lab
          • Elevated growth hormone (GH)
          • Elevated somatomedin C (insulin-like growth factor 1 [IGF-1])

   \[ \text{GH} \quad \text{acts on} \quad \text{LIVER and other tissues (e.g., skeletal muscle)} \quad \text{Increased production and release of} \quad \text{Somatomedins (especially IGF-1)} \]

   ii. Gigantism
       • Occurs in children and adolescents prior to fusion of the growth plates
       • Tall stature and long extremities
   iii. Acromegaly
       • Occurs in adults after the growth plates have fused
       • Prominent jaw
       • Flat, broad forehead
       • Enlarged hands and feet
       • The internal organs are typically enlarged. Cardiac failure is the most common cause of death in acromegaly.
       • Headaches and visual field defects can occur.
       • Metabolic changes include impaired glucose tolerance and diabetes.

   c. Nonfunctional adenomas may produce hypopituitarism.

2. Sheehan syndrome: ischemic necrosis of the pituitary secondary to hypotension from postpartum hemorrhage resulting in panhypopituitarism

3. Diabetes insipidus
   a. Definition: central diabetes insipidus is caused by ADH deficiency, which results in hypotonic polyuria, polydipsia, hypernatremia, and dehydration
   b. Etiology: head trauma, tumors, other
   c. Nephrogenic diabetes insipidus is caused by a lack of renal response to ADH.

4. Syndrome of inappropriate ADH secretion (SIADH)
   a. Definition: SIADH is caused by excessive production of ADH, resulting in oliguria, water retention, hyponatremia, and cerebral edema
   b. Etiology: paraneoplastic syndrome, head trauma, other
5. Craniopharyngioma
   a. Benign pituitary tumor derived from Rathke pouch remnants
   b. Usually located above the sella turcica, but can extend downward to destroy the pituitary
   c. Most common cause of hypopituitarism in children
6. Hypothalamic disorders
   a. Disorders that can alter hypothalamic function can cause
      i. Hypopituitarism (including dwarfism) due to lack of releasing hormones from the hypothalamus
      ii. Central diabetes insipidus due to lack of ADH synthesis
      iii. Precocious puberty is usually due to a midline hamartoma in boys
      iv. Hydrocephalus
      v. Visual field changes
   b. Masses that can affect the hypothalamus include pituitary adenoma, craniopharyngioma, midline hamartoma, and Langerhans histiocytosis.
   c. Inflammatory processes that can affect the hypothalamus include sarcoidosis and menigitis
7. Pinesal diseases
   a. Dystrophic calcification (can be a useful landmark for radiologists).
   b. Tumors are rare, with most being seminomas (most common) or teratomas.

![Diagram of Cushing Syndrome and Its Effects]

Figure 26-2. Summary of Cushing Syndrome and Its Effects
ADRENAL GLAND

1. Cushing syndrome
   a. Definition: characterized by increased levels of glucocorticoids

2. Primary hyperaldosteronism (Conn syndrome)
   a. Definition: adrenocortical adenoma producing aldosterone
   b. Clinical feature: hypertension due to retention of sodium and water
   c. Lab: hypokalemia, elevated aldosterone, and decreased renin

3. Adrenogenital syndromes
   a. Definition: adrenal disorder characterized by excess production of androgens and virilization
      b. Etiology
         i. Adrenocortical adenoma/carcinoma; producing androgens
         ii. Congenital adrenal hyperplasia
            • Autosomal recessive enzyme defect
            • Most common: 21-hydroxylase deficiency

4. Waterhouse-Friderichsen syndrome (acute adrenal insufficiency)
   a. Definition: bilateral hemorrhagic infarction of the adrenal glands associated with
      a Neisseria meningitidis infection in a child
   b. Clinical features
      i. Disseminated intravascular coagulation (DIC)
      ii. Acute respiratory distress syndrome
      iii. Hypotension and shock
      iv. Acute adrenal insufficiency
      v. Often fatal
   c. Treatment: antibiotics and steroid replacement

5. Addison disease (chronic adrenocortical insufficiency)
   a. Definition: caused by destruction of the adrenal cortex, leading to a deficiency of
      glucocorticoids, mineralocorticoids, and androgens
   b. Etiology
      i. Autoimmune adrenalitis—most common cause
      ii. Tuberculosis
      iii. Metastatic cancer
   c. Presentation
      i. Gradual onset of weakness
      ii. Skin hyperpigmentation
      iii. Hypotension
      iv. Hypoglycemia
      v. Poor response to stress
      vi. Loss of libido
   d. Treatment: steroid replacement
6. **Pheochromocytoma** ("dark/dusky-colored tumor")
   a. Definition: uncommon benign tumor of the adrenal medulla, which produces catecholamines (norepinephrine and epinephrine)
   b. Clinical presentation
      i. Severe headache
      ii. Tachycardia and palpitations
      iii. Diaphoresis and anxiety
      iv. Hypertensive episodes
   c. "Rule of 10's"
      i. 10% occur in children
      ii. 10% are bilateral
      iii. 10% occur outside the adrenal gland
      iv. 10% are malignant
      v. 10% are familial (MEN II and III)
   d. Diagnosis: elevated urinary vanillylmandelic acid (VMA) and catecholamines
   e. Treatment involves controlling the patient's blood pressure and surgical removal of the tumor.

**MULTIPLE ENDOCRINE NEOPLASIA (MEN) SYNDROMES**

1. **MEN syndromes**
   a. Autosomal dominant inheritance with incomplete penetrance
   b. Characterized by hyperplasia and tumors of endocrine glands

2. **MEN I (Werner syndrome)**
   a. Features tumors of the pituitary gland, parathyroids, and pancreas
   b. Associated with peptic ulcers and the Zollinger-Ellison syndrome
   c. Genetic mutation of MEN I gene (a tumor suppressor gene that encodes a nuclear protein called menin)

3. **MEN II (IIa or Sipple syndrome)**
   a. Features medullary carcinoma of the thyroid, pheochromocytoma, and parathyroid hyperplasia or adenoma
   b. Genetic mutation of RET proto-oncogene (a receptor tyrosine kinase for members of the glial cell line–derived neurotrophic factor family of extracellular signaling molecules)

4. **MEN III (IIb)**
   a. Features medullary carcinoma of the thyroid, pheochromocytoma, and mucocutaneous neuromas
   b. Genetic mutation of RET ("rearranged during transfection") proto-oncogene

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Bridge to Embryology

The cells of the adrenal medulla are derived from neural crest cells. The cells of the adrenal cortex are derived from mesoderm.
Chapter Summary

* Multinodular goiter is an enlarged thyroid gland with multiple colloid nodules that is frequently asymptomatic and euthyroid.

* General features of hyperthyroidism include tachycardia, nervousness, diaphoresis, heat intolerance, weakness, tremors, diarrhea, and weight loss. Free T4 is elevated and TSH is decreased in primary hyperthyroidism and increased in secondary and tertiary hyperthyroidism.

* Graves disease is an autoimmune disease characterized by production of IgG autoantibodies to the TSH receptor. Clinical features include hyperthyroidism, goiter, exophthalmos, and pretibial myxedema. Hyperthyroidism can also be caused by toxic multinodular goiter, toxic adenoma, and transiently during Hashimoto disease and subacute thyroiditis.

* General features of hypothyroidism include fatigue, lethargy, sensitivity to cold temperatures, decreased cardiac output, myxedema, and constipation. Free T4 is decreased and TSH is elevated in primary hypothyroidism and decreased in secondary and tertiary hypothyroidism.

* Congenital hypothyroidism develops secondary to iodine deficiency during intrauterine and neonatal life and causes mental retardation, musculoskeletal problems, and goiter. Endemic goiter is uncommon in the United States and is due to dietary deficiency of iodine.

* Hashimoto thyroiditis is a chronic autoimmune disease characterized by immune destruction of the thyroid gland and hypothyroidism.

* Subacute thyroiditis is a cause of transient hyperthyroidism following a viral illness.

* Riedel thyroiditis is a rare disease of unknown etiology characterized by destruction of the thyroid gland by dense fibrosis of surrounding structures.

* Thyroid adenomas are usually painless, solitary nodules.

* Thyroid carcinomas occur in a number of histologic types, including papillary (most common with excellent prognosis), follicular (tends to spread hematogenously), medullary (secretes calcitonin), makes amyloid, and may be associated with MEN II or III), and anaplastic (rapidly fatal).

* Primary hyperparathyroidism is most often due to parathyroid adenoma or parathyroid hyperplasia, and can be characterized by elevated serum calcium and PTH, kidney stones, osteoporosis and osteitis fibrosa cystica, metastatic calcifications, and neurologic changes. Many cases are asymptomatic. Secondary hyperparathyroidism can be seen in any disease that results in hypocalcemia leading to increased secretion of PTH by the parathyroid glands, including chronic renal failure, vitamin D deficiency, and malabsorption.

* Hypoparathyroidism is characterized by hypocalcemia, tetany, psychiatric disturbances, and cardiac conduction defects. It can be the result of surgical removal of the glands during thyroidectomy, DiGeorge syndrome, or it can be idiopathic.

* Pituitary adenomas can produce prolactin (causing galactorrhea, amenorrhea, and infertility), growth hormone (causing gigantism and acromegaly), or other pituitary hormones. Sheehan syndrome is ischemic necrosis of the pituitary secondary to hypotension from postpartum hemorrhage resulting in panhypopituitarism. Diabetes insipidus is ADH deficiency resulting in hypotonic polyuria, hyponatremia, and dehydration. SIADH is excessive production of ADH, resulting in oliguria, water retention, hyponatremia, and cerebral edema.

(Continued)
Chapter Summary (continued)

* Cushing syndrome is characterized by increased levels of glucocorticoids, whose origin may be iatrogenic, pituitary corticotroph adenoma, adrenocortical adenoma, or paraneoplastic syndrome.

* Primary hyperaldosteronism occurs when an adrenocortical adenoma produces aldosterone, leading to hypertension, hypokalemia, elevated aldosterone, and decreased renin.

* Adrenogenital syndromes are adrenal disorders characterized by excess production of androgens and virilization and can be due to either an adrenocortical adenoma/carcinoma or congenital adrenal hyperplasia.

* Waterhouse-Friderichsen syndrome is acute adrenal insufficiency with shock and DIC seen in the setting of bilateral hemorrhagic infarction of the adrenal glands, usually in a child with a Neisseria meningitides infection.

* Addison disease is chronic adrenocortical insufficiency and is due to destruction of the adrenal cortex, leading to a deficiency of glucocorticoids, mineralocorticoids, and androgens.

* Pheochromocytoma is an uncommon tumor of the adrenal medulla that produces catecholamines and may present with severe headache, tachycardia, diaphoresis, and hypertensive episodes.

* MEN I features tumors of the pituitary gland, parathyroids, and pancreas. MEN II features medullary carcinoma of the thyroid, pheochromocytoma, and parathyroid lesions. MEN III features medullary carcinoma of the thyroid, pheochromocytoma, and mucocutaneous neuromas.

* Cranopharyngioma is an important cause of hypopituitarism in children. Hypothalamic disorders can cause hypopituitarism, central diabetes insipidus, precocious puberty, hydrocephalus, and visual field defects. Pineal tumors are usually seminomas or teratomas.
NORMAL BONE

1. Composition
   a. Organic matrix
      i. Cells
      ii. Type 1 collagen (90% of bone protein)
      iii. Osteocalcin
      iv. Glycoproteins, proteoglycans, etc.
   b. Inorganic matrix
      i. Calcium hydroxyapatite $\text{Ca}_3(\text{PO}_4)_2(\text{OH})_2$
      ii. Magnesium, potassium, chloride, sodium, fluoride

2. Cell types
   a. Osteoblasts
      i. Responsible for the production of osteoid (unmineralized bone)
      ii. Contain high amounts of alkaline phosphatase
      iii. Have receptors for parathyroid hormone (PTH)
      iv. Modulate osteoclast function
   b. Osteocytes
      i. Responsible for bone maintenance
      ii. Are osteoblasts that have become incorporated in the matrix
   c. Osteoclasts
      i. Responsible for bone resorption
      ii. Contains high amounts of acid phosphatase and collagenase
      iii. Resorb bone within Howship lacunae

3. Bone remodeling
   a. Occurs throughout life
   b. Is necessary to maintain healthy bones
   c. Bone resorption by osteoclasts is tightly balanced with bone formation by osteoblasts

4. Important hormones
   a. Parathyroid hormone (PTH)
   b. Calcitonin
   c. Vitamin D
   d. Estrogen
   e. Thyroid hormone

Clinical Correlate

Elevated levels of serum alkaline phosphatase and osteocalcin are markers of bone formation and are elevated in all bone diseases that result in increased bone turnover.
f. Cortisol
g. Growth hormone

5. Formation of bones
   a. Intramembranous bone
      i. Direct bone formation without a "cartilage model"
      ii. Flat bones such as the cranial bones, clavicles, vertebrae, wrist, and ankle bones
      iii. Also involved in appositional bone growth
   b. Enchondral bone
      i. Indirect bone formation from a "cartilage model"
      ii. Bone is formed from cartilage at the epiphyseal growth plates.
      iii. Long bones such as femur, humerus, tibia, fibula, etc.

HEREDITARY BONE DISORDERS

1. Achondroplasia
   a. Most common form of inherited dwarfism
   b. Hereditary defect
      i. Autosomal dominant
      ii. Mutation in fibroblast growth factor receptor 3 (FGFR3) on chromosome 4
   c. Pathogenesis
      i. Activation of FGFR3 inhibits cartilage synthesis at the epiphyseal growth plate, resulting in decreased enchondral bone formation and premature ossification of the growth plates.
   d. Long bones are short and thick → short extremities → dwarfism
   e. Cranial and vertebral bones spared → relatively large head and trunk
   f. Normal intelligence, life span, and reproductive ability

2. Osteogenesis imperfecta (OBI) ("brittle-bone disease")
   a. Hereditary defect: abnormal synthesis of type I collagen
   b. Pathology
      i. Generalized osteopenia (brittle bones), resulting in recurrent fractures and skeletal deformity
      ii. Most patients have an abnormally thin sclera with a blue hue.
      iii. Laxity of joint ligaments leads to hypermobility.
      iv. Involvement of the bones of the inner and middle ear produces deafness.
      v. Some patients have dentinogenesis imperfecta: small, fragile, and discolored teeth due to a deficiency of dentin.
      vi. The dermis may be abnormally thin, and the skin is susceptible to easy bruising.
   c. Treatment: supportive
### Table 27-1. Clinical Phenotypes of OGI

*Four clinical phenotypes of varying severity. All are rare.*

#### Type I
- (1) Autosomal dominant
- (2) Fractures
- (3) Blue sclerae
- (4) Hearing loss
- (5) Little progression after puberty

#### Type II
- (1) Autosomal recessive
- (2) Stillborn infant or death after birth with generalized crumpled bones

#### Type III
- (1) Autosomal dominant or recessive
- (2) Progressive
- (3) Multiple fractures
- (4) Severe skeletal deformity
- (5) Dentinogenesis imperfecta
- (6) Hearing loss
- (7) Blue → white sclerae

#### Type IV
- (1) Autosomal dominant
- (2) Variable severity
- (3) Fractures
- (4) Skeletal deformity
- (5) Normal sclerae
- (6) Sometimes dentinogenesis imperfecta

### 3. Osteopetrosis

a. Synonyms: marble bone disease, Albers-Schönberg disease

b. Hereditary defect: *decreased osteoclast function*, leading to decreased resorption and *thick sclerotic bones*

c. Pathology
   i. Increased bone density and thickening of bone cortex
   ii. The thickened bones are brittle and fracture easily
   iii. Myelophthisic (replacement of hemopoietic tissue in the bone marrow by abnormal tissue [fibrous tissue or malignant neoplasms]) process
      - Due to narrowing and fibrosis of the medullary cavities
      - May lead to pancytopenia
   iv. Extramedullary hematopoiesis
   v. *Cranial nerve compression*
      - Due to narrowing of cranial foramina
      - May result in blindness, deafness, and facial nerve palsy
   vi. Hydrocephalus due to obstruction of CSF

d. X-ray findings
   i. Symmetrical generalized osteosclerosis
   ii. Long bones may have broadened metaphyses, resulting in an "Erlenmeyer flask"-shaped deformity.
e. Major clinical forms
   i. *Autosomal recessive (malignant type)*
      • Affects infants and children
      • Multiple fractures
      • Early death due to anemia, infection, or hemorrhage
   ii. *Autosomal dominant (benign type)*
      • Affects adults
      • Fractures
      • Mild anemia
      • Cranial nerve impingement
   iii. *Carbonic anhydrase II deficiency*
      • Autosomal recessive
      • Renal tubular acidosis and cerebral calcification

f. Treatment: bone marrow transplantation

**PAGET DISEASE (OSTEITIS DEFORMANS)**

1. Definition: *localized disorder of bone remodeling*, resulting in excessive bone resorption followed by disorganized bone replacement, producing thickened but weak bone that is susceptible to deformity and fracture

2. Epidemiology
   a. Begins after age 40 years
   b. Common in those of European ancestry

3. Etiology
   a. Possible slow-virus infection with paramyxovirus
   b. Possible genetic predisposition

4. Forms of involvement
   a. *Monostotic* (15%): involving one bone
   b. *Polyostotic* (85%): involving multiple bones
   c. Common sites include the skull, pelvis, femur, and vertebrae.

5. Three stages of Paget disease
   a. Osteolytic: osteoclastic activity predominates
   b. Mixed osteolytic-osteoblastic
   c. Osteosclerotic: osteoblastic activity predominates "burnout stage"

6. Pathology
   a. Micro: haphazard arrangement of cement lines, creating a "mosaic pattern" of lamellar bone
   b. Involved bones are thick but weak and fracture easily
   c. Skull involvement
      i. Increased head size
      ii. Foraminal narrowing causes impingement of cranial nerves, often leading to deafness.
      iii. Involvement of facial bones may produce a lionlike facies.
1. Clinical features
   a. Clinical presentation
      i. Asymptomatic in most cases
      ii. Bone pain and deformity
      iii. Fractures
      iv. Warmth of the overlying skin due to bone hypervascularity
   b. X-rays: bone enlargement with lytic and sclerotic areas
   c. Lab
      i. Highly elevated serum alkaline phosphatase
      ii. Increased levels of urinary hydroxyproline
2. Complications
   a. AV shunts within marrow may result in high-output cardiac failure.
   b. Osteosarcoma
   c. Other sarcomas

**OSTEOPOROSIS**

1. Definition: *decreased bone mass (osteopenia)*, resulting in thin, fragile bones that are susceptible to fracture
2. Epidemiology
   a. Most common bone disorder in the United States
   b. Most commonly occurs in *postmenopausal Caucasian women and the elderly*
3. Pathogenesis
   a. Primary causes include
      i. Estrogen deficiency (postmenopausal, Turner syndrome)
      ii. Genetic factors (low density of original bone)
      iii. Lack of exercise
      iv. Old age
      v. Nutritional factors
   b. Secondary causes
      i. Immobilization
      ii. Endocrinopathies (e.g., Cushing disease, thyrotoxicosis)
      iii. Malnutrition (e.g., deficiencies of calcium, vitamins C and D, protein)
      iv. Corticosteroids
      v. Genetic disease (e.g., OGI, Gaucher disease)
4. Clinical features
   a. Clinical presentation
      i. Patients may experience bone pain and fractures.
      ii. Weight-bearing bones are predisposed to fractures
         • Vertebrae (compression fracture)
         • Femoral neck (hip fracture)
         • Distal radius (Colles fracture)
      iii. Loss of height and kyphosis

**Note**

In osteoporosis, bone is formed normally but in decreased amounts.
b. Radiographic
   i. X-rays: generalized radiolucency of bone (osteopenia)
   ii. Dual-energy x-ray absorptiometry (DEXA)
c. Lab: normal serum calcium, phosphorus, and alkaline phosphatase
d. Micro: thinned cortical and trabecular bone

5. Treatment
   a. Estrogen replacement therapy (controversial; not recommended currently)
   b. Weight-bearing exercise
   c. Calcium and vitamin D
   d. Bisphosphonate (alendronate)
   e. Calcitonin

**OSTEOMALACIA AND RICKETS**

1. General
   a. Definition: both diseases are characterized by decreased mineralization of newly formed bone, usually caused by deficiency or abnormal metabolism of vitamin D

   b. Etiology
      i. Dietary deficiency of vitamin D
      ii. Intestinal malabsorption
      iii. Lack of sunlight
      iv. Renal and liver disease
   c. Treatment: vitamin D and calcium

2. Rickets (children)
   a. Occurs in children prior to closure of the epiphyses
   b. Both remodeled bone and bone formed at the epiphyseal growth plate are under-mineralized.
   c. Enchondral bone formation is affected, leading to skeletal deformities.
      i. Craniofacial and frontal bossing: skull deformities
      ii. Rachitic rosary: deformity of the chest wall as a result of an overgrowth of cartilage at the costochondral junction
      iii. Pectus carinatum (pigeon-breast deformity): outward protrusion of the sternum
      iv. Lumbar lordosis: spinal curvature
      v. **Bowing of the legs: curvature of femur/tibia due to weight bearing**
   d. Fractures may also occur.

3. Osteomalacia (adults)
   a. Definition: impaired mineralization of the osteoid matrix results in thin, fragile bones that are susceptible to fracture
   b. Clinical presentation
      i. Bone pain
      ii. Fractures of the vertebrae, hips, and wrist
   c. X-rays: diffuse radiolucency of bone (osteopenia)

**Note**
Rickets and osteomalacia are disorders of osteoid mineralization; osteoid is produced in normal amounts but is not calcified properly.
d. Lab
   i. Low serum calcium and phosphorus
   ii. High alkaline phosphatase

OSTEOMYELITIS

1. Pyogenic osteomyelitis
   a. Routes of infection
      i. Hematogenous spread
         • Most common
         • Seeding of bone after bacteremia
         • Commonly affects the metaphysis
      ii. Direct inoculation
      iii. Spread from an adjacent site of infection
   
   b. Microbiology
      i. Staphylococcus aureus (most common)
      ii. Escherichia coli
      iii. Streptococci
      iv. Gonococci
      v. Haemophilus influenzae
      vi. Salmonella: common in sickle cell disease
      vii. Pseudomonas: common in intravenous drug abusers (IVDA) and diabetics
   
   c. Clinical features
      i. Fever and leukocytosis
      ii. Localized pain, erythema, and swelling
   
   d. X-ray
      i. May be normal for up to 2 weeks
      ii. May initially show periosteal elevation
      iii. Lytic focus with surrounding sclerosis
   
   e. Pathology
      i. Suppurative inflammation
      ii. Vascular insufficiency
      iii. Ischemic necrosis of bone
      iv. Sequestrum: the necrotic bone
      v. Involution: new bone formation that surrounds the sequestrum
   
   f. Diagnosis
      i. Blood cultures
      ii. Bone biopsy and culture
   
   g. Treatment: antibiotics ± surgical drainage
   
   h. Complications
      i. Fracture
      ii. Intramembranous (Brodie) abscess
      iii. Secondary amyloidosis
iv. Sinus tract formation
v. Squamous cell carcinoma of the skin at the site of a persistent draining sinus tract
vi. Osteogenic sarcoma (rare)

2. Tuberculous osteomyelitis
a. Occurs in 1% of cases of TB
b. Pain or tenderness, fever, night sweats, weight loss
c. Caseating granulomas with extensive destruction of the bones
d. Common site: thoracic and lumbar vertebrae ("Pott disease")
e. Complications
   i. Vertebal compression fracture
   ii. Psoas abscesses
   iii. Secondary amyloidosis

MISCELLANEOUS BONE DISORDERS

1. Avascular necrosis
   a. Synonyms: aseptic necrosis, osteonecrosis
   b. Definition: ischemic necrosis of bone and bone marrow
   c. Causes
      i. Trauma and/or fracture (most common)
      ii. Idiopathic
      iii. Steroids
      iv. Sickle cell anemia
      v. Gaucher disease
      vi. Caisson disease
      vii. Other
d. Complications: osteoarthritis and fractures

2. Osteitis fibrosa cystica
   a. Synonym: von Recklinghausen disease of bone
   b. Definition: excessive parathyroid hormone (hyperparathyroidism) causing osteoclast activation and generalized bone resorption
   c. Etiology
      i. Parathyroid adenoma
      ii. Parathyroid hyperplasia
d. Clinical features
      i. Occurs more commonly in primary hyperparathyroidism
      ii. May cause bone pain, bone deformities, and fractures
e. Pathology
      i. Excess bone resorption with increased number of osteoclasts
      ii. Fibrous replacement of marrow
      iii. Cystic spaces in trabecular bone (dissecting osteitis)
      iv. "Brown tumors": brown bone masses produced by cystic enlargement of bones with areas of fibrosis and organized hemorrhage
f. Treatment: treat hyperparathyroidism

3. Hypertrophic osteoarthropathy
   a. Presents with painful swelling of wrists, fingers, ankles, knees, or elbows
   b. Pathology
      i. Ends of long bones have periosteal new bone formation
      ii. Digital clubbing
      iii. Arthritis of adjacent joints is commonly seen.
   c. Etiology
      i. Bronchogenic carcinoma (a paraneoplastic syndrome)
      ii. Chronic lung diseases
      iii. Cyanotic congenital heart disease
      iv. Inflammatory bowel disease
   d. Treatment: often regresses when the underlying disease is treated

4. Osgood-Schlatter disease
   a. Common cause of knee pain in adolescents
   b. Pathophysiology
      i. Stress from quadriceps during rapid growth causes inflammation of the proximal tibial apophysis at the insertion of the patellar tendon.
      ii. Permanent changes to the knees (knobby knees) may develop.
      iii. Not usually biopsied

5. Fibrous dysplasia
   a. Presents with painful swelling, deformity, or pathologic fracture of involved bone (typically ribs, femur, or cranial bones), usually in children and young adults
   b. Pathology
      i. Benign, non-neoplastic replacement of marrow by fibrous tissue
      ii. May involve single or multiple bones
      iii. Linked to a tissue mutation in a stimulatory G protein on chromosome 20 that causes osteoblasts to produce fibrous tissue rather than bone
      iv. Multiple bone involvement may be associated with Albright syndrome (café-au-lait spots on skin, precocious sexual development)

**BENIGN TUMORS OF BONE**

1. Osteoma
   a. Definition: benign neoplasm that frequently involves the skull and facial bones
   b. “Hyperostosis frontalis interna” describes an osteoma that extends into the orbit or sinuses.
   c. Associated with Gardner syndrome

2. Osteoid osteoma
   a. Definition: benign, painful growth of the diaphysis of a long bone, often the tibia or femur
   b. Presentation
      i. Males > females; age 5–25 years
      ii. Pain that is worse at night and relieved by aspirin
   c. X-rays: central radiolucency surrounded by a sclerotic rim
d. Micro
   i. Small (<2 cm) lesion of the cortex
   ii. Central nidus of osteoid surrounded by dense sclerotic rim of reactive cortical bone

3. Osteoblastoma
   a. Similar to an osteoid osteoma but is larger (>2 cm) and often involves vertebrae

4. Osteochondroma (exostosis)
   a. Definition: benign bony metaphyseal growth capped with cartilage that originates from epiphyseal growth plate
   b. Clinical presentation
      i. Adolescent males
      ii. Firm, solitary growths at the ends of long bones
      iii. They may be asymptomatic, cause pain, produce deformity, or undergo malignant transformation (rare).
   c. Osteochondromatosis (multiple hereditary exostosis)
      i. Multiple, often symmetric, osteochondromas

5. Enchondroma
   a. Definition: benign cartilaginous growth within the medullary cavity of bone, usually involving the hands and feet
   b. Typically solitary and asymptomatic and requires no treatment
   c. Multiple enchondromas (enchondromatosis)
      i. Ollier disease
         • Nonhereditary syndrome
         • Multiple enchondromas in the hands and feet
         • Presents with pain and fractures
         • May undergo malignant transformation to chondrosarcoma
      ii. Maffucci syndrome
         • Multiple enchondromas
         • Soft tissue hemangiomas
         • Increased risk of malignant transformation, ovarian carcinoma, and brain gliomas

6. Giant-cell tumor of bone (“osteoclastoma”)
   a. Definition: uncommon benign neoplasm containing multinucleated giant cells admixed with stromal cells
   b. Females > males, age 20–50 years
   c. Clinical features: bulky mass with pain and fractures
   d. X-rays
      i. Expanding lytic lesion surrounded by a thin rim of bone
      ii. May have a “soap bubble” appearance
   e. Gross
      i. Often involves the epiphyses of long bones
      ii. Usually around the knee (distal femur and proximal tibia)
      iii. Red-brown mass with cystic degeneration
f. Microscopically, multiple osteoclast-like giant cells are distributed within a background of mononuclear stromal cells.

g. Treatment: surgery (curettage or en bloc resection)

h. Prognosis: locally aggressive with a high rate of recurrence (40–60%); approximately 4% will metastasize to the lungs.

**MALIGNANT TUMORS OF BONE**

1. **Osteosarcoma** (osteogenic sarcoma)
   a. Most common primary malignant tumor of bone
   b. Incidence
      i. Males > females
      ii. Most occur in teenagers (ages 10–25 years)
      iii. Patients with familial retinoblastoma have a high risk.
   c. Clinical features: localized pain and swelling
   d. Classic x-ray findings
      i. *Codman triangle* (periosteal elevation)
      ii. “Sunburst” pattern
      iii. Bone destruction
   e. Gross
      i. Often involves the metaphyses of long bones
      ii. Usually around the knee (distal femur and proximal tibia)
      iii. Large, firm, white-tan mass with necrosis and hemorrhage
   f. Micro: anaplastic cells producing osteoid and bone
   g. Treatment: surgery and chemotherapy
   h. Prognosis
      i. Poor
      ii. Hematogenous metastasis to the lungs is common
      iii. Prognosis is improved with aggressive management, such as resecting single pulmonary metastases.
   i. Secondary osteosarcomas
      i. Occur in elderly persons
      ii. Associated with Paget disease, irradiation, and chronic osteomyelitis
      iii. Highly aggressive

2. **Chondrosarcoma**
   a. Definition: malignant tumor of chondroblasts
   b. Males > females; age 30–60 years
   c. Etiology: the tumor may arise *de novo* or secondary to a preexisting enchondroma, exostosis, or Paget disease
   d. Clinical presentation: enlarging mass with pain and swelling
   e. Typically involves the pelvic bones, spine, and shoulder girdle
   f. Micro: composed of atypical chondrocytes and chondroblasts, often with multiple nuclei in a lacuna
3. **Ewing sarcoma**

   a. Definition: malignant neoplasm of undifferentiated cells arising within the marrow cavity
   
   b. Incidence
   
   i. Males are affected slightly more often than females.
   
   ii. Most occur in teenagers (ages 5–20 years)

   c. Clinical features are pain, swelling, and tenderness.

   d. Genetics: classic translocation t(11;22), which produces the EWS-FLI1 fusion protein

   e. X-ray: concentric "onion-skin" layering of new periosteal bone

   f. Gross
   
   i. Often affects the diaphyses of long bones
   
   ii. Most common sites are the femur, pelvis, and tibia.
   
   iii. White-tan mass with necrosis and hemorrhage

   g. Micro
   
   i. Sheets of undifferentiated small, round, blue cells resembling lymphocytes
   
   ii. Homer Wright pseudorosettes
   
   iii. Tumor cells erode through the cortex and periosteum and invade surrounding tissues.

   h. Treatment: chemotherapy, surgery, and/or radiation

   i. Prognosis: 5-year survival rate 75%

5. **Metastasis to bone**

   a. Much more common than primary bone tumors

   b. Common primary sites
   
   i. Prostate (often osteoblastic)
   
   ii. Breast
   
   iii. Lung
   
   iv. Thyroid
   
   v. Kidney
Chapter Summary

* Normal bone is composed of an organic matrix (containing collagen, osteocalcin, glycoproteins, and cells) and an inorganic matrix (containing calcium hydroxyapatite and other minerals). Cells types within bone include osteoblasts (live at edge and make bone), osteocytes (live within and maintain bone), and osteoclasts (live at edge and resorb bone).

* Bone remodeling occurs throughout life and is under complex hormonal control by PTH, calcitonin, vitamin D, estrogen, cortisol, growth hormone, and thyroid hormone.

* Intramembranous bone formation occurs in flat bone and axial bone without a "cartilage model"; endochondral bone formation occurs in long bones by replacement of preexisting cartilage.

* Autosomal dominant achondroplasia is the most common form of inherited dwarfism and is clinically characterized by short extremities, normal head and trunk, and normal life span and intelligence.

* Osteogenesis imperfecta has variable genetics and severity but is in general characterized by brittle bones and often blue sclera, joint hypermobility, deafness, and teeth abnormalities.

* Osteopetrosis, or marble bone disease, is a hereditary disease (variable genetics) characterized by thick sclerotic bones that fracture easily and may secondarily compromise marrow cavities (leading to pancytopenia), foramina (leading to nerve palsies, blindness, or deafness), and CSF flow (leading to hydrocephalus).

* Paget disease of bone is an acquired localized (as opposed to the general involvement in osteopetrosis) disorder of bone remodeling, resulting in excessive bone resorption followed by disorganized bone replacement (in a characteristic "mosaic" microscopic pattern), producing thickened bone that fractures easily and may impinge on cranial nerves.

* Osteoporosis is a common disease in which bone mass decreases, resulting in thin, fragile bones that are susceptible to fracture. Predisposing factors include estrogen deficiency, genetically low density of original bone, lack of exercise (or immobilization), old age, nutritional deficiencies, and corticosteroid use.

* Both osteomalacia (adults) and rickets (children) are characterized by decreased mineralization of newly formed bone, often secondary to vitamin D deficiency or abnormal metabolism. Rickets tends to present with skeletal deformities while osteomalacia tends to present with fractures.

* Pyogenic osteomyelitis produces local symptoms accompanied by fever and can be due to many bacteria (most commonly Staphylococcus aureus) that may reach bone via blood, direct inoculation, or spread from nearby infection.

* Complications include ischemic necrosis of bone, sequestrum formation, fracture, intraosseous abscess, secondary amyloidosis, sinus tract formation (which may rarely develop squamous cell carcinoma of the skin), and (rarely) osteogenic sarcoma. Tuberculous osteomyelitis is a rare but very destructive and difficult-to-treat complication of tuberculosis.

* Avascular necrosis of bone (particularly common in the femoral head) is an ischemic necrosis of bone and bone marrow (predisposing for osteoarthritis and fractures) that can be idiopathic or occur secondary to trauma, steroid use, sickle cell anemia, or other diseases.

(Continued)
Chapter Summary (continued)

* Osteitis fibrosa cystica is the name for the generalized bone resorption with accompanying histologic changes seen in hyperparathyroidism; hemorhage and fibrosis within the bone may produce "brown tumors."

* Hypertrophic osteoarthropathy may complicate other diseases (bronchogenic carcinoma, chronic lung disease, cyanotic congenital heart disease, and inflammatory bowel disease) and is due to periosteal new bone formation with pain and swelling of the ends of long bones, notably in wrists, fingers, ankles, knees, or elbows. Osgood-Schlatter disease is a common cause of knee pain in adolescents. Fibrous dysplasia usually occurs in children and young adults, and presents with painful swelling, deformity, or pathologic fracture of the involved bone; multiple bone involvement may be associated with Albright syndrome.

* Benign tumors of bone include osteoma (head, may be associated with Gardner syndrome), osteoid osteoma (tibia or femur of older children to young adults), osteoblastoma (vertebrae), osteochondroma (long bones of adolescent boys, bony outgrowth with cartilage cap, may be hereditary syndrome if multiple), and enchondroma (cartilage in medullary cavity, may be part of Ollier disease or Maffucci syndrome if multiple). Giant-cell tumor of the bone is a benign neoplasm that tends to involve the knee of young to middle-aged adults and on x-ray shows an expanding lytic lesion surrounded by a thin rim of bone that may resemble a "soap bubble."

* Osteosarcoma is the most common primary (aggressively) malignant tumor of bone. It often causes a large mass, of the knee in teenagers or young adults, and it may be associated with familial retinoblastoma. Osteosarcoma has a characteristic x-ray pattern with periosteal elevation (Codman triangle), "sunburst" pattern, and bone destruction. Chondrosarcoma tends to cause an enlarging mass of pelvis, spine, or shoulder in middle-aged individuals (male > female) and may arise de novo or secondary to a pre-existing enchondroma, exostosis, or Paget disease. Ewing sarcoma is an aggressive (but often responsive to therapy) malignant neoplasm of small, undifferentiated cells that develops within the marrow cavity of femur, pelvis, and tibia of children and teenagers.

* Metastases to bone are more common than primary bone tumors; common primary sites include prostate (may cause new bone formation), breast, lung, thyroid, and kidney.
Joint Pathology

Table 28-1. Osteoarthritis (OA) Versus Rheumatoid Arthritis (RA)

<table>
<thead>
<tr>
<th>Osteoarthritis (OA)</th>
<th>Rheumatoid Arthritis (RA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Wear and tear&quot;</td>
<td>Systemic autoimmune disease</td>
</tr>
<tr>
<td></td>
<td>(+) Rheumatoid factor</td>
</tr>
<tr>
<td></td>
<td>(+) Rheumatoid nodules</td>
</tr>
<tr>
<td>Degeneration of articular cartilage</td>
<td>Synovial proliferation</td>
</tr>
<tr>
<td>Weight bearing joints</td>
<td>Small joints</td>
</tr>
<tr>
<td>• Knees, hips, spine</td>
<td>• Hands and feet</td>
</tr>
<tr>
<td>Asymmetrical</td>
<td>Symmetrical and migratory</td>
</tr>
</tbody>
</table>

OSTEOARTHRITIS (DEGENERATIVE JOINT DISEASE)

1. Definition: degeneration and loss of articular cartilage with no to minimal inflammation

2. Incidence
   a. Most common form of arthritis
   b. Risk increases with age
   c. Affects at least one joint in 80% of people over 70 years old

3. Clinical features
   a. Insidious onset of joint stiffness
   b. Deep, aching joint pain, which worsens with repetitive motion
   c. Decreased range of motion
   d. Crepitus
   e. Joint effusions and swelling
   f. Osteophytes may cause nerve compression.

4. X-ray
   a. Narrowing of the joint space due to loss of cartilage
   b. Osteosclerosis and bursa cysts
   c. Osteophytes (osteophytic lipping)

5. Pathogenesis
   a. Biomechanical: aging or wear and tear of articular cartilage
   b. Biochemical: chondrocyte injury and abnormal collagen activity
   c. Predisposing factors include obesity, previous joint injury, ochronosis, diabetes, trauma, and hemarthrosis.
6. Pathology
   a. Weight-bearing joints $\rightarrow$ knees, hips, and spine
   b. Asymmetrical involvement
   c. Degeneration and loss of articular cartilage
   d. Eburnation (exposed bone becomes polished)
   e. Subchondral bone sclerosis
   f. Subchondral bone cysts
   g. Loose bodies (joint mice): free-floating fragments of cartilage and bone
   h. Osteophytes (bone spurs): reactive bony outgrowths
      i. Heberden nodes: osteophytes at the distal interphalangeal (DIP) joints
      ii. Bouchard nodes: osteophytes at the proximal interphalangeal (PIP) joints

RHEUMATOID ARTHRITIS

1. Definition: a systemic, chronic, inflammatory disease characterized by progressive arthritis, production of rheumatoid factor, and extra-articular manifestations

2. Incidence
   a. Females > males (4:1)
   b. Highest incidence at age 20–50 years
   c. Genetic predisposition (HLA-DR4 and DR1)

3. Etiology
   a. Thought to be caused by an autoimmune reaction triggered by an infectious agent in a genetically susceptible individual

4. Clinical features
   a. Hand, wrist, knee, and ankle joints most commonly involved
   b. Tends to have symmetrical involvement
   c. Morning stiffness that improves with activity
   d. Fusiform swelling, redness, and warmth of the proximal interphalangeal (PIP) joint

5. X-rays
   a. Juxta-articular osteoporosis and bone erosions
   b. Joint effusion

6. Pathology
   a. Diffuse proliferative synovitis
   b. Pannus formation: proliferation of the synovium and granulation tissue over the articular cartilage of the joint
   c. Fibrous and bony ankylosis (joint fusion)
   d. Joint deformities
      i. Radial deviation of the wrist and ulnar deviation of the fingers
      ii. Swan neck: hyperextension of PIP and flexion of distal interphalangeal (DIP) joints
      iii. Boutonniere: flexion of PIP and extension of DIP joints
   e. Baker cysts: synovial cysts in the popliteal fossa
7. Lab
   a. Elevated sedimentation rate and hypergammaglobulinemia
   b. Rheumatoid factor (RF)
      i. Usually an IgM autoantibody against the Fc fragment of IgG
      ii. Positive in 80% of patients with RA
      iii. May circulate and form immune complexes
      iv. Titer of RF correlates with the severity of the arthritis and prognosis.

8. Extra-articular manifestations
   a. Systemic symptoms include low-grade fever, malaise, fatigue, lymphadenopathy, and weakness.
   b. Rheumatoid nodules (25%)
      i. Subcutaneous skin nodules
      ii. Usually on extensor surfaces of the forearms or elbows
      iii. Composed of central fibrinoid necrosis surrounded by epithelioid macrophages, lymphocytes, and granulation tissue
      iv. May also be found in the heart valves, lung, pleura, pericardium, and spleen
   c. Arteries may show acute necrotizing vasculitis due to circulating antigen-antibody complexes.
   d. Sjögren syndrome (15%)
   e. Felty syndrome: RA + splenomegaly + neutropenia
   f. Caplan syndrome: association with pneumoconiosis
   g. Secondary amyloidosis

SERONEGATIVE SPONDYLOARTHROPATHIES

1. Ankylosing spondylitis
   a. Occurs predominantly in young men with HLA-B27 (90%)
   b. Usually involves the sacroiliac joints and spine
   c. May be associated with inflammatory bowel disease

2. Reiter syndrome
   a. Males > females; onset usually in the 20s or 30s
   b. Classic triad: conjunctivitis, urethritis, arthritis
   c. Arthritis affects the ankles and knees
   d. Onset often follows a venereal disease or bacillary dysentery
   e. Associated with HLA-B27 (90%)

3. Enteropathic arthritis
   a. Occurs in 10–20% of patients with ulcerative colitis
   b. May develop peripheral arthritis or spondylitis
   c. May respond with treatment of the ulcerative colitis
   d. Associated with HLA-B27

4. Psoriatic arthritis
   a. Affects 5–10% of patients with psoriasis
   b. Often mild and slowly progressive arthritis
   c. Pathology similar to rheumatoid arthritis
   d. Associated with HLA-B27
ARTHRITIS RELATED TO CRYSTAL DEPOSITION

1. Gout
   a. Definition: hyperuricemia and deposition of monosodium urate crystals in joints, resulting in recurrent bouts of acute arthritis
   b. Pathogenesis
      i. Overproduction or underexcretion of uric acid
      ii. Primary gout (90%) idiopathic
      iii. Secondary gout (10%)
         - Excessive cell breakdown, as in leukemia
         - Renal disease
         - Lesch-Nyhan syndrome
   c. Incidence
      i. Males > females
      ii. Usually affects older men
   d. Distribution of disease: great toe (podagra), ankle, heel, wrist
   e. Presentation: exquisitely painful, inflamed big toe
   f. Joint aspiration
      i. Negatively birefringent, needle-shaped uric acid crystals
      ii. Neutrophils
   g. Gross
      i. Tophi appear as chalky-white deposits.
      ii. Skin ulceration and destruction of adjacent joints may occur.
   h. Complications
      i. Joint destruction and deformity
      ii. Uric acid renal calculi
      iii. Renal failure
   i. Treatment
      i. NSAIDs
      ii. Colchicine
      iii. Probenecid
      iv. Allopurinol

2. Pseudogout (chondrocalcinosis)
   a. Definition: deposition of calcium pyrophosphate crystals in joints, leading to inflammation
   b. Age > 50 years
   c. Positively birefringent (weak), rhomboid-shaped crystals
   d. Knee joint most commonly involved
   e. Associated with many metabolic diseases (e.g., diabetes, hypothyroidism, ochronosis)
   f. May mimic osteoarthritis or rheumatoid arthritis
INFECTIONOUS ARTHRITIS

1. Suppurative arthritis
   a. Routes of infection
      i. Hematogenous spread
         • Most common
         • Seeding of joint during bacteremia
      ii. Spread from an adjacent site of infection
      iii. Direct inoculation
   b. Organisms
      i. Gonococci
      ii. *Staphylococcus*
      iii. *Streptococcus*
      iv. *Haemophilus influenzae*
      v. Gram-negative bacilli
   c. Clinical features
      i. Tender, painful, swollen, and erythematous joint
      ii. Large joints (knee, hip, shoulder)
      iii. Usually is a monoarticular arthritis
   d. Joint aspiration
      i. Cloudy synovial fluid that clots readily
      ii. High neutrophil count
      iii. Positive Gram stain and culture in 50–70% of cases
   e. Treatment: requires rapid intervention with antibiotics to prevent permanent joint damage

2. Lyme disease
   a. Spirochete: *Borrelia burgdorferi*
   b. Arthropod borne disease: deer ticks (*Ixodes dammini*)
   c. Skin rash (*erythema chronic migrans*)
   d. Migratory arthritis involving the knees, shoulders, and elbows
   e. Histologically similar to rheumatoid arthritis
   f. CNS and cardiac involvement

NEUROPATHIC ARTHRITIS (CHARCOT JOINT)

1. Definition: Joint damage secondary to impaired joint innervation (neuropathy) leading to inability to sense pain

2. Different underlying neurologic diseases tend to affect different joints.
   i. *Diabetes mellitus* (most common cause) tends to damage the tarsometatarsal joint in the mid foot.
   ii. *Syringomelia* (cavity in spinal cord) tends to damage the shoulder, elbow, and wrist joints.
   iii. *Tabes dorsalis* (neurosyphilis) tends to damage the hip, knee, and ankle joints.

3. The damage leads to destruction of joint surfaces, debris in joints, deformity, and dislocations.

Bridge to Microbiology

Arthropod-borne diseases that are transmitted by ticks include:
   • Rocky Mountain spotted fever
   • *Lyme*
   • Babesiosis
   • Tularemia
   • Lyme disease
Chapter Summary

* Degenerative joint disease is an important cause of chronic joint pain in the elderly populations; most seriously affects the weight-bearing joints and is related to destruction of the articular cartilage as a result of "wear and tear." Reactive bony spurs (osteoarthropathies, called Heberden nodes if they involve the DIP joints and Bouchard nodes if they involve the PIP joints) and free-floating fragments of cartilage or bone (joint mice) may contribute to the joint pathology.

* Rheumatoid arthritis is a systemic, chronic, inflammatory, autoimmune disease primarily of the hands, wrists, knees, and ankle joints of middle-aged women. It is characterized by progressive arthritis, production of rheumatoid factor, genetic predisposition (HLA-DR4 and DR1), morning stiffness that improves with activity, pannus formation within the joint, and rheumatoid nodules, and it often coexists with other diseases (Sjögren syndrome, Felty syndrome, Caplan syndrome, secondary amyloidosis).

* The seronegative spondyloarthropathies (all associated with HLA-B27) include ankylosing spondylitis (young men, sacroiliac joints and spine, association with inflammatory bowel disease), Reiter syndrome (young men, history of venereal disease or bacillary dysentery, ankles and knees, conjunctivitis, urethritis), enteropathic arthritis (patients with ulcerative colitis who develop peripheral arthritis or spondylitis that may respond as the ulcerative colitis improves), and psoriatic arthritis (some patients with psoriasis develop a rheumatoid arthritis-like condition).

* Gout is an arthritis that classically involves the great toe (also may affect ankle, heel, wrist) as a result of hyperuricemia (primary or secondary due to leukemia, renal disease, or Lesch-Nyhan syndrome) leading to deposition of monosodium urate crystals in joints (can be seen in joint aspirates as negatively birefringent, needle-shaped crystals) and subcutaneous tissues (causing tophi). Pseudogout (chondrocalcinosis) is due to deposition of calcium pyrophosphate crystals (positively birefringent, rhomboid shaped) and commonly involves the knee of older adults.

* Suppurative arthritis typically causes tender, erythematous swelling of a single large joint (primarily knee, hip, and shoulder) as a result of bacterial infection (gonococci, *Staphylococcus*, *Streptococcus*, *Haemophilus influenzae*, and Gram-negative bacilli) that has usually reached the joint through a hematogenous route. Lyme disease causes a migratory arthritis (clinically and histologically similar to rheumatoid arthritis) due to the spirochete *Borrelia burgdorferi*, which is spread by the deer tick *Ixodes dammini*. The arthritis is often preceded by a migratory rash (erythema chronicum migrans) and may be accompanied or followed by CNS and cardiac involvement.

* Neuropathic arthropathy is joint damage secondary to impaired joint innervation (neuropathy) leading to inability to sense pain. Examples of neurologic disease that cause this are diabetes mellitus, syringomyelia, and tabes dorsalis.
Skeletal Muscle and Peripheral Nerve Pathology

**SKELETAL MUSCLE**

Table 29-1. Type I (Slow-Twitch) Versus Type II (Fast-Twitch) Muscles

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twitch rate</td>
<td>Slow twitch</td>
<td>Fast twitch</td>
</tr>
<tr>
<td>Function</td>
<td>Postural weight bearing</td>
<td>Purposeful movement</td>
</tr>
<tr>
<td></td>
<td>Sustained tension</td>
<td>Short, quick bursts</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Aerobic (Krebs cycle)</td>
<td>Anaerobic (glycolysis)</td>
</tr>
<tr>
<td>Energy source</td>
<td>Fatty acids</td>
<td>Glycogen</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>Many</td>
<td>Few</td>
</tr>
<tr>
<td>Color</td>
<td>Red</td>
<td>White</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Slow fatigue</td>
<td>Rapid fatigue</td>
</tr>
</tbody>
</table>

**Note**

Skeletal muscle fiber type is determined by innervation.

**INFLAMMATORY MYOPATHIES**

1. Polymyositis
   a. Definition: chronic inflammation of muscle fibers due to unknown cause
   b. Clinical presentation
      i. Adults
      ii. Bilateral proximal muscle weakness
   c. Micro
      i. Endomysial lymphocytic inflammation (mostly cytotoxic T8)
      ii. Skeletal muscle fiber degeneration and regeneration

2. Dermatomyositis
   a. Definition: a connective-tissue disorder involving inflammation of skeletal muscle and skin
   b. Clinical presentation
      i. Children or adults
      ii. Bilateral proximal muscle weakness
      iii. Skin rash of the upper eyelids
      iv. Periorbital edema
   c. Micro
      i. Perimysial and vascular lymphocytic inflammation
ii. Perifascicular fiber atrophy
iii. Skeletal muscle fiber degeneration and regeneration
d. Increased risk of lung, stomach, and ovarian cancers

3. Inclusion body myositis
   a. Clinical presentation
      i. Adults > age 50 years
      ii. Asymmetrical distal muscle weakness
   b. Micro: cytoplasmic vacuoles with basophilic granules and amyloid
   c. EM: filamentous inclusions

**MYASTHENIC SYNDROMES**

1. Myasthenia gravis
   a. Definition: autoimmune disease characterized by autoantibodies against the neuromuscular junction, resulting in muscular weakness
   
   ![Image of neuromuscular transmission](image)

   **Figure 29-1. Neuromuscular Transmission**

   b. Clinical presentation
      i. Females > males
      ii. Muscular weakness predominantly affecting the facial muscles
      iii. Extraocular muscle weakness may lead to ptosis and diplopia
      iv. Weakness worsens with repeated contractions.
      v. Respiratory muscle involvement may lead to death.
   c. Mechanism: autoantibodies against the acetylcholine (ACh) receptor
   d. Associated with thymic hyperplasia and thymomas
   e. Treatment: anticholinesterase agents, steroids, and thymectomy
2. Eaton-Lambert syndrome
   a. Definition: commonly a paraneoplastic syndrome of small cell lung cancer
   b. Clinical presentation
      i. Proximal muscular weakness
      ii. Weakness improves with repeated contraction
   c. Mechanism: production of autoantibodies directed against the calcium channels of the neuromuscular junction

MUSCULAR DYSTROPHY

1. Duchenne muscular dystrophy
   a. Definition: a severe recessive X-linked form of muscular dystrophy leading to rapid progression of muscle degeneration
   b. Most common and severe form of muscular dystrophy
   c. Genetics
      i. X-linked inheritance
      ii. *Dystrophin gene* is on the X chromosome (Xp21)
      iii. Dystrophin protein is an important muscle structural protein.
      iv. Mutation results in a virtual absence of dystrophin protein
   d. Clinical presentation
      i. Normal at birth with onset of symptoms by age 5
      ii. Progressive muscular weakness
      iii. Calf pseudohypertrophy
      iv. Proximal weakness of shoulder and pelvic girdles
      v. Heart failure and arrhythmias may occur.
      vi. Respiratory insufficiency and pulmonary infections due to decreased mucociliary clearance
   e. Lab: elevated serum creatine kinase
   f. Micro
      i. Muscle fibers of various sizes
      ii. Necrosis, degeneration, and regeneration of fibers
      iii. Fibrosis
      iv. Fatty infiltration
   g. Diagnosis
      i. Muscle biopsy: immunostains show decreased dystrophin protein
      ii. DNA analysis by PCR

2. Becker muscular dystrophy
   a. Definition: a recessive X-linked inherited disorder leading to slowly progressive muscle weakness of the legs and pelvis
   b. Less common and not as severe as Duchenne muscular dystrophy
   c. Mutation produces an altered dystrophin protein.
   d. Later onset with variable progression
   e. Cardiac involvement is rare.
   f. May have a relatively normal life span
Figure 29-2. Gower Sign in Duchenne Muscular Dystrophy
INFLAMMATORY NEUROPATHY

1. Guillain-Barré syndrome
   a. Definition: autoimmune disease leading to destruction of Schwann cells and peripheral nerve demyelination
   b. Clinical presentation
      i. Preceded by a viral illness
      ii. Muscular weakness with an ascending paralysis
      iii. Loss of deep tendon reflexes
   c. Pathology: inflammation and demyelination of peripheral nerves and spinal nerve roots, resulting in muscular weakness
   d. Diagnosis
      i. Nerve conduction studies
      ii. Lumbar puncture: elevated protein
   e. Prognosis: fatal in 5% because of respiratory paralysis

SOFT TISSUE TUMORS AND TUMOR-LIKE CONDITIONS

1. Lipoma
   a. Benign adipose tissue tumor that is the most common benign soft tissue tumor
   b. Usually arises in subcutaneous tissue of trunk, neck, or proximal extremities
   c. More of a cosmetic problem than a medical problem

2. Liposarcoma
   a. Malignant adipose tissue tumor that is the most common adult sarcoma
   b. Most often arises in the thigh or retroperitoneum
   c. Distinguished from lipoma by the presence of lipoblasts

3. Dermatofibroma
   a. Benign dermal spindle cell proliferation most often seen on the extremities
   b. Forms a small red nodule that indents when squeezed

4. Fibromatosis
   a. Non-neoplastic proliferative connective tissue disorder that can histologically resemble a sarcoma
   b. Fibrous tissue infiltrates muscle or other tissue and may cause a mass lesion.

5. Fibrosarcoma
   a. Malignant fibrous tumor
   b. Common sites are thigh and upper limb.
   c. May arise spontaneously or after therapeutic or accidental irradiation

6. Malignant fibrous histiocytoma
   a. Malignant tumor that often has strikingly pleomorphic cells
   b. Common sites are retroperitoneum and thigh.
   c. May develop following radiation therapy and scarring

7. Rhabdomyoma
   a. Benign striated muscle tumor that can occur in heart, tongue, and vagina
   b. Cardiac rhabdomyomas may be associated with tuberculous sclerosis.
8. Embryonal rhabdomyosarcoma
   a. Most common sarcoma of children; derived from striated muscle
   b. Typically presents as a grape-like, necrotic mass protruding from the penis or vagina

9. Leiomyoma
   a. Benign smooth muscle tumor that occurs most often in the uterus and stomach

10. Leiomyosarcoma
    a. Malignant smooth muscle tumor that is the most common sarcoma of the gastrointestinal tract and uterus

11. Neurofibrosarcoma
    a. Malignant neural tumor that involves major nerve trunks and is associated with neurofibromatosis

12. Synovial sarcoma
    a. Malignant biphasic (glands plus spindle cells) tumor that arises from the mesenchymal cells around joints

Chapter Summary

* Type I (red) skeletal muscle is used in postural weight bearing and produces a slow twitch as a result of aerobic metabolism of fatty acids; type II (white) skeletal muscle is used for purposeful movement and produces a fast twitch as a result of anaerobic glycolysis of glycogen.

* Inflammatory myopathies include polymyositis (adults, bilateral proximal muscle weakness, cytotoxic T4 lymphocytes, and skeletal muscle degeneration and regeneration), dermatomyositis (children or adults with bilateral proximal muscle weakness; periorbital edema with skin rash of eyelids; muscle biopsy with lymphocytes and perifascicular fiber atrophy; and increased risk of lung, stomach, and ovarian cancers), and inclusion body myositis (older adults with asymmetrical distal muscle weakness and odd microscopy with cytoplasmic vacuoles, basophilic granules, amyloid, and, by EM, filamentous inclusions).

* Myasthenic syndromes include myasthenia gravis (autoantibody attack on muscle acetylcholine receptor sometimes related to thymic disease, produces muscle weakness that worsens with use, may cause ptosis and diplopia, and may cause death secondary to respiratory muscle failure) and Eaton-Lambert syndrome (paraneoplastic syndrome of small cell carcinoma of lung with autoantibodies against calcium channels, producing proximal muscle weakness that improves with muscle use).

* Muscular dystrophies include Duchenne muscular dystrophy (X-linked abnormality of the muscle structural protein dystrophin causes progressive muscular weakness related to muscle necrosis and degeneration beginning by age 5, involving initially shoulder and pelvic girdles; death may be due to heart failure, arrhythmias, respiratory insufficiency, or pulmonary infections) and Becker muscular dystrophy (less common, milder variant of Duchenne with relatively normal life span).

* Guillain-Barré syndrome is an inflammatory neuropathy that typically follows a viral illness and may lead to paralysis and sometimes death (respiratory paralysis) as a result of inflammation and demyelination of peripheral nerves and spinal nerve roots.

* Benign soft tissue tumors and tumor-like conditions include lipomas, dermatofibromas, fibromatosis, rhabdomyomas, and leiomyomas. Malignant soft tissue tumors include liposarcoma, fibrosarcoma, malignant fibrous histiocytoma, embryonal rhabdomyosarcoma, leiomyosarcoma, neurofibrosarcoma, and synovial sarcoma.
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