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Lecture Notes

Pathology

Author and Executive Editor

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

Contributors

Earl J. Brown, M.D.
Associate Professor
Department of Pathology
James H. Quillen College of Medicine
East Tennessee State University
Chief of Hematopathology
Pathology and Laboratory Medicine Service
James H. Quillen Veterans Affairs Medical Center
Mountain Home, TN

William DePond, M.D.
Associate Professor, University of Missouri/Kansas City
Vice Chairman, Department of Pathology
Truman Medical Center
Kansas City, MO

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

Elissa Levy, M.D.
Kaplan Medical

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

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

Executive Director of Curriculum
Richard Friedland, M.D.

Director of Publishing and Media
Michelle Covello

Managing Editor
Kathlyn McGreevy

Medical Illustrator
Christine Schaar

Production Artist
Michael Wolff

Cover Design
Joanna Myllo

Cover Art
Christine Schaar

Contents

Fundamentals of Pathology

1

A. DEFINITION OF PATHOLOGY

1. Literal translation: "the study of suffering (pathos)"
2. The study of the essential nature of disease, disease processes, and the structural and functional changes in organs and tissues that cause or are caused by disease
3. The study of the gross and microscopic patterns of disease

B. OVERVIEW OF PATHOLOGY

1. **Etiology (cause)**
   a. Genetic
   b. Acquired
2. **Pathogenesis:** sequence and patterns of cellular injury that lead to disease
3. **Morphologic changes**
   a. Gross changes
   b. Microscopic changes
4. **Clinical significance**
   a. Signs and symptoms
   b. Disease course
   c. Prognosis

C. METHODS USED IN PATHOLOGY

1. **Gross examination of organs**
   a. Gross examination of organs on the exam has two major components
      i. Determining what organ are you looking at!
      ii. Determining what's wrong (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

Hematoxylin	Eosin
Stains blue to purple	Stains pink to red
• Nuclei	• Cytoplasm
• Nucleoli	• Collagen
• Bacteria	• Fibrin
• Calcium	• RBCs
• Many others	• Thyroid colloid
	• Many others

b. Other histochemical stains (chemical reactions)
   i. Prussian blue
   ii. Congo red
   iii. Acid fast (Ziel-Neelson, Fite)
   iv. Periodic acid-Schiff (PAS)
   v. Gram stain
   vi. Trichrome
   vii. Reticulin
c. Immunohistochemical (antibody) stains
   i. Cytokeratin
   ii. Vimentin
   iii. Desmin
   iv. Prostate specific antigen (PSA)
   v. Many others

3. **Ancillary techniques**
   a. Immunofluorescence microscopy (IFM)
      i. Renal diseases
      ii. Autoimmune diseases
   b. Transmission electron microscopy (EM)
      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)

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 and eosin 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.

Review Questions

1. A 27-year-old homeless man comes to the clinic because of a 3-week history of a fever, weight loss, night sweats, shortness of breath, and a cough with blood-tinged sputum. He says that a few of his acquaintances have similar symptoms. His temperature is 38.2°C (100.8°F), blood pressure is 120/80 mm Hg, pulse is 70/min, and respirations are 20/min. Crackles are heard over the upper lobes on auscultation. A chest x-ray shows upper lobe infiltrates and a 1-cm cavity in the left upper lobe. Three sputum samples are taken and sent to pathology for microscopic evaluation. Which of the following is the most appropriate histochemical stain to use for these specimens?

   A. Acid-fast
   B. Congo red
   C. Periodic acid-Schiff
   D. Prussian blue
   E. Trichrome

2. A 48-year-old man comes to the physician because of an "odd discoloration" of his skin. He recently began to notice that he looks suntanned, even though it is the middle of the winter. A full work-up for this abnormal skin pigmentation shows diabetes mellitus and increased levels of serum ferritin and transferrin saturation. He is admitted to the hospital for a liver biopsy. The biopsy is sent to pathology for microscopic evaluation. In addition to hematoxylin and eosin (H&E), which of the following is the most appropriate histochemical stain to use for this specimen?

   A. Acid-fast
   B. Congo red
   C. Gram stain
   D. Periodic acid-Schiff
   E. Prussian blue

Answers

1. **Answer: A.**
2. **Answer: E.**

Cellular Injury and Adaptation

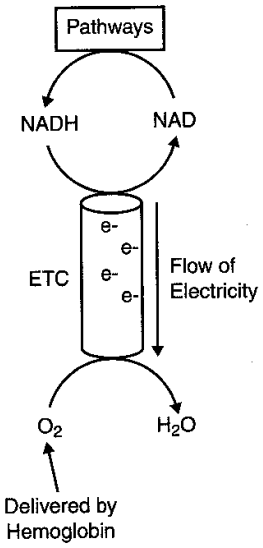
2

A. 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 causes of hypoxia
      i. *Ischemia:* loss of blood supply
         - Most common cause of hypoxia
         - Decreased arterial flow or decrease venous outflow
         - e.g., arteriosclerosis, thrombus, thromboembolus
      ii. *Cardiopulmonary failure*
      iii. *Decreased oxygen-carrying capacity of the blood* (example: anemia)
2. **Infections**
   a. Viruses, bacteria, parasites, and fungi (and probably 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 Section VI for a more detailed discussion of specific genetic disorders])
      i. Enzyme defects leading to the accumulation of toxic products
      ii. Enzyme defects leading to a deficiency of an important product
      iii. Genetic defects in structural proteins
      iv. Cytogenetic disorders
      v. Congenital malformations caused by abnormal development
5. **Chemical injury**
   a. Drugs
   b. Poisons (cyanide, arsenic, mercury, etc.)
   c. Pollution

Note

Overview of the Electron Transport Chain



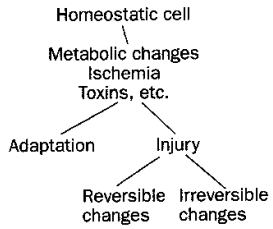
Note

Genetic defects involving enzymes are most often inherited in a recessive manner, whereas those involving structural proteins are most often inherited in a dominant fashion.

d. Occupational exposure (CCl_4, asbestosis, 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
   d. Radiation
   e. Pressure changes
7. **Nutritional or vitamin imbalance**
   a. Inadequate calorie/protein intake
      i. Marasmus and kwashiorkor
      ii. Anorexia nervosa
   b. Excess caloric intake
      i. Obesity
      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

In a Nutshell



B. CELLULAR CHANGES DURING INJURY

1. **General**
   a. Cellular responses to injury
      i. Adaptation
      ii. Reversible injury
      iii. Irreversible injury and cell death (necrosis/apoptosis)
   b. Cellular response to injury depends on several important factors
      i. The *type* of injury
      ii. The *duration* 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
      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) by peroxidation caused by oxygen-derived free radicals
      - Superoxide anion ($O_2^{\cdot -}$)
      - Hydroxyl radical ($OH^{\cdot}$)
      - Hydrogen peroxide (H_2O_2)
   ii. ATP depletion
   iii. Increased cell membrane permeability
   iv. Influx of calcium
      - Second messenger
      - Activates a wide spectrum of enzymes
      - Proteases → protein breakdown
      - ATPases → contributes to ATP depletion
      - Phospholipases → cell membrane injury
      - Endonucleases → DNA damage
   v. Mitochondrial dysfunction
      - Decreased oxidative phosphorylation
      - 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 → hydrogen peroxide
3. Glutathione peroxidase
   Hydroxyl ions or hydrogen peroxide → water
4. Catalase
   Hydrogen peroxide → oxygen and water

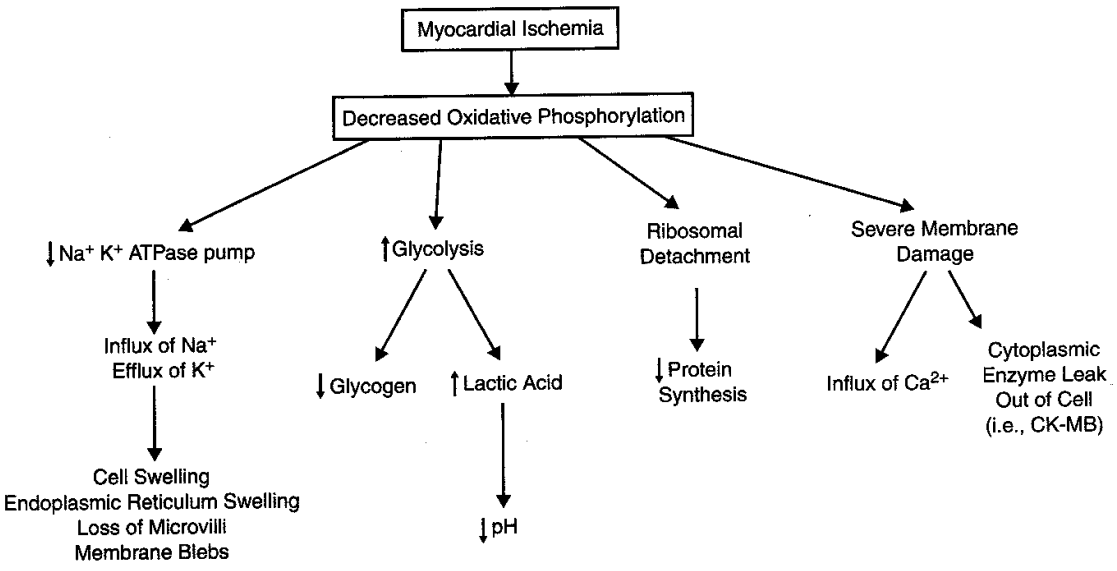


Figure 2-1. Classic Example of Cellular Injury Caused by Hypoxia

Note

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

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 cellular death and organ injury.

Clinically important examples:

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

Note

Liquefaction by leukocyte enzymes is called suppuration, and the resultant fluid is called pus.

2. **Reversible cell injury**
   a. Decreased synthesis of ATP by oxidative phosphorylation
   b. Decreased function of Na^+K^+ ATPase membrane pumps
      i. Influx of Na^+ and water
      ii. Efflux of K^+
      iii. Cellular swelling (hydropic swelling)
      iv. Swelling of the endoplasmic reticulum
   c. Switch to glycolysis
      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. Massive influx of calcium
      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
      i. *Pyknosis:* degeneration and condensation of nuclear chromatin
      ii. *Karyorrhexis:* nuclear fragmentation
      iii. *Karyolysis:* dissolution of the nucleus

C. CELL DEATH

1. **Morphologic types of necrosis**
   a. Coagulative necrosis
      i. Most common form of necrosis
      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 and heterolysis
      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 tuberculosis
d. **Fat necrosis**
   i. Caused by the action of lipases on fatty tissue
   ii. Grossly, fat necrosis has a chalky white appearance
e. **Fibrinoid necrosis**
   i. Necrotic tissue that histologically resembles fibrin
   ii. Micro: has an eosinophilic (pink) homogeneous appearance
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*
   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

Bridge to Biochemistry

Damage to fat cells releases triglycerides. The triglycerides are broken down by the action of lipases to fatty acids. The fatty acids may associate with calcium and form calcium soaps (saponification).

Note

Necrotic tissue within the body evokes an inflammatory response that removes the dead tissue and is followed by wound healing and repair. Necrotic debris may also undergo dystrophic calcification.

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

D. 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 malignancy

2. **Atrophy**
a. Definition: decrease in cell size and functional ability
b. Causes of atrophy
i. Deceased 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. Example: cervical dysplasia

E. 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**

d. **Exogenous pigments**
   i. Anthracotic pigmentation of the lung is secondary to the inhalation of carbon dust
   ii. Tattoos
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
      - Found in melanocytes and substantia nigria
   iii. Hemosiderin
      - Golden yellow-brown granular pigment
      - Found in areas of hemorrhage or bruises
      - Systemic iron overload → hemosiderosis → hemochromatosis
      - Prussian blue stain

2. **Hyaline change**
   a. Definition: nonspecific term used to describe *any intracellular or extracellular alteration that has a pink homogenous appearance* 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
         - Monckeberg's 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 can produce a variety of histologic patterns, including coagulative necrosis, liquefaction necrosis, caseous necrosis, fibrinoid necrosis, and gangrenous necrosis.

Apoptosis is a specialized form of programmed cell death that can be regulated genetically or by cellular or tissue triggers.

Review Questions

1. A 67-year-old man comes to the physician because of "tingling" feet. He says he has notice that he has had difficulty walking over the past few months. He is constantly "stubbing" h toes against furniture and walls and has a "generalized klutzy" feeling. Laboratory studi show:

Hematocrit	37%
Hemoglobin	11 g/dl
MCV	103 mm^3

A peripheral blood smear shows hypersegmented neutrophils and large, oval-shaped eryth rocytes with poikilocytosis and a teardrop-shaped configuration. Supplementation wit which of the following vitamins/nutrients would most likely have prevented this conditio

A. Folic acid
B. Vitamin A
C. Vitamin B_{12}
D. Vitamin C
E. Vitamin D
F. Vitamin K

2. A 49-year-old alcoholic comes to the emergency department because of a 2-h history c severe abdominal pain. The pain is located in the epigastrium and radiates to his back. H says that he is "extremely" nauseous and has had several episodes of emesis, including on in the hospital waiting room. Physical examination shows epigastric tenderness and periumbilical discoloration. Laboratory studies show elevated levels of amylase and lipas Which of the following is the most likely diagnosis?

A. Acute cholecystitis
B. Diverticulitis
C. Hepatitis
D. Myocardial infarction
E. Pancreatitis

Answers

1. **Answer: C.**

2. **Answer: E.**

Inflammation 3

A. ACUTE INFLAMMATION

1. **General**
   a. Acute inflammation is an immediate response to injury
   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)
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

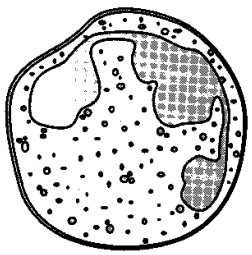
B. NEUTROPHILS

1. **Important cells in acute inflammation**
   a. Neutrophils
      i. Synonyms: segmented neutrophils, polymorphonuclear leukocytes (PMN)
      ii. Primary (azurophilic) granules
         • Myeloperoxidase
         • Phospholipase A2
         • Lysozyme
         • Acid hydrolases

Note

Important components of acute inflammation

- Hemodynamic changes
- Neutrophils
- Chemical mediators



Lobed Nucleus, Small Granules

Neutrophil

- Elastase
- Defensins
- Bactericidal permeability increasing protein (BPI)

iii. Secondary (specific) granules

- Phospholipase A2
- Lysozyme
- Leukocyte alkaline phosphatase (LAP)
- Collagenase
- Lactoferrin
- Vitamin B12 binding proteins

b. Macrophages

i. Acid hydrolases

ii. Elastase

iii. Collagenase

Note

Selectins: weak binding; initiate rolling

Integrins: stable binding and adhesion

2. **Neutrophil margination and adhesion**

a. Adhesion is mediated by complementary molecules on the surface of neutrophil and endothelium

i. Step 1: at sites of inflammation, the endothelial cells have increased expressio of *E-selectin* and *P-selectin*

ii. Step 2: neutrophils weakly bind to the endothelial selectins and roll along th 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 endotheli cell

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

	Endothelium	Leukocyte
Selectins	P-Selectin	Sialyl-Lewis X & PSGL-1
	E-Selectin	Sialyl-Lewis X & PSGL-1
	GlyCam-1/CD34	L-Selectin
Integrins	ICAM-1	LFA-1 & MAC-1
	VCAM-1	VLA-4

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 surfac with exposure to inflammatory mediators such as histamine

ii. Additional synthesis: Cytokines IL-1 and TNF induce production of E-selectir ICAM-1, and VCAM-1 in endothelial cells

iii. Increased binding affinity: Chemotactic agents cause a conformational change i the leukocyte integrin LFA-1, which is converted to a high-affinity binding stat

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**
   a. Leukocytes emigrate from the vasculature 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. **Phagoctosis 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)

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*)

ii. Myeloperoxidase deficiency
- Autosomal recessive
- Infections with candida

C. 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 → kallikrein
b. Kallikrein cleaves high molecular weight kininogen (HMWK) → bradykinin
c. Effects of bradykinin
i. Increases vascular permeability
ii. Pain
iii. Vasodilation
iv. Bronchoconstriction

3. **Arachadonic 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 E_2: pain
      iv. Prostaglandins PGE2, PGD2, and PGF2: vasodilatation
   b. Lipoxygenase 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
5. **Cytokines**
      i. IL-1 and TNF
         • Fever and acute phase reactants
         • Enhances adhesion molecules
         • Stimulates and activates fibroblasts, endothelial cells, and neutrophils
      ii. IL-8 neutrophil chemoattractant produced by macrophages

In a Nutshell

Mediators of Pain

- Bradykinin
- Prostaglandins (E_2)

In a Nutshell

Mediators of Fever

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

D. FOUR OUTCOMES OF ACUTE INFLAMMATION

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

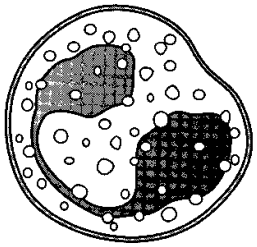
E. CHRONIC INFLAMMATION

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

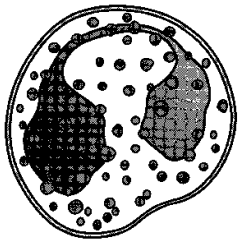
2. **Important cells in chronic inflammation**
   a. Macrophages
      i. Macrophages are derived from blood monocytes
      ii. Tissue-based macrophages
         • Connective tissue (histiocyte)
         • Lung (pulmonary alveolar macrophages)
         • Liver (Kupffer cells)
         • Bone (osteoclasts)
         • 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. Tissue-based basophils are called mast cells
      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 surrounded by a rim of lymphocytes
   b. Composition of a granuloma
      i. Epithelioid cell
         • IFN-γ transforms macrophages → epithelioid cells
         • Enlarged cell with abundant pink cytoplasm



Bilobed Nucleus,
Large Granules (Pink)

Eosinophil



Bilobed Nucleus,
Large Granules (Blue)

Basophil

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 rare in other granulomatous diseases

c. Granulomatous diseases
- Tuberculosis (caseating granulomas)
- Cat-scratch fever
- Syphilis
- Leprosy
- Fungal infections (e.g., coccidioidomycosis)
- Parasitic infections (e.g., schistosomiasis)
- Foreign bodies
- Beryllium
- Sarcoidosis

F. 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. **Five 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

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 vessel. 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, 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, and cytopathic/cytoproliferative inflammation.

Review Questions

1. An 18-year-old college student comes to the student health clinic because of an 8-h history of a severe headache and "stiff neck." She says that two other students in her dormitory have similar symptoms. Her temperature is 39.3°C (102.8°F). Physical examination shows nuchal rigidity and palpable purpura on her trunk and lower extremities. Gram stain analysis of cerebrospinal fluid obtained by a lumbar puncture shows Gram-negative intracellular diplococci. Which of the following types of inflammation is most likely associated with this patient's neurologic condition?

   A. Cytopathic inflammation
   B. Exudative inflammation
   C. Granulomatous inflammation
   D. Interstitial inflammation
   E. Necrotizing inflammation

2. A 69-year-old woman comes to the emergency department because of a 7-d history of fever, cough, chills, and pleuritic chest pain. She says that her sputum was initially a rust color, but it has been more yellowish over the past few days. Diffuse rales are heard on auscultation. A chest x-ray shows patchy infiltrates. A Gram stain of a sputum sample reveals Gram-positive diplococci. Which of the following is the most likely tissue response to this infectious organism?

   A. Acute inflammatory response with neutrophils
   B. Cell killing by cytotoxic T lymphocytes
   C. Diffuse mononuclear interstitial infiltrate
   D. Granulomatous inflammation with lymphocytes and macrophages
   E. Severe tissue damage and extensive cell death

Answers

1. **Answer: B.**

2. **Answer: A.**

Wound Healing and Repair

A. REGENERATION AND REPAIR

1. **Wound healing**
   a. Regeneration and repair of damaged cells and tissues starts almost as soon as the inflammatory process begins
   b. Wound healing involves two separate processes
      i. *Regeneration* of the damaged tissue by cells of the same type
      ii. *Tissue repair* with replacement by connective tissue
2. **Regeneration**
   a. Different tissues have different regenerative capacities
   b. Labile cells
      i. Regenerate throughout life
      ii. Examples: surface epithelial cells (skin and mucosal lining cells), hematopoietic cells, stem cells, etc.
   c. Stable 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
      i. Cannot replicate
      ii. Examples: neurons and cardiac muscle
3. **Tissue repair**
   a. Replacement of a damaged area by a connective tissue scar
   b. Tissue repair is mediated by various growth factors and cytokines
      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 skin edges 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

B. ABERRATIONS IN WOUND HEALING

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

C. CONNECTIVE TISSUE COMPONENTS

1. **Collagen (over 14 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

Clinical Correlate

Scurvy: Vitamin C deficiency first affecting 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.

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

Chapter Summary

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

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 through 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.

Tissue repair with replacement of a damaged area by a connective tissue scar is mediated by many growth factors and cytokines. 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.

Review Questions

1. A 16-year-old girl comes to the physician because of a "large growth" on her earlobe. S says that she began to notice it about 3 weeks after she got her ears pierced, and it has b growing "exponentially" ever since. Physical examination shows a 3-cm, firm tumor ha ing from her left earlobe. Excessive production of which of the following types of colla is associated with this condition?

   A. Collagen type I
   B. Collagen type II
   C. Collagen type III
   D. Collagen type IV
   E. Collagen type VI

2. A wealthy 87-year-old woman comes to the physician because of 3-week history of "ble ing gums." She says that her gums have always been "a bit sensitive," but they now they bl whenever she eats something hard or when she brushes her teeth. Her cook passed awa months ago, and she has been eating "tea and toast" ever since. Physical examination sho erythematous, inflamed gums. Which of the following is the most likely diagnosis?

   A. Ehlers-Danlos syndrome
   B. Marfan syndrome
   C. Osteogenesis imperfecta
   D. Rickets
   E. Scurvy

Answers

1. **Answer: C.**

2. **Answer: E.**

Circulatory Pathology

5

A. EDEMA

1. Definition: presence of excess fluid in the intercellular space
2. Increased hydrostatic pressure
   a. Congestive heart failure (generalized edema)
   b. Portal hypertension
   c. Renal retention of salt and water
   d. Venous thrombosis (local edema)
3. Hypoalbuminemia and decreased colloid osmotic pressure
   a. Liver disease
   b. Nephrotic syndrome
   c. Protein deficiency (e.g., Kwashiorkor)
4. Lymphatic obstruction (lymphedema)
   a. Tumor
   b. Surgical removal of lymph node drainage
   c. Parasitic infestation (filariasis → elephantiasis)
5. Increased endothelial permeability
   a. Inflammation
   b. Type I hypersensitivity reactions
   c. Drugs (e.g., bleomycin, heroin, etc.)
6. Anasarca: severe generalized edema
7. Effusion: fluid within the body cavities
8. Transudate versus exudate
   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
      ii. Specific gravity >1.020
      iii. Types of exudates
         • Purulent (pus)
         • Fibrinous
         • Eosinophilic
         • Hemorrhagic

Note

Edema can be localized or generalized, depending on the etiology and severity.

9. 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 5-1. Properties of Active Hyperemia and Congestion (Passive Hyperemia)

	Active Hyperemia	Congestion (Passive Hyperemia)
Type	Active process	Passive process
Mechanism	Vasodilatation mediated by • Vasoactive mediators • Hormones • Neurogenic reflexes	Decreased venous outflow
Examples	Inflammation Exercise Blushing	CHF DVT Budd-Chiari syndrome

B. 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
      i. The vascular wall
      ii. Platelets
      iii. Coagulation system
2. **Vascular wall injury**
   a. Transient vasoconstriction is mediated by endothelin
   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_2], tissue plasminogin 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

Note

Clotting is a balance between two opposing forces: those favoring the formation of a stable thrombus versus those factors causing breakdown of the clot.

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

Alpha Granules	Dense Bodies
• Fibrinogen	• ADP (potent platelet aggregator)
• Fibronectin	• Calcium
• Factor V and vWF	• Histamine and serotonin
• Platelet factor 4	• Epinephrine
• Platelet-derived growth factor (PDGF)	

ii. Platelet synthesis of thromboxane A2

iii. Membrane expression of the phospholipid complex, which is an important platform for the coagulation cascade

d. **Step 3: platelet aggregation**

i. Additional platelets are recruited from the blood stream

ii. ADP and thromboxane A2 are potent mediators of aggregation

iii. Platelets bind to each other by binding to fibrinogen using Gp IIb-IIIa

e. Laboratory tests for platelets

i. Platelet count (normal 150 to 400 K)

ii. Bleeding time test (normal 2 to 7 minutes)

iii. Platelet aggregometry

Table 5-3. Common Platelet Disorders

Thrombocytopenia	Qualitative Defects
Decreased production • Aplastic anemia (drugs, virus, etc.) • Tumor	• von Willebrand disease • Bernard-Soulier syndrome • Glanzmann thrombasthenia • Drugs (aspirin) • Uremia
Increased destruction • Immune thrombocytopenia (ITP) • Thrombotic thrombocytopenia purpura (TTP) • Disseminated intravascular coagulation (DIC) • Hypersplenism	

4. **Immune thrombocytopenia purpura (ITP)**

a. Etiology

i. *Antiplatelet antibodies* against platelet antigens such as Gp IIb-IIIa and Gp Ib-IX

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

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

b. 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

c. 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

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

5. **Thrombotic thrombocytopenic purpura (TTP)**

a. Pathology
   i. Widespread formation of platelet thrombi with scant fibrin (hyaline thrombi)
   ii. No activation of the coagulation system

b. Clinical findings
   i. Most often affects adult women
   ii. *Pentad* of characteristic signs
      • Fever
      • Thrombocytopenia
      • Microangiopathic hemolytic anemia
      • Neurologic symptoms
      • Renal failure

c. Lab
   i. Decreased platelet count and prolonged bleeding time
   ii. Normal PT and PTT
   iii. Peripheral blood smear shows thrombocytopenia and schistocytes, and reticulocytosis

d. **Hemolytic uremic syndrome (HUS)**
   i. Occurs most commonly in children
   ii. Follows a gastroenteritis with bloody diarrhea
   iii. Organism: verotoxin-producing *E. coli 0157:H7*
   iv. Similar clinical pentad

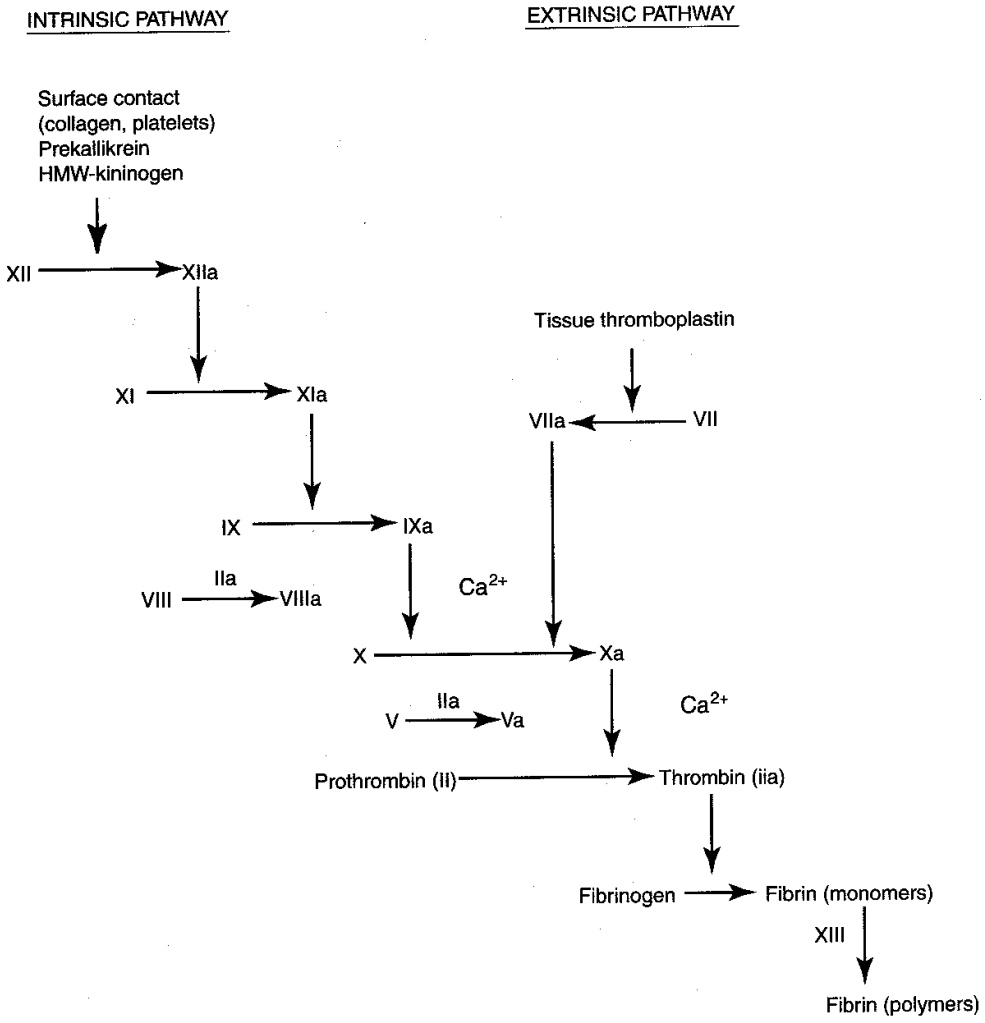


Figure 5-1. Coagulation Cascade

6. **Coagulation**
   a. Coagulation factors
      i. The majority of the clotting factors are produced by the liver
      ii. Are proenzymes that must be converted to the active form
      iii. Some conversions occur on a phospholipid surface
      iv. Some conversions require calcium
   b. Intrinsic coagulation pathway is activated by the contact factors
      i. Contact with subendothelial collagen
      ii. High molecular weight kininogen (HMWK)
      iii. Kallikrein

c. 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
      • VII, X, V, prothrombin, fibrinogen
   ii. *Partial thromboplastin time* (PTT)
      • Tests the intrinsic and common coagulation pathways
      • 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)

7. **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. Spontaneous hemorrhages into joints (hemarthrosis)
      iv. Easy bruising and hematoma formation after minor trauma
      v. Severe prolonged bleeding after surgery or lacerations
      vi. No petechiae or ecchymoses
   d. Lab
      i. Normal platelet count and bleeding time
      ii. Normal PT and *prolonged PTT*
   e. Treatment: factor VIII concentrate
8. **Hemophilia B (Christmas disease)**
   a. Deficiency of factor IX
   b. X-linked recessive
   c. Clinically identical to hemophilia A
9. **Acquired coagulopathies**
   a. Vitamin K deficiency: decreased synthesis of factors II, VII, IX, X, and protein C & S
   b. Liver disease: decreased synthesis of virtually all clotting factors
10. **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 I) with desmopressin (an antidiuretic hormone [ADH] analog), which releases vWF from Weibel Palade bodies of endothelial cells

11. **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. Micro-organisms (especially meningococcus and rickettsia)

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

C. THROMBOSIS

1. **General**

a. Definition: pathologic formation of an intravascular fibrin-platelet thrombus

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. *Hypercoaguability of blood*

- Clotting disorders (factor 5 leiden, deficiency of antithrombin III, protein C, or protein S)
- Tissue injury (postoperative and trauma)
- Neoplasia
- Nephrotic syndrome
- Advanced age
- Pregnancy
- Oral contraceptives

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

	Thrombus	Blood Clot
Location	Intravascular	Extravascular or intravascular (postmortem)
Composition	Platelets Fibrin RBCs and WBCs	Lacks platelets Fibrin RBCs and WBCs
Lines of Zahn	Present	Absent
Shape	Has shape	Lacks shape

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

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

D. 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%)
   b. Atheromatous emboli—severe atheroscerosi
   c. Fat emboli—bone fractures and soft-tissue trauma
   d. Bone marrow emboli—bone fractures and cardiopulmonary resuscitation (CPR)
   e. Gas emboli—decompression sickness ("the bends" and Caisson disease)
   f. Amniotic fluid emboli—complication of labor
   g. Tumor emboli—metastasis
   h. Talc emboli—intravenous drug abuse (IVDA)
   i. Bacterial/septic emboli—infectious endocarditis
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%) arise in *deep leg veins* (DVT)

ii. Pelvic venous plexuses of the prostate and uterus
iii. Right side of the heart

c. Diagnosis
i. V/Q scan mismatch
ii. Doppler ultrasound of the leg veins to detect a DVT

d. Potential outcomes of PEs
i. No sequela (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 pulmonary hypertension (3%)
- Caused by recurrent PEs
- Increased pulmonary resistance
- Pulmonary hypertension
- May lead to cor pulmonale

4. **Systemic arterial emboli**
a. Most arise in the heart
b. Most cause infarction
c. Common sites of infarction
i. Lower extremities
ii. Brain
iii. Intestine
iv. Kidney
v. 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

E. 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 torsion)

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 bed-ridden patient who gets out of bed and collapses.

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

d. Common sites of infarction
   i. Heart
   ii. Brain
   iii. Lungs
   iv. Intestines

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

F. 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
e. 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 acidosis, electrolyte imbalances, and renal insufficiency
   c. Stage III: irreversible
      i. Irreversible tissue injury and organ failure
      ii. Ultimately resulting in death
4. **Pathology**
   a. Kidneys
      i. Acute tubular necrosis
      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 centrilobular necrosis ("shock liver")
   e. Adrenals undergo the Waterhouse-Friderichsen 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, 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.

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 hemarthrosis, 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.

(Continued)

Chapter Summary (*continued*)

The term embolism is used for any intravascular mass that has been carried downstream from its site of origin, resulting in occlusion of a vessel. Ninety-eight percent of emboli are thromboembolia, 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.

Review Questions

1. A 5-year-old girl is brought to the emergency department by her father because of a nosebleed "that just won't stop." The father says that they have "tilted her head back" and applied ice packs for several hours, but nothing has worked. She has been well except for a runny nose and a sore throat 12 days ago. Physical examination shows epistaxis and diffuse ecchymoses and petechiae. A bone marrow biopsy shows increased number of megakaryocytes with immature forms. Which of the following groups of laboratory studies is most consistent with this disorder?

	Platelets	Bleeding Time	Prothrombin Time	Partial Thromboplastin Time
A.	Normal	Prolonged	Normal	Prolonged
B.	Normal	Normal	Normal	Prolonged
C.	Normal	Normal	Prolonged	Prolonged
D.	Decreased	Prolonged	Prolonged	Prolonged
E.	Decreased	Prolonged	Normal	Normal

2. A 24-year-old pregnant woman comes to the emergency department because of vaginal bleeding, abdominal pain, and uterine contractions. A placental abruption is diagnosed on the basis of clinical suspicion. Oxytocin is given, and the baby is delivered vaginally. All of a sudden, the woman develops shortness of breath and oozing from the intravenous site on her right arm. The blood that is passing from the genital tract is not clotting. Laboratory studies show a decreased platelet count, prolonged prothrombin time and partial thromboplastin time, decreased fibrinogen, and elevated fibrin split products. Which of the following is the most likely diagnosis?

   A. Disseminated intravascular coagulation
   B. Hemophilia A
   C. Immune thrombocytopenia purpura
   D. Thrombotic thrombocytopenia purpura
   E. von Willebrand disease

Answers

1 **Answer: E.**

2. **Answer: A.**

Genetic Disorders

6

A. DISORDERS INVOLVING AN EXTRA AUTOSOME

1. **Down syndrome (trisomy 21)**
   a. Karyotype: 47 XX or XY +21
   b. Most common of the chromosomal disorders
   c. Most common cause of inherited mental retardation
   d. Incidence: 1 in 700 births
   e. Risk increases with maternal age
   f. Pathogenesis
      i. Meiotic nondisjunction (95%)
      ii. Robertsonian translocation (4%)
      iii. Mosaicism due to mitotic nondisjunction during embryogenesis (1%)
   g. Clinical findings
      i. Severe 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
         • Atrioventricular canal
      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)
2. **Edward syndrome (trisomy 18)**
   a. Karyotype: 47 XX or XY +18
   b. Risk increases with maternal age
   c. Caused by nondisjunction
   d. Clinical findings
      i. Mental retardation
      ii. Low set ears and micrognathia
      iii. Congenital heart defects
      iv. Overlapping flexed fingers
      v. Rocker-bottom feet

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.

Note

Mosaicism is defined as the presence of two or more populations of cells within an individual.

e. Very poor prognosis due to severe congenital malformations

3. **Patau syndrome (trisomy 13)**
   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

B. 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 cat-like cry
      ii. Mental retardation
      iii. Congenital heart disease
      iv. Microcephaly
2. **Microdeletions**
   a. Of 13q14—the retinoblastoma gene
   b. Of 11p13—the Wilm tumor gene

C. DISORDERS INVOLVING SEX CHROMOSOMES

Note

Presence of a Y chromosome determines male phenotype due to the presence of the testes-determining gene on the Y chromosome.

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. 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

D. 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) or Wolffian (male) 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
   d. Ductal sex: often mixed
   e. Phenotypic sex: ambiguous genitalia
   f. Exceptionally rare
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 tumors)
      iii. Exogenous androgens

In a Nutshell

Lyon's Hypothesis of X-Inactivation

- Only one X is genetically active
- The other X chromosome is inactivated (becomes the Barr body) in the blastocyst stage of development
- Females are mosaics
- Either the maternal or paternal X chromosome is inactivated at random

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*
      i. Most common cause
      ii. Defect: mutation of the androgen receptor (Xq11-12)

E. 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 mutation
      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. Three major patterns of inheritance
      i. Autosomal dominant
      ii. Autosomal recessive
      iii. X-linked

Table 6-1. General Characteristics of Autosomal Dominant and Recessive Diseases

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

F. 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 in amino acid position 508 (ΔF508)
   d. Pathogenesis: defective chloride channel protein leads to abnormally thick viscous mucous, which obstructs the ducts of exocrine organs
   e. Distribution of disease
      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
         - Obstruction of the vas deferens and epididymis
         - May lead to male infertility
      iv. Liver: plugging of the biliary canaliculi may result in biliary cirrhosis
      v. GI tract: small intestinal obstruction (meconium ileus)
   f. Diagnosis
      i. Sweat test (elevated NaCl)
      ii. DNA probes
   g. Prognosis
      i. Mean survival: 30 years
      ii. Most common cause of death is pulmonary infections
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. Diagnosis: screened at birth
   d. Treatment: dietary restriction of phenylalanine

Bridge to Biochemistry

Phenylalanine hydroxylase converts phenylalanine into tyrosine.

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 (ochronosis)
   c. Clinical features
      i. Black urine
      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 glucosidase (acid maltase)*
      ii. Hepatomegaly
      iii. Skeletal muscle hypotonia
      iv. Cardiomegaly
      v. Death from cardiac failure by age 2
   d. **Type V (McArdle syndrome)**
      i. Enzyme defect: deficiency of *muscle 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

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

- Tay-Sachs
- Niemann-Pick
- Gaucher
- Mucopolysaccharidoses
- Fabry's
- Metachromatic leukodystrophy

Table 6-2. Lysosomal Storage Diseases

Disease	Enzyme Deficiency	Accumulating Substance
Tay-Sachs disease	Hexosaminidase A	GM_2 ganglioside
Niemann-Pick disease	Sphingomyelinase	Sphingomyelin
Gaucher disease	Glucocerebrosidase	Glucocerebroside
Fabry disease	α-Galactosidase A	Ceramide trihexoside
Metachromatic leukodystrophy	Aryl sulfatase A	Sulfatide
Hurler syndrome	α-1-Iduronidase	Dermatan sulfate Heparan sulfate
Hunter syndrome	L-Iduronosulfate sulfatase	Dermatan sulfate Heparan sulfate

c. Common in Ashkenazi Jews (1 in 30 carrier rate)
d. Distribution of disease
   i. Retina: cherry-red spot (accentuation of the macula)
   ii. CNS: dilated neurons with cytoplasmic vacuoles
e. 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
f. EM: distended lysosomes with whirled membranes
g. 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
   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
   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 **glucocerebroside** predominately in the lysosomes of the reticuloendothelial system
   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's cells*: enlarged macrophages with a fibrillary (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-1-iduronidase*
      ii. Severe form
   d. MPS II (Hunter syndrome)
      i. X-linked recessive inheritance
      ii. Deficiency of L-iduronosulfate sulfatase
      iii. Milder form

G. 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
      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. Mutation causes
   i. Increased levels of circulating cholesterol
   ii. Loss of feedback inhibition of *HMG coenzyme A 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. Xanthelasma 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 necrosis → 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 Type III collagen
      iii. EDS Type 6—AR defect in lysyl hydroxylase (enzyme responsible for hydroxylation of lysine residues [a recessive disease])

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. Genetics
- Tumor suppressor gene: NF-1
- Chromosome 17 (17q11.2)
- Normal gene product (neurofibromin) inhibits *p21 ras oncoprotein*

iii. Frequency: 1 in 3,000
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 nodule*)
vii. Increased risk of meningiomas and pheochromocytoma

b. **Type 2 (bilateral acoustic neurofibromatosis)**
i. Accounts for 10% of cases of neurofibromatosis
ii. Genetics
- Tumor suppressor gene: NF-2
- Chromosome 22
- Normal gene product (merlin) has unknown function

iii. Frequency: 1 in 45,000
iv. Bilateral acoustic neuromas
v. Neurofibromas and cafe-au-lait spots
vi. Increased risk of meningioma and ependymomas

5. **von Hippel-Lindau disease**
   a. Genetics
      i. Tumor suppressor gene
      ii. Chromosome 3p
   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

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

I. GENOMIC IMPRINTING

1. **Definition:** differential expression of genes based on chromosomal inheritance from maternal versus paternal origin.
2. **Prader-Willi syndrome**
   a. Deletion 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. Deletion on *maternal* chromosome 15 {del[15]]q11;q13}}

Note

Most common genetic causes of mental retardation:

- Down's syndrome
- Fragile X syndrome

b. Clinical presentation
   i. Mental retardation
   ii. Seizures
   iii. Ataxia
   iv. Inappropriate laughter
4. May play a role in Huntington disease, neurofibromatosis, and myotonic dystrophy

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 Wilms 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 (preductal coarctation 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.

(Continued)

Chapter Summary (*continued*)

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.

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 GM_2 ganglioside deposition with progressive mental deterioration, culminating in death by age two to three.

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

Gaucher disease is an autosomal recessive deficiency of glucocerebrosidase, leading to accumulation of glucocerebroside, with hepatosplenomegaly 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, diaphragmatic 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.

(Continued)

Chapter Summary (*continued*)

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.

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").

Review Questions

1. A 37-year-old woman gives birth to an 8-pound baby boy. She is concerned that he looks "different" from the other newborns in the hospital nursery. He has a broad neck, prominent epicanthal folds, a prominent tongue, "stubby" hands and feet, and poor muscle tone. There is a single line that extends across the entire palm. The mother asks if there are going to be any future complications due to this disease or if he will just look a bit "different." He will most likely have which of the following disorders by age 40?

   A. Acute myelogenous leukemia
   B. Alzheimer disease
   C. Bilateral acoustic neuromas
   D. Coarctation of the aorta
   E. Dissecting aortic aneurysm

2. A 16-year-old girl is brought to the physician by her mother because she has not yet begun to menstruate. She is concerned because all of her other friends "got their periods years ago." She is not sexually active and denies excessive dieting or exercise. Physical examination reveals normal adult-type breasts, a sparse amount of axillary and pubic hair, and a blind-ending vagina. A sonogram reveals that the uterus and ovaries are absent. She has male levels of testosterone. Which of the following is the most likely cause of her condition?

   A. Androgen-producing tumor
   B. Congenital adrenal hyperplasia
   C. Maternal intake of androgens
   D. Meiotic nondisjunction
   E. Mutation of the androgen receptor

Answers

1. **Answer: B.**
2. **Answer: E.**

Immunopathology

7

A. HYPERSENSITIVITY REACTIONS

1. **Type I 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 basophils
   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 (cytotoxic type)**
   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. Example: autoimmune hemolytic anemia
   c. Antibody-dependent cell-mediated cytoxicity (ADCC)
      i. Cytotoxic killing of an antibody-coated cell
      ii. Example: pernicious anemia
   d. Anti-receptor antibodies
      i. Antibodies activate or interfere with receptors
      ii. Example: Graves disease
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+ T-cell lymphocyte 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

B. AUTOIMMUNE DISEASES

1. **Systemic lupus erythematosis (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
      iii. African American > Caucasian
   c. Autoantibodies
      i. Antinuclear antibody (ANA) (>95%)
      ii. *Anti-dsDNA* (40–60%)
      iii. *Anti-Sm* (20–30%)
   d. Mechanism of injury: type II and III hypersensitivity reactions
   e. Distribution of disease
      i. Hematologic
         - Hemolytic anemia
         - Thrombocytopenia
         - Neutropenia
         - Lymphopenia
      ii. Arthritis: polyarthralgia and synovitis without joint deformity
      iii. Skin
         - *Malar "butterfly" rash*
         - Maculopapular rash
         - Ulcerations and bullae formation
      iv. WHO classification of kidney manifestations
         - Class I: normal
         - Class II: mesangial lupus nephritis
         - Class III: focal proliferative glomerulonephritis

Note

Multiple autoantibodies may be produced and are commonly directed against nuclear antigens (DNA, histones, nonhistone nuclear RNA proteins) and blood cells.

- Class IV: diffuse proliferative glomerulonephritis (most common and severe)
- Class V: membranous glomerulonephritis

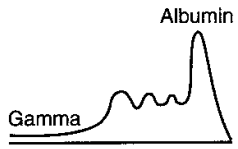
v. Heart: *Libman-Sacks endocarditis* (nonbacterial verrucous endocarditis)
vi. Serosal surfaces: pericarditis, pleuritis, and pleural effusions
vii. CNS: focal neurologic symptoms, seizures, and psychosis

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

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
      ii. Keratoconjuctivitis 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 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
   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
         - Esophagus—dysphagia
         - GI tract—malabsorption
         - Pulmonary fibrosis—dyspnea on exertion
         - Cardiac fibrosis—arrhythmias
         - 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



Hypogammaglobulinemia

C. 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 *agammablobulinemia*
   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
      iii. Common infections: pharyngitis, otitis media, bronchitis, and pneumonia
      iv. Organisms: *H. Influenza*, *S. pneumococcus*, and *S. aureus*
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 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. Bone marrow transplant
      ii. Gene therapy (experimental)
   e. Prognosis: without treatment most infants die of infection within a year

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
   c. Treatment: bone marrow transplant
   d. Complications
      i. Increased risk of lymphoma
      ii. Death due to infection or hemorrhage

D. SECONDARY IMMUNE DEFICIENCY SYNDROMES

1. **Systemic diseases**
   a. Diabetes mellitus
   b. Collagen vascular disease (e.g., SLE)
   c. Alcohol abuse
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 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 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
3. **Acquired immunodeficiency syndrome (AIDS)**
   a. Definition: HIV positive and CD4 count <200 **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

Note

Cardiac Transplantation

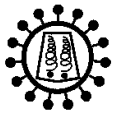
The major complication in long- term cardiac transplant patients is accelerated graft arteriosclerosis.

Clinical Correlate

There is no evidence that AIDS is transmitted by casual contact.

c. Transmission of HIV
   i. Sexual contact
      - Homosexuals
      - Increasing rate of heterosexual transmission
      - Cofactors: herpes and syphilis
   ii. Parenteral transmission
      - Intravenous drug abuse (IVDA)
      - 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
      - Macrophages
      - Lymph node follicular dendritic cells
      - Langerhans cells
   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)



Retrovirus

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

CD4 Count (cells/μL)	
700–1,500	Normal
200–500	Oral thrush, Kaposi sarcoma, tuberculosis, zoster
100–200	*Pneumocystis carinii* pneumonia, dementia
<100	Toxoplasmosis, cryptococcus, cryptosporidiosis
<50	Cytomegalovirus, *Mycobacterium-avium* complex, progressive multifocal leukoencephalopathy

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 adenopathy
   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)
      • *Herpes zoster*
   v. Average duration of latent phase: 10 years

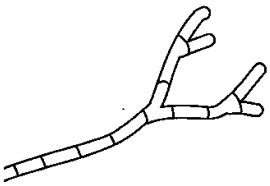
j. Progression to AIDS
   i. Reduction of CD4 count
   ii. Reemergence of viremia
   iii. AIDS-defining diseases occur
   iv. Death

Note

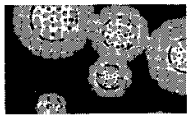
Macrophages and follicular dendritic cells are reservoirs for the virus.

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

Opportunistic infection	Common sites of infection
Pneumocystis carinii	Lung (pneumonia), bone marrow
Mycobacterium tuberculosis	Lung, disseminated
Mycobacterium avium-intracellulare	Lung, GI tract, disseminated
Coccidioidomycosis	Lung, disseminated
Histoplasmosis	Lung, disseminated
Cytomegalovirus	Lung, retina, adrenals, and GI tract
Giardia lamblia	GI tract
Cryptosporidium	GI tract
Herpes simplex virus	Esophagus and CNS (encephalitis)
Candida	Oral pharynx and esophagus
Aspergillus	CNS, lungs, blood vessels
Toxoplasmosis	CNS
Cryptococcus	CNS (meningitis)
JC virus	CNS (progressive multifocal leukoencephalopathy)



Septate Hyphae



Cryptococcus neoformans

Note

Other entities associated with HHV8:

- Castleman disease
- Squamaus cell carcinoma
- Body cavity lymphoma

k. Hairy leukoplakia: Epstein-Barr virus (EBV)–associated
l. Kaposi sarcoma
   i. Common in homosexual males
   ii. Associated with human herpes virus 8 (HHV8)
   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 antiribonucleoprotein 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 alcohol abuse.

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.

Review Questions

1. A 32-year-old woman comes to the physician because of a difficulty swallowing and shortness of breath on exertion. She says that these symptoms started about 6 months ago and have been getting progressively worse. Physical examination shows symmetric skin thickening of the proximal and distal extremities, face, and trunk. Bilateral basilar rales are heard on auscultation. Laboratory studies show antitopoisomerase I antibodies. Which of the following is the most likely diagnosis?

   A. Dermatomyositis
   B. Polymyositis
   C. Scleroderma
   D. Sjögren syndrome
   E. Systemic lupus erythematosus

2. A 32-year-old woman comes to the physician because of palpitations and weight loss despite an increased appetite. She says that friends have recently begun to tell her that he eyes look like they are "popping out." Her blood pressure is 120/80 mm Hg, and her pulse is 86/min. Physical examination shows a stare with lid lag, an asymmetrically enlarged, lobular thyroid gland, and plaquelike, thickened lesions on the anterior aspect of her legs. Laboratory studies show an elevated level of thyroxine and an undetectable level of thyroid-stimulating hormone. Which of the following is the most likely mechanism of this disease?

   A. CD4+ T-cell lymphocyte-mediated granuloma formation
   B. CD 8+ T-cell lymphocytes destroying antigen-containing cells
   C. Deposition of antibody-antigen immune complexes in the thyroid gland
   D. IgE-mediated release of chemical mediators from mast cells
   E. IgG or IgM antibodies directed against a specific receptor

Answers

1. **Answer: C.**

2. **Answer: E.**

Amyloidosis

8

A. DEFINITION

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

B. COMMON FEATURES OF AMYLOID

1. Individual subunits form β-*pleated sheets*
2. Micro
   a. Amorphous eosinophilic deposits on H&E stain
   b. Deposits stain red with the *Congo red* stain
   c. *Apple green birefringence* under polarized light

C. COMPOSITION OF AMYLOID

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

D. SYSTEMIC TYPES OF AMYLOID

1. **Primary amyloidosis**
   a. Type of amyloid: AL
   b. Fibrillary 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: AA
   b. Fibrillary protein: serum amyloid A (SAA)
   c. SAA is an acute phase reactant produced by the liver
   d. SAA is elevated with ongoing inflammation and neoplasia
   e. Rheumatoid arthritis (RA), system lupus erythematosus (SLE), TB, osteomyelitis, Crohn disease, cancer, etc.
3. **Familial Mediterranean fever**
   a. Type of amyloid: AA
   b. Fibrillary protein: serum amyloid A (SAA)
   c. Autosomal recessive disease
   d. Recurrent inflammation, fever, and neutrophil dysfunction

Clinical Correlate

Carpal tunnel syndrome is caused by compromise of the median nerve within the tunnel formed by the carpal bones and flexor retinaculum.

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

E. LOCALIZED TYPES OF AMYLOID

1. **Senile cerebral amyloidosis (Alzheimer disease)**
   a. Type of amyloid: Aβ
   b. Fibrillary protein: β-amyloid precursor protein (βAPP)
   c. Found in Alzhiemer plaques and in cerebral vessels
   d. The gene for βAPP is located on chromosome 21
2. **Senile cardiac amyloidosis**
   a. Type of amyloid: ATTR
   b. Fibrillary protein: transthyretin
   c. Men >70 years old
   d. May cause heart failure
3. **Endocrine type**
   a. Medullary carcinoma of the thyroid (procalcitonin)
   b. Adult-onset diabetes (amylin)
   c. Pancreatic islet cell tumors (amylin)

F. 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
      ii. Malabsorption
2. Diagnosis: biopsy of the rectal mucosa, gingiva, or the abdominal fat pad
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 fibrillary 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 fibrillary protein is kappa or lambda light chains.

Reactive systemic amyloidosis (secondary amyloidosis) can complicate neoplasia and ongoing inflammation due to many chronic diseases including rheumatoid arthritis, systemic lupus erythematosus, tuberculosis, osteomyelitis, and Crohn disease. The amyloid protein in reactive systemic amyloidosis is AA, and the fibrillary 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 fibrillary protein SAA.

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

Localized forms of amyloidosis are seen in senile cerebral amyloidosis (amyloid protein Aβ and fibrillary protein β-amyloid precursor protein); senile cardiac amyloidosis (amyloid protein ATTR and fibrillary protein transretin); 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.

Review Questions

1. An 82-year-old woman comes to the physician because of shortness of breath. She says that she used to be able to walk eight blocks without any difficulty, but over the past few months she has noticed that she has difficulty breathing after two blocks. Lately she has been "much more tired than usual." She has recently started sleeping with two pillows (up from one pillow), and she frequently has to go over to the window to "catch her breath." Her blood pressure is 130/80 mm Hg, pulse is 65/min, and respirations are 26/min. An echocardiogram shows symmetric thickening of the left ventricular wall. She is treated for congestive heart failure, and 2 years later has a myocardial infarction and dies. At autopsy, the pathologist suspects amyloidosis and takes a couple of biopsies from her heart. Which of the following is the best histochemical stain to confirm this diagnosis?

   A. Acid-fast
   B. Congo red
   C. Periodic acid-Schiff
   D. Prussian blue
   E. Trichrome

2. A 69-year-old man is brought to the physician by his wife because of "forgetfulness." She says that his "memory problem" started a few years ago and has been getting progressively worse. He has also developed personality changes, including agitation and aggression. He used to be "the kindest and gentlest" man, and she does not know "what has gotten into him now." She is actually scared to be alone with him sometimes. He accuses her of stealing his money and hiding his wallet. He is unable to perform the activities of daily living. He does not seem to be depressed. A full work-up for reversible causes of dementia is negative. Which of the following fibrillary proteins is most likely associated with this patient's condition?

   A. β-amyloid precursor protein
   B. β2-microglobin
   C. Kappa light chains
   D. Serum amyloid A
   E. Transthyretin

Answers

1. **Answer: B.**

2. **Answer: A.**

The Fundamentals of Neoplasia

A. EPIDEMIOLOGY

1. **General facts**
   a. Most (90%) neoplasms arise from epithelium
   b. The remainder arise from mesenchymal cells
   c. Cancer is the second leading cause of death in the United States
      i. Estimated new cancers in 2000: 1,220,100
      ii. Estimated deaths from cancer in 2000: 552,200

Table 9-1. Fifteen Leading Causes of Death in the United States, 2001*

Rank	Cause of Death	Number of Deaths†	Percentage of Total Deaths
1	Heart diseases	700,142	29.0
2	Cancer	553,768	22.9
3	Cerebrovascular diseases	163,538	6.8
4	Chronic lower respiratory diseases (COPD)	123,013	5.1
5	Accidents (unintentional injuries)	101,537	4.2
6	Diabetes mellitus	71,372	3.0
7	Pneumonia and influenza	62,034	2.6
8	Alzheimer disease	53,852	2.2
9	Nephritis, nephrotic syndrome, and nephrosis	39,480	1.6
10	Septicemia	32,238	1.3
11	Suicide	30,618	1.3
12	Cirrhosis and chronic liver disease	27,035	1.1
13	Hypertension and hypertensive renal disease	19,250	0.8
14	Homicide (assault)	17,386	0.7
15	Parkinson disease	16,544	0.7

*Data borrowed with permission from Lippincott Williams & Wilkins, "Cancer Statistics" by Ahmedin Jemal, D.V.M, Ph.D., *et al.*; *CA Cancer J Clin* 2004([vol 1]:18).

†Out of a total of 2,416,425 deaths

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

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

*Data borrowed with permission from Lippincott Williams & Wilkins, "Cancer Statistics" by Ahmedin Jemal, D.V.M, Ph.D., *et al.*; *CA Cancer J Clin* 2004([vol 1]:28).

Table 9-3. Estimated New Cancer Cases by Site and Sex,* Year 2004, in the United States†

Males		Females	
Site	**Percentage**	**Site**	**Percentage**
Prostate	33	Breast	32
Lung and bronchus	13	Lung and bronchus	12
Colon and rectum	11	Colon and rectum	11
Urinary bladder	6	Uterine corpus	6
Melanoma of skin	4	Non-Hodgkin lymphoma	4
Non-Hodgkin lymphoma	4	Ovary	4
Kidney	3	Melanoma of the skin	4
Leukemia	3	Thyroid	3
Oral cavity	3	Urinary bladder	2
Pancreas	2	Pancreas	2

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

†Data borrowed with permission from Lippincott Williams & Wilkins, "Cancer Statistics" by Ahmedin Jemal, D.V.M, Ph.D., *et al.*; *CA Cancer J Clin* 2004([vol 1]:11).

Table 9-4. Estimated New Cancer Mortality by Site and Sex, Year 2004, in the United States*

Males		Females	
Site	**Percentage**	**Site**	**Percentage**
Lung and bronchus	32	Lung and bronchus	25
Prostate	10	Breast	15
Colon and rectum	10	Colon and rectum	10
Pancreas	5	Ovary	6
Leukemia	5	Pancreas	6
Non-Hodgkin lymphoma	4	Leukemia	4
Esophagus	4	Non-Hodgkin lymphoma	3
Liver	3	Uterine corpus	3
Urinary bladder	3	Multiple myeloma	2
Kidney	3	Brain	2

*Data borrowed with permission from Lippincott Williams & Wilkins, "Cancer Statistics" by Ahmedin Jemal, D.V.M, M.D., *et al.*; *CA Cancer J Clin* 2004([vol 1]:11).

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

B. 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. Promotors
   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. Polycylic 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. Benezene: leukemia
   xi. Napthylamine: bladder cancer

e. Potential carcinogens are screened by the Ames test
   i. Detects any mutagenic effects 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 onogenes and tumor suppressor genes
   iii. Increased risk of skin cancer
   iv. *Xeroderma pimentosum:* 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 G2 of the cell cycle are most sensitive
   iii. Causes cross-linking and chain breaks in nucleic acids
   iv. Atomic bomb: leukemias, thyroid cancer, other
   v. Uranium miners: lung cancer

3. **Oncogenic viruses**

a. RNA oncogenic viruses. The human T-cell leukemia virus (HTLV-1) causes adult T-cell leukemia/lymphoma.

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

iii. Human papilloma virus (HPV) causes
- Benign squamous papillomas (warts)
- Cervical cancer

iv. Kaposi-sarcoma–associated herpesvirus (HHV8) causes Kaposi sarcoma.

4. **Loss of immune regulation**
   a. Immunosurvellience 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.

C. 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
2. **Activation of growth promoting oncogenes**
   a. Protooncogenes are normal cellular genes involved with growth and cellular differentiation
   b. Oncogenes are derived from proto-oncogenes 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

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

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
      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"*: both 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-Fraumini syndrome
         - Germ-line mutation of p53 on chromosome 17
         - High rate of many types of tumors

Table 9-6. Clinically Important Tumor Suppressor Genes

Chromosome	Gene	Tumors
3p25	VHL	von Hippel-Lindau disease, renal cell carcinoma
11p13	WT-1	Wilm tumor
11p15	WT-2	Wilm tumor
13q14	Rb	Retinoblastoma, osteosarcoma
17q13.1	p53	Lung, breast, colon, etc.
17q12-21	BRCA-1	Hereditary breast and ovary cancer
13q12-13	BRCA-2	Hereditary breast cancer
5q21	APC	Adenomatous polyps and colon cancer
18q21	DCC	Colon cancer
17q11.2	NF-1	Neurofibromas
22q12	NF-2	Acoustic neuromas, meningiomas

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

D. DIAGNOSIS OF CANCER

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

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

1. **Histologic diagnosis of cancer**
   a. Microscopic examination of tissue 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. Monoclonal antibodies which 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

Table 9-8. Expression of Intermediate Filaments by Normal and Malignant Cells

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

c. Ancillary tests
   i. Electron microscopy
   ii. Flow cytometry
   iii. Cytogenetics
   iv. PCR/DNA probes

4. **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. Use of tumor markers
      i. Screening (e.g., prostate specific antigen [PSA])
      ii. Monitoring treatment efficacy
      iii. Detecting recurrence
   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: ovarian cancer
      vi. CA19-9: pancreatic cancer
      vii. Placental alkaline phosphatase: seminoma
      viii. Prostatic acid phosphatase: prostate cancer
      ix. PSA: prostate cancer
5. **Grading and staging**
   a. Tumor grade
      i. Histologic estimate of the malignancy of a tumor
      ii. Criteria
         - Degree of differentiation
         - 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

6. **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

7. **Metastasis**
   a. Initial routes of metastasis
      i. Lymphatic spread is the most common route of spread for epithelial carcinomas
      ii. Hematogenous spread
         - Most sarcomas
         - Renal cell carcinoma
         - Hepatocellular carcinoma
         - Follicular carcinoma of the thyroid
         - Choriocarcinoma
      iii. Seeding of body cavities and surfaces, as 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 larger; tend to be more rapidly growing; 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 that may be obtained by complete excision or biopsy of the lesion, fine needle aspiration, or cytologic smears. Immuriohistochemistry 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.

Review Questions

1. A 32-year-old woman comes to the physician because of vaginal bleeding after sexual intercourse. She has also had a foul-smelling vaginal discharge for the past few months. She has not been to the doctor in "ages" and has never had a pelvic examination or a Pap smear. Pelvic examination shows a friable, beefy red cervix. A biopsy is taken and sent to pathology for histologic examination. The results come back as invasive squamous-cell carcinoma. Which of the following viruses is most likely associated with this patient's disease?

   A. Epstein-Barr virus
   B. Hepatitis B virus
   C. Hepatitis C virus
   D. Human papilloma virus
   E. Human herpes virus 8

2. A 43-year-old man comes to the physician because of a "black growth" on his foot. He first noticed this "growth" about 4 months ago, and it has been getting progressively darker and larger. Physical examination shows a 5-cm plaquelike lesion on the sole of his left foot. It is brownish black and has irregular borders. A biopsy is taken from the center of the lesion and is sent to pathology for microscopic evaluation. Which of the following markers will be most helpful in establishing the diagnosis?

   A. CD markers
   B. CA-19-9
   C. CA-125
   D. ER/PR
   E. S100

Answers

1. **Answer: D.**
2. **Answer: E.**

Environment and Lifestyle-Related Pathology

10

A. OCCUPATION-ASSOCIATED PNEUMOCONIOSIS

1. **Pneumoconioses**
   a. Definition: fibrosing pulmonary diseases caused by inhalation of an aerosol (mineral dusts, particles, vapors, or fumes)
   b. Key factors
      i. Type of aerosol and its *ability to stimulate fibrosis*
      ii. Dose and duration of exposure
      iii. Size of the particle
2. **Coal-worker's pneumoconiosis**
   a. Occupation: coal mining
   b. *Anthracosis*
      i. Carbon pigment (anthracotic pigment) accumulates in macrophages along the pleural lymphatics
      ii. Asymptomatic
   c. *Simple coal worker's pneumoconiosis*
      i. Synonym: black lung disease
      ii. Coal-dust macules and nodules in the upper lobes
      iii. Little pulmonary dysfunction
   d. *Complicated coal worker's pneumoconiosis*
      i. Progressive massive fibrosis
      ii. Increasing respiratory distress
      iii. Pulmonary hypertension and cor pulmonale
   e. Caplan syndrome: pneumonconiosis plus rheumatoid arthritis
3. **Asbestosis**
   a. Family of crystalline silicates
      i. Serpentine
         - Curved, flexible fibers
         - Most common type: chrysotile
      ii. Amphibole
         - Straight, brittle fibers
         - Types: crocidolite, tremolite, and amosite
         - More pathogenic and highly associated with mesotheliomas
   b. Occupations: shipyard workers, insulation and construction industries, brake-lining

c. Lung pathology
   i. *Diffuse interstitial fibrosis*, which is most severe in the lower lobes
   ii. *Asbestos bodies* that may become coated with iron (ferruginous bodies)
   iii. Slowly progressive dyspnea
   iv. Pulmonary hypertension and cor pulmonale
d. Fibrous pleural adhesions
e. Pleural plaques
f. Bronchogenic carcinoma
   i. Most common tumor in asbestos-exposed individuals
   ii. Synergistic effect of smoking and asbestos exposure
g. Malignant mesotheliomas
   i. Rare highly malignant neoplasm
   ii. Occupation *exposure to asbestos* in 90% of cases
   iii. Presents with recurrent pleural effusions, dyspnea, chest pain
   iv. Gross: encases and compresses the lung
   v. Micro: carcinomatous and sarcomatous elements (biphasic pattern)
   vi. EM: long, thin microvilli
   vii. Poor prognosis
h. Increased risk of laryngeal, stomach, and colon cancers
i. *Family members also have increased risk of cancer*
j. Caplan syndrome

4. **Silicosis**
   a. Occupations: sandblasters, metal grinders, miners
   b. Exposure to silicon dioxide (silica)
   c. Pathology
      i. Dense nodular fibrosis of the upper lobes
      ii. Birefringent silica particles can be seen with polarized light
      iii. May develop progressive massive fibrosis
   d. Clinical course
      i. X-ray: fibrotic nodules in the upper zones
      ii. Insidious onset of dyspnea
      iii. Slowly progressive despite cessation of exposure
   e. Increased risk of tuberculosis
   f. Caplan syndrome
5. **Berylliosis**
   a. Occupation: aerospace industry and nuclear reactors
   b. Etiology
      i. Beryllium exposure
      ii. Genetic susceptibility
      iii. Type IV hypersensitivity reaction, resulting in granuloma formation
   c. Acute exposure: acute pneumonitis

d. Chronic exposure
   i. Pulmonary noncaseating granulomas and fibrosis
   ii. Hilar lymph node granulomas
   iii. Systemic granulomas

Table 10-1. Industrial Toxins

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

B. ADVERSE DRUG REACTIONS

1. **Aspirin**
   a. Pathology of acute toxicity
      i. Common cause of overdose in children (accidental) and adults (suicide)
      ii. Headache, tinnitus, vomiting, tachypnea, and confusion
      iii. Respiratory alkalosis and metabolic acidosis
      iv. Seizures, coma, and death
   b. Pathology of chronic toxicity
      i. Acute erosive gastritis and upper GI bleeding
      ii. Bleeding tendency due to reduced platelet aggregation
2. **Estrogens**
   a. Hormone replacement therapy (HRT)
      i. Benefits of HRT
         - Decreased osteoporosis
         - Decreased ischemic heart disease
      ii. Unopposed estrogens have an increased risk of endometrial and breast carcinoma
   b. Oral contraceptives
      i. Increased risk of DVT and thromboembolism in smokers
      ii. Oral contraceptives have a decreased risk of ovarian and endometrial cancer
      iii. Slight increase in risk of breast and cervical cancer

Bridge to Pharmacology

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

Clinical Correlate

Newer oral contraceptive preparations contain far less estrogen than previous compositions and have decreased side effects.

C. POISONING

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
      iii. Forms carboxyhemoglobin, which shifts the oxygen dissociation curve
      iv. Causes systemic hypoxia
   c. Symptoms depend on the 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: 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
   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
4. **Lead poisoning (plumbism)**
   a. Epidemiology
      i. Most common type of chronic metal poisoning in the United States
      ii. Primarily affects *children* in poor urban areas
   b. Sources: lead paint, lead plumbing, and leaded gasoline
   c. CNS toxicity
      i. Lethargy and somnolence
      ii. Cognitive impairment and behavioral problems

Bridge to Biochemistry

Lead interferes with heme production by inhibiting d-aminolevulinic acid dehydratase and ferrochelatase.

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: chelating drugs

5. **Mercury poisoning**
a. Neurotoxicity
i. Intention tremors
ii. Dementia and delirium ("mad as a hatter")
b. Nephrotoxicity (acute tubular necrosis)

6. **Cyanide poisoning**
a. Clinical finding: "bitter almond" scented breath
b. Mechanism: blocks cellular respiration by binding to mitochondrial cytochrome oxidase
c. Systemic asphyxiant

D. 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 (#1 cause of cancer death in the United States)
ii. Oral cavity, pharynx, and larynx

Note

Top 3 Causes of Death in Smokers

- Heart disease
- Lung cancer
- COPD

iii. Esophagus and stomach
iv. Cervical cancer
v. Pancreas
vi. Kidney, ureter, and bladder
vii. Leukemia (benzene)

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 and Korsakoff syndromes
viii. Cancers
- Hepatocellular carcinoma
- Orophyanyx, larynx, and esophagus

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.

Bridge to Biochemistry

Alcohol induces the cytochrome P-450 enzymes, resulting in increased metabolism of other drugs.

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

E. 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 glomerulosclerosis
   e. Amyloidosis
   f. Treatment: for reversal use naloxone (an opiate antagonist)
2. **Cocaine**
   a. Euphoria
   b. Seizures
   c. Cardiac arrhythmias and sudden death
   d. Hypertension and stroke
   e. Chronic use
      i. Perforation of the nasal septum
      ii. Dilated cardiomyopathy

Clinical Correlate

The telltale sign of IVDA are "track marks" in the antecubital fossa, which are produced from the healing of skin abscesses.

Chapter Summary

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.

Asbestosis 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.

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

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 hemorrhagic gastritis and coma; chronic arsenic poisoning causes abdominal pain and neuromuscular problems. Lead poisoning can cause mental impairment, peripheral nerve damage, abdominal pain, renal failure, and anemia. Mercury damages the brain and kidney. Cyanide is a systemic asphyxiant.

Smoking is the number one cause of preventable premature deaths 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, cardiomyopathy, Wernicke and Korsakoff syndromes, and cancers of the liver, oropharynx, larynx, and esophagus. 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, glomerulosclerosis, and amyloidosis. Cocaine abuse can produce seizures, cardiac arrhythmias that may lead to sudden death, hypertension, stroke, cardiomyopathy, and perforated nasal septum.

Review Questions

1. A 6-year-old boy is brought to the physician by his mother because of "sleepiness." She says that he has been so tired lately that he cannot even play with friends after school. Physical examination shows pale skin and mucous membranes. Laboratory studies show a decreased hemoglobin and hematocrit. Basophilic stippling is seen on a peripheral blood smear. Which of the following is the most likely diagnosis?

   A. Arsenic poisoning
   B. Carbon monoxide poisoning
   C. Cyanide poisoning
   D. Lead poisoning
   E. Mercury poisoning

2. A 29-year-old woman comes to the physician for a periodic health maintenance examination. She has no specific complaints. She drinks alcohol "socially" and smokes about a pack of cigarettes per day. She exercises regularly, takes 1,500 mg of calcium a day, and eats a low-fat diet. She wants to know if she can get a prescription for oral contraceptive pills (OCPs). Which of the following is the most appropriate response on the part of the physician?

   A. "In your case, OCPs will increase your risk of developing endometrial cancer."
   B. "In your case, OCPs may increase you risk of developing thromboemboli and deep venous thrombi."
   C. "OCPs are a good way to lower your risk for cervical cancer."
   D. "OCPs are not a good idea in your case because they will increase your risk for ovarian cancer."
   E. "OCPs are not a good idea in your case because they will increase your risk for osteoporosis."

Answers

1. **Answer: D.**

2. **Answer: B.**

Vascular Pathology 11

A. VASCULITIS

1. **Polyarteritis 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
         - Aneurysms (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
   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.
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 and veins
   c. Clinical features
      i. Bilateral pnuemonitis 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 massive 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. 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

B. RAYNAUD DISEASE VERSUS PHENOMENON

1. **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. **Raynaud phenomenon**
   a. Arterial insufficiency secondary to an *underlying disease*
   b. Examples: scleroderma (CREST), SLE, Buerger disease, atherosclerosis, etc.

C. ARTERIOSCLEROSIS

1. **Monckeberg medial calcific sclerosis**
   a. Medial calcification of medium-sized arteries
   b. Femoral, tibial, radial, and ulnar arteries
   c. Asymptomatic; may be detected by x-ray
2. **Arteriolosclerosis**
   a. Occurs in diabetes, hypertension, and aging
   b. Affects small arteries and arterioles
   c. Micro
      i. *Hyaline arteriolosclerosis:* pink, glassy arterial wall thickening with luminal narrowing
      ii. *Hyperplastic arteriolosclerosis:* smooth-muscle proliferation resulting in concentric ("onion skin") wall thickening and luminal narrowing
3. **Atherosclerosis**
   a. Definition: *lipid deposition and intimal thickening* of large and medium-sized arteries, resulting in fatty streaks and atheromatous plaques
   b. Distribution of disease: aorta, coronary, corotid, cerebral, iliac, and popiteal arteries

Table 11-1. Major and Minor Risk Factors for Atherosclerosis

Major Risk Factors	Minor Risk Factors
Hyperlipidemia	Male gender
Hypertension	Obesity
Smoking	Sedentary lifestyle
Diabetes	Stress (type A personality)
	Elevated homocysteine
	Oral contraceptive use
	Increasing age
	Familial/genetic factors

   c. Fatty streak
      i. Gross: flat, yellow intimal streak
      ii. Micro: lipid-laden macrophages (foam cells)
   d. 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
      i. Dystrophic calcification (brittle eggshell quality)
      ii. Ulceration and atheroemboli
      iii. Plaque rupture with superimposed thrombus

In a Nutshell

Arteriosclerosis

Definition: A group of diseases that results in arterial wall thickening ("hardening of the arteries").

- Monckeberg
- Arteriolosclerosis
- Atherosclerosis

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

D. HYPERTENSION (HTN)

1. Definition: a sustained diastolic pressure >90 mm Hg and/or a systolic pressure >140 mm Hg
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
   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., 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)

Note

Another useful classification of hypertension (measurements in mm Hg):

	Systolic Pressure	Diastolic Pressure
Optimal	<120	<80
Normal	<130	<85
High normal	130–139	85–89
Hypertension		
Stage 1 (mild)	140–159	90–99
Stage 2 (moderate)	160–179	100–109
Stage 3 (severe)	180–209	110–119

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)

E. ANEURYSMS AND ARTERIOVENOUS FISTULA

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
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 (luetic) aortitis causes an *obliterative 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 (*cystic medial necrosis*) 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
   b. Associated with adult polycystic kidney disease
   c. May burst and cause a subarachnoid hemorrhage
   d. Presents as the worse headache of his/her life
6. **Microaneurysms:** small aneurysms commonly seen in HTN and diabetes
7. **Mycotic aneurysms:** aneurysm usually due to bacterial infections
8. **Arteriovenous (AV) fistulas**
   a. Definition: a direct communication between a vein and an artery without an intervening capillary bed
   b. Etiology: may be congenital or acquired (e.g., trauma)

c. Potential complications
   i. Shunting of blood may lead to high output heart failure
   ii. Risk of rupture and hemorrhage

In a Nutshell

Venous Thrombosis

- Phleothrombosis: venous thrombosis without inflammation or infection
- Thrombophlebitis: venous thrombosis due to inflammation and bacterial infection

F. VENOUS DISEASE

1. **Deep vein thrombosis (DVT)**
   a. Clinical features
      i. Deep leg veins (90%): iliac, femoral, popiteal veins
      ii. Often asymptomatic: commonly missed diagnosis
      iii. Unilateral leg swelling, warmth, erythema, Homan sign
   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
      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 hemorrhages
   d. Anal region (hemorrhoids)
      i. Constipation and pregnancy
      ii. May bleed (streaks of red blood on hard stools)
      iii. Thrombosis (painful)

G. VASCULAR NEOPLASMS

1. **Hemangiomas**
   a. Extremely common, benign vascular tumors
   b. Occur on the skin, mucous membranes, or internal organs
   c. Major types: capillary and cavernous hemangiomas
   d. May spontaneously regress
2. **Hemangioblastomas**
   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. Extravasaded 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 immunosupression
   g. African form
      i. African children and young men
      ii. Generalized lymphatic spread 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 Raynaud phenomenon is used when similar changes are observed secondary to a systemic disease such as scleroderma or systemic lupus erythematosus.

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

Arteriolosclerosis 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, atheroemboli, aneurysm formation, peripheral vascular disease, and mesenteric artery occlusion.

Hypertension is defined as a 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., 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.

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.

(Continued)

Chapter Summary (*continued*)

Aortic dissecting aneurysm 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 necrosis.

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.

Hemangioblastomas 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.

Review Questions

1. A 78-year-old woman comes to the physician because of a severe right-sided headache, weight loss, and "achy muscles" over the past few weeks. She holds her hand over her temple as she describes the intermittent, throbbing pain that is sometimes associated with blurry vision. Her temperature is 37.3°C (99.2°F). Physical examination shows a tender, firm right temporal artery. Laboratory studies show:

Hemoglobin	10 g/dl
Hematocrit	32%
Erythrocyte sedimentation rate	103 mm

Which of the following is the most appropriate next step in establishing the diagnosis?

A. Arteriogram of the head
B. CT scan of the head
C. Laboratory studies for c-ANCA
D. Laboratory studies for p-ANCA
E. Temporal artery biopsy

2. A previously healthy 3-year-old boy is brought to the emergency department by his mother because of a 2-day history of a high fever, rash, and "red eyes." His temperature is 39.5°C (103.1°F). Physical examination shows bilateral conjunctival injection, an enlarged left-sided cervical lymph node (1.8 cm), fissured lips, a red tongue with red papillae, pharyngeal hyperemia, erythematous and edematous palms and soles, and a confluent, blanching erythematous rash on the trunk. Laboratory studies show:

Erythrocyte sedimentation rate	28 mm/h
Platelet count	490,000/mm^3

Due to this condition, the patient is at increased risk for which of the following complications?

A. Blindness
B. Coronary aneurysm
C. Glomerulonephritis
D. Hepatitis
E. Splenic rupture

Answers

1. **Answer: E.**

2. **Answer: B.**

Cardiac Pathology

12

A. 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 (vasodilitation)
   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 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

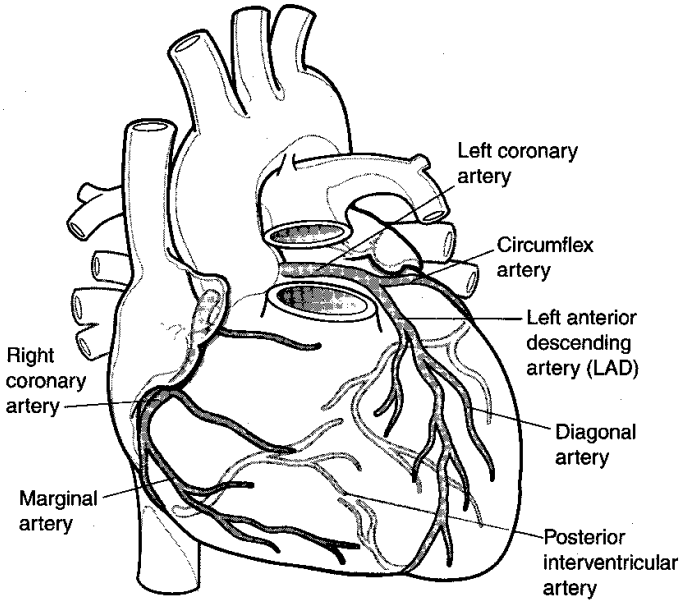


Figure 12-1. Arterial Supply to the Heart

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
   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"

Clinical Correlate

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

Table 12-1. Serum Markers Used to Diagnose Myocardial Infarctions

	Elevated by	Peak	Returns to Normal by
CK-MB	4–8 h	18 h	2–3 d
Troponin I & T	3–6 h	16 h	7–10 d
LDH	24 h	3–6 d	8–14 d

h. EKG
   i. ST segment elevation
   ii. Q waves representing myocardial necrosis develop in 24 to 48 hrs
i. Gross and microscopic sequence of changes
   i. The microscopic and gross changes represent a spectrum
   ii. The time intervals are variable and depend on the size of the infarct, as well as other factors

Table 12-2. Gross Sequence of Changes

Survival Time	Predominant Finding
0–18 h	No gross change
18–24 h	Vague pallor and softening
1–7 d	Yellow pallor
7–28 d	Central pallor with a red border
Months	White, firm scar

Table 12-3. Microscopic Sequence of Changes

Survival Time	Predominant Finding
1–4 h	Wavy myocyte fibers and contraction bands
4–24 h	Coagulative necrosis
1–4 d	Neutrophilic infiltrate
4–7 d	Macrophages
7–28 d	Granulation tissue
Months	Fibrotic scar

j. Complications
   i. Sudden cardiac death
   ii. Cardiac arrhythmias
   iii. Congestive heart failure
   iv. Cardiogenic shock
   v. Mural thrombus and thromboembolism
   vi. Fibrinous pericarditis
   vii. Cardiac rupture (most common 4–7 days post-MI)
      - Ventricular free wall → cardiac tamponade
      - Interventricular septum → left to right shunt
      - Papillary muscle → mitral insufficiency
   viii. Ventricular aneurysm

4. **Sudden cardiac death**
   a. Definition: death within 1 hour of the onset of symptoms
   b. Mechanism: fatal cardiac arrhythmia; usually ventricular fibrillation

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).

c. Etiology
   i. Coronary artery disease (80%)
   ii. Hypertrophic cardiomyopathy
   iii. Mitral valve prolapse
   iv. Aortic valve stenosis
   v. Congenital heart abnormalities
   vi. Myocarditis

B. 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 "boxcar" 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

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").

ii. Pulmonary or tricuspid valve disease
iii. Cor pulmonale

b. Presentation: jugular venous distention (JVD), hepatospleenomegaly, 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 cirrhosis (only with long-standing congestion)

Note

Cor pulmonale = Right-sided heart failure caused by pulmonary hypertension from intrinsic lung disease:

Lung disease → pulmonary HTN → ↑ right ventricular pressure → right ventricular hypertrophy (RVH) → right-sided heart failure.

C. VALVULAR HEART DISEASE

1. **Degenerative calcific aortic valve stenosis**
   a. Most 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: valve replacement
2. **Mitral valve prolapse**
   a. Epidemiology
      i. Young women
      ii. Affects 5–10% of the US 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 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 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
   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 12-4. Jones Criteria of Rheumatic Fever

Major	Minor
Migratory polyartheritis	Fever
Pancarditis	Arthralgias
Subcutaneous nodules	Elevated acute phase reactants
Skin rash (erythema marginatum)	
Sydenham chorea	
Diagnosis 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 stenosis* 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 IVDA

c. **Acute endocarditis**
   i. High virulence organism: *Staphylococcus aureus*
   ii. Can colonize a normal valve
   iii. Produces large destructive vegetations
   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

Clinical Correlate

Endocarditis involving the right side of the heart is highly suggestive of intravenous drug abuse.

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

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

D. 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

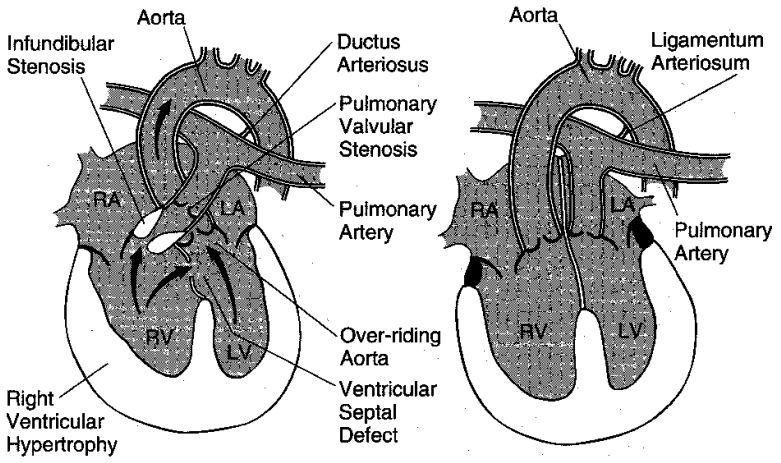
2. **Coarctation of the aorta**
a. Definition: segmental narrowing of the aorta
b. **Preductal coarctation (infantile-type)**
i. Associated with Turner syndrome
ii. Severe narrowing of aorta *proximal* to the ductus arteriosis
iii. Usually associated with a patent ductus arteriosis (PDA), which supplies 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
c. **Postductal coarctation (adult-type)**
i. Narrowing of the aorta *distal* to the ductus arteriosis
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

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

Table 12-5. Comparison of Left Versus Right Shunt Congenital Disease

Right → Left Shunt	Left → Right Shunt
Early cyanosis (blue babies)	Late cyanosis (blue kids)
Blood shunted past the lungs	Pulmonary HTN → reversal of shunt (Eisenmenger syndrome)
Tetralogy of fallot Transposition of the great vessels Tricuspid atresia Truncus arteriosis	Ventricular septal defect (VSD) Atrial septal defect (ASD) Patent ductus arteriosus (PDA)

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. Clinicale cyanosis, shortness of breath (SOB), digital clubbing, and polycythemia
   d. Prognosis: progressive pulmonary outflow stenosis and cyanosis over time
   e. Treatment: surgical correction



A. Tetralogy of Fallot **B.** Transposition of the Great Vessels

Figure 12-2. Common Forms of Cyanotic Congenital Heart Disease

4. **Transposition of the great arteries**
   a. Definition: abnormal development of the truncoconal 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 arteriosis**
   a. Definition: failure to develop a dividing septum between the aorta and pulmonary artery, resulting in a common trunk
   b. Massive blood flow to the lungs causes pulmonary hypertension
   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. Most common congenital heart defect
   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*
   d. Large VSD may lead to 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 arteriosis after birth
   b. Associated with prematurity and congenital rubella infections
   c. Clinical: *machinery murmur*, late cyanosis, and CHF
   d. Complication: Eisenmenger syndrome

Bridge to Embryology

In utero the ductus arteriosis 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.

E. THE CARDIOMYOPATHIES

1. **Dilated cardiomyopathy**
   a. Most common form of cardiomyopthy
   b. Definition: cardiac enlargement with *dilatation of all four chambers* resulting in progressive congestive heart failure
   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. Echocardiogram: decreased ejection fraction
   e. Presentation: progressive CHF
   f. Complications: mural thrombi and cardiac arrhythmias
   g. Prognosis: poor; 5 year survival = 25%
   h. 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. Common cause of *sudden cardiac death in young athletes*
   d. 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.
   e. 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

Bridge to Pharmacology

To keep PDA open: prostaglandin E2

To close PDA: indomethacin

F. 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 which have metastasized to the liver
   b. Plaque-like thickening 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)

G. 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 angiomyolipomas
- 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 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 serum markers 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 *Staphylococcus aureus*, and produces large destructive lesions with a high mortality rate. Subacute endocarditis is caused by low-virulence organisms, notably viridans streptococci, and usually involves previously damaged valves.

Marantic endocarditis refers to the formation of small, sterile 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 over-riding aorta.

Transposition of the great arteries is an abnormal development of the truncoconal 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 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 cardiomyopathy and consists of cardiac enlargement with dilatation of all four chambers, resulting in progressive congestive heart failure. 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.

Review Questions

1. A 48-year-old man comes to the emergency department 2 hours after experiencing severe chest pain while he was shoveling snow from his driveway. He describes the pain as an "elephant standing on his chest" and says that it radiates to his jaw. He experienced several episodes of vomiting in the car and in the waiting room. An electrocardiogram shows ST elevation. Which of the following changes would be seen in the heart at autopsy?

   A. Central pallor with a red border
   B. Coagulative necrosis
   C. Neutrophilic infiltrate
   D. No gross changes
   E. Yellow pallor

2. A 27-year-old man comes to the emergency department because of fever, chills, and pleuritic chest pain for the past 2 days. His temperature is 39°C (102.2°F). Physical examination shows pinpoint lesions in between his toes and a medium-pitched, midsystolic heart murmur that is best heard at the lower left sternal border. He has multiple hyperpigmented lesions and scars on his inner thighs and upper arms. A chest x-ray shows patchy infiltrates. Which of the following is the most likely cause of this patient's condition?

   A. Aortic valve prosthesis
   B. Calcific aortic stenosis
   C. Injection drug use
   D. Rheumatic valvular disease
   E. Ventricular septal defect

Answers

1. **Answer: D.**

2. **Answer: C.**

Respiratory System Pathology 13

A. ATELECTASIS

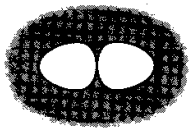
1. Definition: area of collapsed or nonexpanded lung
2. Major types
   a. Obstruction/resorption atelectasis
      i. Collapse of lung due to resorption of air distal to an obstruction
      ii. Examples: aspiration of a foreign body, chronic obstructive pulmonary disease (COPD), or postoperative
   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
4. Reversible disorder

B. 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 can spread.



Streptococcus pneumoniae

f. **Lobar pneumonia**
   i. Consolidation of entire lobe
   ii. Organism: *Streptococcus pneumoniae* (95%) or Klebsiella
   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 supporative 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
   iv. Organism: Staphylococci, Streptococci, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, etc.
   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
   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. Amyloidosis

3. **Atypical pneumonia**
   a. Definition: *interstitial pneumonitis* 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. Miliary systemic spread
   i. Meninges
   ii. Cervical lymph nodes (scrofula)
   iii. Liver/spleen, kidneys, adrenals, ileum
   iv. Lumbar vertebrae bone marrow (Pott disease)
   v. Fallopian tubes and epididymis

C. SARCOIDOSIS

1. Epidemiology
   a. Unknown etiology
   b. Females > males, age: 20–60
   c. Most common in African American women
2. 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
3. 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
   d. Eye: Mikulicz syndrome: involvement of uvea and parotid
   e. Bone marrow: especially in the phalanges
4. Lab: elevated serum *angiotensin converting enzyme* (ACE)
5. X-ray: bilateral hilar lymphadenopathy
6. Micro
   a. Noncaseating granulomas
   b. *Schaumann bodies:* laminated calcifications
   c. *Asteroid bodies:* stellate giant-cell cytoplasmic inclusions
7. Diagnosis of exclusion
8. Prognosis: favorable with a variable clinical course

D. OBSTRUCTIVE VERSUS RESTRICTIVE LUNG DISEASE

Table 13-1. Obstructive Versus Restrictive Lung Disease

Obstructive Airway Disease	Restrictive Lung Disease
Definition: Increased resistance to airflow secondary to obstruction of airways	Decreased lung volume and capacity
Pulmonary function tests (spirometry) FEV_1/FVC ratio is decreased	Decreased TLC and VC
Examples: Chronic obstructive airway disease • Asthma • Chronic bronchitis • Emphysema • Bronchiectasis	Chest wall disorders • Obesity, kyphoscoliosis, polio, etc. Interstitial/ infiltrative diseases • ARDS, pneumoconiosis • Pulmonary fibrosis

Table 13-2. Summary of Obstructive Versus Restrictive Pattern

Variable	Obstructive Pattern, e.g., Emphysema	Restrictive Pattern, e.g., Fibrosis
Total lung capacity	↑	↓
FEV_1	↓	↓
Forced vital capacity	↓	↓
FEV_1/FVC	↓	↑ or normal
Peak flow	↓	↓
Functional residual capacity	↑	↓
Residual volume	↑	↓

E. CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

1. **Chronic bronchitis**
   a. Clinical diagnosis: persistent cough and copious sputum production for at least 3 months in 2 consecutive years
   b. Highly associated with smoking (90%)
   c. Clinical findings
      i. Cough, sputum production, dyspnea, frequent infections
      ii. Hypoxia, cyanosis, weight gain

d. Micro
   i. Hypertrophy of bronchial mucous glands (Reid index)
   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. 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 13-3. Manifestations Related to Area of Involvement

Centriacinar (Centrilobular)	Panacinar (Panlobular)
Proximal respiratory bronchioles involved, distal alveoli spared	Entire acinus involved
Most common type (95%)	
Associated with smoking	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 muscles to breathe
   iii. Barrel chest
   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:* 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 of bronchial wall smooth muscle
   vi. Thickened basement membranes

4. **Bronchiectasis**
   a. Definition: abnormal permanent airway dilatation due to chronic necrotizing infection
   b. Cough, fever, malodorous purulent sputum, dyspnea
   c. Causes
      i. Bronchial obstruction: foreign body, mucous, tumor, etc.
      ii. Necrotizing pnuemonias
      iii. Cystic fibrosis
      iv. Kartagener syndrome
         - Autosomal recessive
         - Immotile cilia due to defect of dynein arms
         - Bronchiectasis, sinusitis, situs inversus
   d. Gross: dilated bronchi and bronchioles extending out to the pleura
   e. Complications: abscess, septic emboli, cor pulmonale, amyloidosis

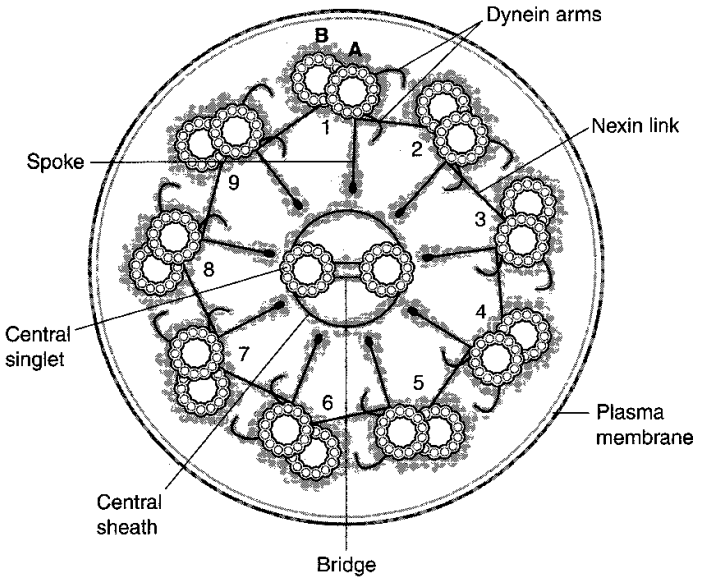


Figure 13-1. Structure of the Axoneme of a Cilium

F. RESPIRATORY DISTRESS SYNDROMES

1. **Adult respiratory distress syndrome (ARDS)**
   a. Synonyms: diffuse alveolar damage (DAD), shock lung
   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
   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

G. 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**
   a. Most (90–95%) pulmonary emboli arise from deep vein thrombosis (DVT) in the leg
   b. Only 10% of pulmonary emboli cause infarction
   c. Infarcts usually occur in patients with *underlying cardiopulmonary disease*
   d. Gross: wedge-shaped, hemorrhagic infarction
   e. Diagnosis: V/Q lung scan → V/Q mismatch
   f. Complications
      i. Large emboli (saddle emboli) may cause sudden death
      ii. Septic emboli may result in a pulmonary abscess

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)
   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)

Clinical Correlate

Dietary drugs fenfluramine and phentermine have been associated with primary pulmonary hypertension.

H. 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
   c. Common genetic mutations
      i. Oncogenes
         • L-myc: small cell carcinomas
         • K-ras: adenocarcinomas
      ii. Tumor suppressor genes 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 → dysplasia → carcinoma *in situ* → 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 disseminate early
   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 SVC 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
   iii. Acanthosis nigricans

In a Nutshell

Horner Syndrome
- Ptosis
- Miosis
- Anhidrosis
- Enophthalmos

iv. Hypertrophic pulmonary osteoarthropathy
- Periosteal new bone formation
- Clubbing
- Arthritis

m. Treatment
i. Nonsmall-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. **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

4. **Laryngeal squamous cell carcinoma**
a. Uncommon
b. Risk factors: smoking, alcohol, and frequent cord irritation
c. Hoarseness, difficulty swallowing, pain, hemoptysis, and eventual respiratory compromise
d. Complications: direct extension, metastases, and infection

I. 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:* young adults with rupture of emphysematous blebs
d. *Tension:* life threatening shift of thoracic organs across midline

3. **Mesothelioma**
a. Rare, highly malignant neoplasm
b. Occupation *exposure to asbestos* in almost 90%
c. Recurrent pleural effusions, dyspnea, chest pain
d. Gross: 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 fissure accompanied by hilar lymph node granulomas. Secondary tuberculosis tends to involve the lung apex. Progressive pulmonary tuberculosis can take the forms of cavitary 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 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.

Adult 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 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, and air pollution. 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.

Review Questions

1. A previously healthy 19-year-old college student comes to the clinic because of a headache, sore throat, muscle aches, and a constant, irritating, dry cough for the past 4 days. She says that she is "never sick" and has only been to this clinic for her "immunizations." She exercises regularly, does not smoke cigarettes, and has an "occasional glass of wine on the weekends with sorority sisters." Her temperature is 38.8°C (101.8°F), blood pressure is 120/80 mm Hg, pulse is 68/min, and respirations are 16/min. Scattered rhonchi are heard in the left lower lobe. A chest x-ray shows diffuse interstitial infiltrates in the left lower lobe. Laboratory studies show elevated cold agglutinin titers. Which of the following is the most likely diagnosis?

   A. *Haemophilus influenzae*
   B. Influenza virus
   C. *Mycoplasma pneumoniae*
   D. *Pneumocystis carinii pneumonia*
   E. Respiratory syncytial virus
   F. *Streptococcus pneumoniae*

2. A 28-year-old woman comes to the physician because of a 2-month history of an "annoying cough," difficulty breathing when she climbs the steps to her fifth-floor apartment, and eye irritation. She says that she has been unusually tired lately, frequently going to sleep at 8:30 in the evening. She is generally healthy, except for an episode of nephrolithiasis 6 months ago. Her temperature is 37.8°C (100°F). A chest x-ray shows hilar lymphadenopathy and parenchymal infiltrates. Laboratory studies show an elevated level of angiotensin-converting enzyme. Which of the following is the most likely diagnosis?

   A. Asthma
   B. Primary pulmonary hypertension
   C. Sarcoidosis
   D. Systemic lupus erythematosus
   E. Tuberculosis

Answers

1. **Answer: C.**

2. **Answer: C.**

Renal Pathology 14

A. CONGENITAL ANOMALIES OF THE KIDNEY

1. **Renal agenesis**
   a. Bilateral agenesis
      i. Ultrasound: oligohydramnios
      ii. Potter facies: flattened nose, low-set ears, and recessed chin
      iii. Talipes equinovarus
      iv. Pulmonary hypoplasia
      v. Incompatible with life
   b. Unilateral agenesis
      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 are a decreased number of calyces and lobes
3. **Horseshoe kidney**
   a. Common; 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

B. 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 capsule

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

Clinical Correlate

The cysts involve less than 10% of nephrons, but they gradually expand and compress the rest of the kidney, interfering with its function. This is the reason why kidney function can remain normal for many years.

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

h. Extrarenal manifestations

i. Liver cysts

ii. Berry aneurysms of the circle of Willis

iii. Mitral valve prolapse

iv. Colonic diverticula

C. GLOMERULAR DISEASES

1. **Diagnosis of glomerular diseases**

a. Clinical syndrome

Table 14-1. Clinical Syndromes in Glomerular Disease

Nephritic Syndrome	Nephrotic Syndrome
Hematuria (RBC casts)	Severe proteinuria (>3.5 g/day)
Hypertension	Hypoalbuminemia (<3 g/dl)
Azotemia	Generalized edema
Oliguria	Hyperlipidemia
Proteinuria (<3.5 g/day)	Lipiduria

b. Renal biopsy

i. Light microscopy (LM)

ii. Immunofluorescence (IF)

iii. Electron microscopy (EM)

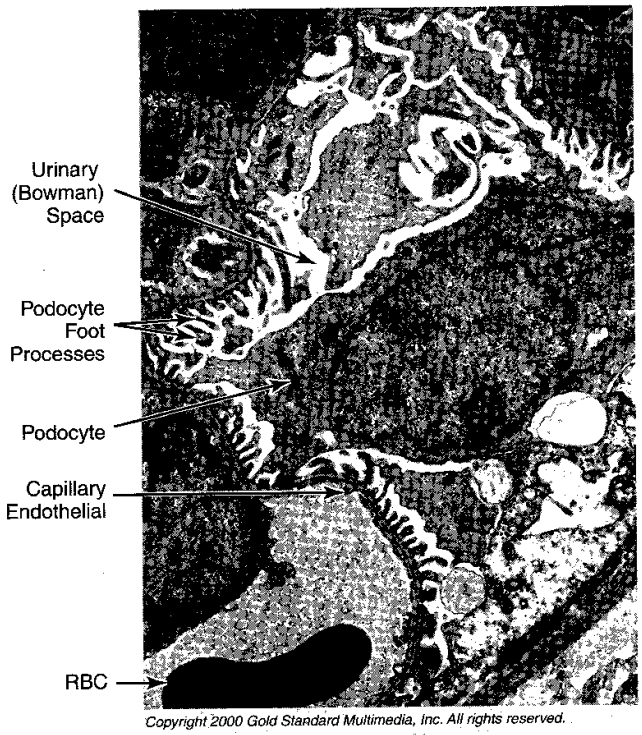


Figure 14-1. Transmission Electron Micrograph Demonstrating Podocytes

D. 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

Clinical Correlate

The classic presentation is a young child with fever, malaise, periorbital edema, hypertension, smoky urine, and oliguria, beginning approximately 2 weeks after a strep throat infection.

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%)

2. **Goodpasture syndrome (anti-GBM disease)**
   a. Pathogenesis
      i. Production of antibodies directed against basement membrane (anti-GBM antibodies), which result in damage of the lungs and the kidney
      ii. 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 precedes renal disease
      iv. Present with pulmonary hemorrhage and recurrent hemoptysis
      v. Most develop rapidly progressive glomerulonephritis (RPGN)
   c. Light microscopy: hypercellularity, crescents, and fibrin
   d. Electron microscopy: no deposits, but there is glomerular basement membrane (GBM) disruption
   e. Immunofluorescence: *smooth and linear pattern* of IgG and C3 in the GBM
   f. Treatment: plasma exchange, steroids, and cytotoxic drugs
   g. Prognosis
      i. Poor
      ii. Pulmonary hemorrhage may be severe and life threatening
      iii. Rapidly progressive renal failure is common
      iv. Early aggressive treatment may prevent end-stage renal failure

3. **Rapidly progressive glomerulonephritis (RPGN)**
   a. Synonym: crescentic glomerulonephritis
   b. Clinical feature: rapid progression to *severe renal failure in weeks or months*
   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

Note

The characteristic finding in RPGN is the formation of crescents within Bowmen's space. The crescents are composed of fibrin, parietal epithelial cells, monocytes, and macrophages.

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)

In a Nutshell

Henoch-Schönlein Purpura

- Systemic childhood disorder
- Onset often follows URI
- IgA nephropathy
- Abdominal pain
- GI bleeding
- Arthralgia
- Palpable purpura on legs and buttock

Note

Most patients with MPGN type II disease have an autoantibody called C3 nephritic factor. This antibody stabilizes C3 convertase, which leads to enhanced degradation and low serum levels of C3.

d. Light microscopy
   i. Lobulated appearance of the glomeruli
   ii. *Mesangial proliferation* and basement-membrane thickening
   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

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.

E. 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
      vi. There may be a genetic predisposition
   c. Light microscopy
      i. There is a diffuse *membrane-like 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: lipoid nephrosis, nil 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 complexes

e. Electron microscopy
i. *Effacement of epithelial (podocyte) foot processes*
ii. Microvillous 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 abuse
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

Note

Focal: only some of the glomeruli are affected

Segmental: only a portion of the glomerular tuft exhibits sclerosis

F. 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: *hyalinization of glomeruli*, interstitial fibrosis, atrophy of tubules, and a lymphocytic infiltrate
5. Urinalysis shows *broad waxy casts*
6. Treatment: dialysis and renal transplantation

G. DISEASES OF THE TUBULES AND INTERSTITIUM

1. **Acute tubular necrosis (ATN)**
   a. Definition: acute renal failure associated with 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 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

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.

H. 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 bladder
   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
   e. Treatment: lithotripsy or endoscopic removal

I. 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 from 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
   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 vena 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 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
   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%

J. 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. **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

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.

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's 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 world-wide, 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 membrane-like 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.

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 abuse, AIDS, and morbid obesity.

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 pyelonephritis is a bacterial infection involving the renal pelvis, tubules, and interstitium and is most commonly due to *Escherichia coli*, *Proteus*, *Klebsiella*, or *Enterobacter*.

(Continued)

Chapter Summary (*continued*)

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.

Cystitis, or 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.

Review Questions

1. A 42-year-old man is brought to the emergency department because of the acute onset of the "worst headache" of his life. His wife says that he is generally pretty healthy except for a few episodes of "red urine" over the past few weeks. His blood pressure is 150/90 mm Hg. Physical examination shows bilateral abdominal masses and flank pain. A CT scan of his head shows blood in the subarachnoid space. A sonogram of his kidneys shows bilateral kidney enlargement with many large cysts. Which of the following cardiac abnormalities is most often associated with this disease?

   A. Aortic stenosis
   B. Aortic regurgitation
   C. Mitral stenosis
   D. Mitral valve prolapse
   E. Tricuspid stenosis

2. A 3-year-old boy is brought to the physician by his mother because of a 2-day history of "puffy eyes and smoky urine." His mother says that he had a "skin infection" 2 weeks before the onset of these symptoms. His temperature is 38.1°C (100.5°F), and his blood pressure is 140/90 mm Hg. He has significant periorbital edema. Laboratory studies show elevated levels of antistreptolysin O titers and a low serum complement. Which of the following is the most likely electron microscopic finding associated with this patient condition?

   A. Glomerular basement membrane disruption and no deposits
   B. Effacement of epithelial foot processes
   C. Mesangial immune complex deposits
   D. Subendothelial and mesangial immune complex deposits
   E. Subepithelial immune complex deposits

Answers

1. **Answer: D.**

2. **Answer: E.**

Gastrointestinal Tract Pathology

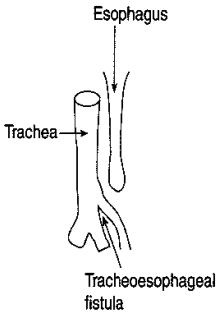
15

A. 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: 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, Mallory-Weiss tears typically occur acutely as a result of retching/vomiting. Esophageal varices result from portal hypertension and will usually present with a more significant bleeding episode.

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 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

B. 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
iii. Often associated with intestinal malrotation
iv. Complications: respiratory compromise

2. **Hypertrophic gastropathy**
a. **Ménétrier disease**
i. Middle-aged men
ii. Gross: enlarged rugal folds in the body and fundus
iii. Micro: massive foveolar hyperplasia with replacement of the parietal and chief cells
iv. Decreased acid production
v. Protein losing enteropathy
vi. Increased risk of gastric cancer

b. **Zollinger-Ellison syndrome**
i. Pancreatic gastrinoma producing gastrin
ii. Gross: enlarged rugal folds

Clinical Correlate

Pyloric stenosis is congenital hypertrophy of the pylori, which presents with projectile vomiting and a palpable abdominal "olive."

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
         - Smoking
         - Postsurgery
         - Burns
         - Ischemia
         - Stress
         - Uremia
         - Chemotherapy
      iii. Presentation
         - Epigastric abdominal pain
         - Gastric hemorrhage, hematemesis, and melena
   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 B12 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

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: H_2 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%)

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.

- 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%

C. SMALL AND LARGE INTESTINE

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, cecum, and small bowel

iv. Complication: 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 distention, and vomiting
- Associated with Down syndrome

Note

Acquired megacolon may be caused by Chagas disease or ulcerative colitis (toxic megacolon).

Bridge to Anatomy

Auerbach plexus = myenteric ganglia

Meissner plexus = submucosal ganglia

iv. Gross
- Affected segment is narrowed
- Proximal dilatation (megacolon)

v. Micro: absence of ganglion cells in Auerbach and Meissner plexuses

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

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 B_{12}, 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: *Trophermyma whippleii*

iv. Presentation: malabsorption, weight loss, and diarrhea

v. Micro: small bowel lamina propria is filled with macrophages stuffed with PAS-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 15-1. Crohn Disease Versus Ulcerative Colitis

	Crohn Disease	Ulcerative Colitis
Most common site	Terminal ileum	Rectum
Distribution	Mouth to anus	Rectum → colon "back-wash" ileitis
Spread	Discontinuous/"skip"	Continuous
Gross features	• Focal aphthous ulcers with intervening normal mucosa • Linear fissures • Cobblestone • Thickened bowel wall • "Creeping fat"	Extensive ulceration Pseudopolyps
Micro	Noncaseating granulomas	Crypt abscesses
Inflammation	Transmural	Limited to mucosa and submucosa
Complications	• Strictures • "String sign" on barium studies • Obstruction • Abscesses • Fistulas • Sinus tracts	Toxic megacolon
Genetic association		HLA-B27
Extraintestinal manifestations	Uncommon	Common (e.g., arthritis, spondylitis, primary sclerosing cholangitis, erythema nodosum, pyoderma gangrenosum)
Cancer risk	Slight 1–3%	5–25%

Bridge to Anatomy

The splenic flexure of the colon receives blood from both the superior and inferior mesenteric arteries.

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
   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
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*
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*

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

In a Nutshell

Osler-Weber-Rendu Syndrome
- a.k.a. Hereditary hemorrhagic telangiectasia
- Autosomal dominant
- Telangiectasias of skin and mucous membranes
- Common on lips, tongue, and fingertips
- May develop iron deficiency anemia

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

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

Note

Given that only two layers of the bowel wall are involved, these acquired outpouchings are technically pseudodiverticula.

6. **Neoplasia**

a. **Adenomatous colonic polyps**

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

iii. Prognostic features
- Tubular versus villous histology
- Pedunculated versus sessile appearance
- Size of polyps
- Degree of dysplasia

iv. Diagnosis
- Hemoccult positive stools
- Endoscopy

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.

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.

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
- p53 gene

Table 15-2. Right-Sided Cancer Versus Left-Sided Cancer

	Right-Sided Cancer	Left-Sided Cancer
Gross	Polypoid mass	Circumferential growth producing a "napkin-ring" configuration
Barium studies	Polypoid mass	"Apple core" lesion
Presentation	Bleeding • Occult blood in stool • Iron deficiency anemia	Change in bowel habits • Constipation or diarrhea • Reduced caliber stools • Obstruction

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' (Astler-Coller) staging system

vii. Treatment
- Surgical resection
- Chemotherapy for metastatic disease
- Monitor CEA levels

Table 15-3. The Modified Dukes' Staging System

Stage	Extent of Disease
A	Limited to the mucosa and submucosa
B1	Invasion into but not through the muscularis propria
B2	Invasion through the muscularis propria
C1	Positive lymph nodes; invasion into but not through the muscularis propria
C2	Positive lymph nodes; invasion through the muscularis propria
D	Distant metastasis

Note

Histologically, carcinoid tumors appear similar to other neuroendocrine tumors with nests of small uniform cells.

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)

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's 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's 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*.

Meckel's 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 Duke's 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.

Review Questions

1. A 42-year-old man comes to the physician because of abdominal pain for the past few months. He smokes two packs of cigarettes/day, does not exercise, has a job on the floor of the stock exchange, and takes approximately 4–5 nonsteroidal anti-inflammatory drugs a day for a variety of "aches and pains." Physical examination is unremarkable. The relation of the pain to which of the following factors is most helpful in differentiating a duodenal ulcer from a gastric ulcer?

   A. Deep breathing
   B. Exercise
   C. Food
   D. Position

2. An 83-year-old man with metastatic pancreatic carcinoma is hospitalized for pneumonia. He is being treated with ampicillin. Six days into his hospital stay, he suddenly develops a profuse amount of watery diarrhea and severe abdominal cramps. His temperature is 39°C (102.2°F). He is becoming severely dehydrated. The symptoms begin to resolve when the ampicillin is discontinued and he is given metronidazole. Microscopic evaluation of a biopsy taken during a colonoscopy at the time of the diarrhea would most likely have shown which of the following?

   A. Absence of ganglion cells in the Auerbach and Meissner plexuses
   B. Black pigmentation within the colonic epithelium
   C. Multiple herniations of the mucosa and submucosa through the muscularis propria
   D. Small bowel lamina propria filled with macrophages and PAS-positive, rod-shaped bacilli
   E. Superficial colonic necrosis with exudates composed of neutrophils, mucin, fibrin, and necrotic cellular debris

Answers

1. **Answer: C.**
2. **Answer: E.**

Pancreatic Pathology

16

A. INFLAMMATION OF THE PANCREAS

1. **Acute hemorrhagic pancreatitis**
   a. Etiology
      i. Gallstones
      ii. Alcohol
      iii. Hypercalcemia
      iv. Drugs
      v. Shock
      vi. Infections
      vii. Trauma
      viii. Scorpion stings
   b. Mechanism: Pancreatic acinar cell injury results in activation of pancreatic enzymes and enzymatic destruction of the pancreatic parenchyma
   c. Clinical presentation
      i. Stabbing epigastric abdominal pain radiating to the back
      ii. Shock
      iii. Hypocalcemia
   d. Lab: elevation of serum amylase and lipase
   e. Gross
      i. Focal pancreatic hemorrhage and liquefication
      ii. Chalky, white-yellow fat necrosis of adjacent adipose tissue
   f. Micro
      i. Liquefactive necrosis of pancreatic parenchyma
      ii. Acute inflammation
      iii. Enzymatic fat necrosis
      iv. Necrosis of blood vessels causes hemorrhage
   g. Complications
      i. May develop acute respiratory distress syndrome (ARDS) or disseminated intravascular coagulation (DIC)
      ii. Pseudocyst
      iii. Pancreatic calcifications
   h. Prognosis: Severe cases have a 30% mortality rate

2. **Chronic pancreatitis**
   a. Middle-age male alcoholics
   b. Definition: chronic inflammation, atrophy, and fibrosis of the pancreas secondary to repeated bouts of pancreatitis
   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. Diabetes (late complication)

Clinical Correlate

Measurement of glycosylated hemoglobin (HbA1c) is an excellent measurement of long-term exposure to hyperglycemia.

B. 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 I, 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
      ii. Absolutely dependent on insulin to prevent ketoacidosis and coma
   e. Etiology: thought to be caused by an autoimmune reaction triggered by an infection (Coxsackie 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 II, adult onset diabetes
   b. Epidemiology
      i. Represents 90% of cases of diabetes
      ii. Affects obese adults usually older than 30 years
      iii. Incidence increases with age.
      iv. Affects 10 million in the United States (half are undiagnosed)
   c. Risk factors: obesity, increasing age, and genetic predisposition
   d. Pathogenesis
      i. Relatively reduced insulin secretion
      ii. *Peripheral 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 extremity
      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. Thickened 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
e. 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. Increased rate of cataracts and glaucoma
8. **Diabetic neuropathy**
   a. Peripheral neuropathy
   b. Neurogenic bladder
   c. Sexual impotence

Clinical Correlate

Diabetic nephropathy is the most common reason for renal transplantation in adults.

C. 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 16-1. Summary of Insulin-Related Pathophysiologic States

	Glucose	Insulin	C peptide	Ketoacidosis
Type 2 diabetes	↑	↑, ↔	↑, ↔	–
Type 1 diabetes	↑	↓	↓	+
Insulinoma	↓	↑	↑	–
Factitious hypoglycemia (self-injection of insulin)	↓	↑	↓	–

   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 (δ-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
      iii. Most common between ages 60 and 80
      iv. Risk factor: smoking
   b. Presentation
      i. Vague signs and symptoms until late in the course
      ii. Abdominal pain
      iii. Migratory thrombophlebitis
      iv. Obstructive jaundice
   c. Site: pancreatic head (60%), body (15%), and tail (5%)
   d. Micro
      i. Adenocarcinoma arising from the duct epithelium
      ii. Tumor desmoplasia and perineural invasion are common
   e. Tumor markers: CEA and CA19-9
   f. Treatment: surgical excision (Whipple procedure)
   g. Prognosis: very poor; 1-year survival ~10%

Clinical Correlate

Trousseau Syndrome

Spontaneous venous thrombosis, which may resolve and recur in other areas (migratory thrombophlebitis), associated with a visceral malignancy.

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.

Review Questions

1. A 49-year-old woman comes to the emergency department because of severe abdominal pain for the past few hours. She says that it feels as if someone were stabbing her in the "stomach," and it is worse after she eats. She also complains of back pain. Physical examination shows epigastric tenderness. Laboratory studies show:

Leukocyte count	18,000/mm^3
Calcium	7 mg/dl
Amylase	155 U/l

A CT scan shows an edematous, swollen pancreas. This patient is at greatest risk for which of the following complications?

A. Adult respiratory distress syndrome
B. Colonic carcinoma
C. Cushing syndrome
D. Diabetes insipidus
E. Diverticulitis

2. A 52-year-old man with insulin-dependent diabetes mellitus comes to the emergency department because of increased urination and thirst over the past few days. He says he has been taking his insulin when he "remembers" and that his portable blood glucose monitor broke "a long time ago" and he does not have the money to replace it. Physical examination shows three gangrenous toes on his right foot and a 3-cm erythematous lesion on the plantar aspect his left foot. Which of the following studies will give the most accurate measurement of this patient's glucose control over the past few weeks?

A. Fasting blood glucose
B. Glucose tolerance test
C. Glycosylated hemoglobin
D. Postprandial glucose level
E. Urinary glucose

Answers

1. **Answer: A.**
2. **Answer: C.**

Gallbladder and Biliary Tract Pathology

17

A. 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.

B. 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

Clinical Correlate

Murphy sign: inspiratory arrest in response to palpation of the RUQ during deep inspiration

C. MISCELLANEOUS CONDITIONS

1. **Cholesterolosis**
   a. Gross: yellow speckling of the red-tan mucosa ("strawberry gallbladder")
   b. 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)

Clinical Correlate

Courvoisier Law: An enlarged palpable gallbladder is more likely to be caused by obstruction due to malignancy than by stones.

"Porcelain gallbladder": Calcification of the gallbladder due to chronic inflammation; high association with carcinoma.

D. 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* (fluke)
      ii. Primary sclerosing cholangitis
   e. Presentation: biliary tract obstruction
   f. 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.

Cholesterolosis 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 (mucocele).

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.

Review Questions

1. A 28-year-old woman comes to the physician because of severe abdominal pain, nausea, and vomiting over the past 24 hours. The pain is constant and refers to her right scapula. She has had similar but less severe episodes on two previous occasions. Her temperature is 38.1°C (100.5°F). Physical examination shows right upper quadrant tenderness, voluntary guarding, arrest of inspiration with right upper quadrant palpation, and a palpable gallbladder. An ultrasound of the abdomen shows multiple gallstones. Treatment options are discussed, and she decides that she "cannot" have surgery at this time because she has a wedding to go to next week. A nasogastric tube is placed, and intravenous fluids, antibiotics, and analgesics are given. This patient is at greatest risk for which of the following conditions?

   A. Cholesterolosis
   B. Colonic carcinoma
   C. Large bowel obstruction
   D. Primary biliary cirrhosis
   E. Small bowel obstruction

2. A 72-year-old man comes to the emergency department because of fever and a cough for the past 3 days. The x-ray technician makes a mistake and performs an abdominal x-ray instead of a chest x-ray. The film is reviewed and calcification of the gallbladder is reported as the only abnormality seen. A chest x-ray shows right lower lobe pneumonia, and he is given a prescription for an antibiotic and sent home. He returns to the hospital 2 months later for an elective cholecystectomy. The pathologic findings are monocytes and macrophages, Rokitansky-Aschoff sinuses, and areas of calcification. Which of the following is the most likely diagnosis?

   A. Acute cholecystitis
   B. Cholesterolosis
   C. Chronic cholecystitis
   D. Gallbladder carcinoma
   E. Hydrops of the gallbladder

Answers

1. **Answer: E.**
2. **Answer: C.**

Liver Pathology 18

A. 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 18-1. Unconjugated Versus Conjugated Bilirubinemia

Unconjugated (Indirect) Bilirubinemia	Conjugated (Direct) Bilirubinemia
Increased RBC turnover (hemolytic anemias)	Biliary tract obstruction
Physiologic (newborn babies)	Biliary tract disease (PSC and PBC)
Hereditary (Gilbert and Crigler-syndromes)	Hereditary (Dubin-Johnson and Najjar Rotor syndromes)
	Liver disease (cirrhosis and hepatitis)

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 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

B. 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. α-1-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 angiomata
      iii. Palmar erythema
      iv. Gynecomastia
   c. Decreased synthesis
      i. Hypoalbuminemia
      ii. Decreased clotting factors
   d. Hepatorenal syndrome

Clinical Correlate

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

C. 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 <u>any</u> of the hepatitis viruses
   c. Micro
      i. Lobular disarray
      ii. Hepatocyte swelling (balloon cells)
      iii. Apoptotic hepatocytes (Councilman's bodies)
      iv. Lymphocytes in portal tracts and in the lobule
      v. Hepatocyte regeneration
      vi. Cholestasis

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 virus 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 18-2. The Hepatitis Viruses

Common Virus Name	Hepatitis A (HAV)	Hepatitis B (HBV)	Hepatitis C (HCV)	Hepatitis D (HDV)	Hepatitis E (HEV)
Common disease name	"Infectious"	"Serum"	"Post-transfusion" or"non-A, non-B"	"Delta"	"Enteric"
Virus	Picornavirus naked capsid RNA	Hepadnavirus enveloped DNA	Flavivirus enveloped RNA	Defective enveloped circular-RNA	Calicivirus naked capsid RNA
Transmission	Fecal-oral	Parenteral, sexual	Parenteral, sexual	Parenteral, sexual	Fecal-oral
Severity	Mild	Occasionally severe	Usually subclinical	Co-infection with HBV occasionally severe; super-infection with HBV often severe	Normal patients: mild; pregnant patients: severe
Chronicity or carrier state	No	Yes	Yes (high)	Yes	No
Clinical diseases	Acute hepatitis	• Acute hepatitis • Chronic hepatitis • Cirrhosis • Hepatocellular carcinoma (HCC)	• Acute hepatitis • Chronic hepatitis • Cirrhosis • HCC	• Acute hepatitis • Chronic hepatitis • Cirrhosis • HCC	Acute hepatitis
Laboratory diagnosis	Symptoms and anti-HAV IgM	Symptoms and serum levels of HBsAg, HBeAg, and anti-HBc IgM	Symptoms and anti-HCV ELISA	Anti-HDV ELISA	
Prevention	Vaccine, hygiene	Vaccine			Hygiene

Table 18-3. Hepatitis B Terminology and Markers

Abbreviation	Name and Description
HBV	Hepatitis B virus, a hepadnavirus (enveloped, partially double-stranded DNA virus); Dane particle = infectious HBV
HBsAg	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
HBsAb	Antibody to HBsAg; provides immunity to hepatitis B
HBcAg	Antigen associated with core of HBV
HBcAb	Antibody to HBcAg; positive during window phase; IgM HBcAb is an indicator of recent disease
HBeAg	A second, different antigenic determinant on the HBV core; important indicator of transmissibility
HBeAb	Antibody to e antigen; indicates low transmissibility
Delta agent	Small RNA virus with HBsAg envelope; defective virus that replicates only in HBV-infected cells

Table 18-4. Hepatitis A Serology

Acute or recent infection	anti-HAV IgM
Prior infection or immunization	anti-HAV IgG

Table 18-5. Hepatitis B Serology

	HBsAg HBeAg* HBV-DNA	HBcAb IgM	HBcAb IgG	HBsAb IgG
Acute infection	+	+	–	–
Window period	–	+	–	–
Prior infection	–	–	+	+
Immunization	–	–	–	+
Chronic infection	+	+	+	–

*HBeAg—Correlates with viral proliferation and infectivity.

D. 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

E. 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

F. 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: decrease 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's 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 (HLA-H gene on chromosome 6p)
      ii. 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 ration [RR])
      ii. Pancreas: 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. **α-1-Antitrypsin deficiency**
   a. Definition: autosomal recessive disorder characterized by production of defective α-1-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 then 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

In a Nutshell

Protease-Antiprotease Imbalance

- α-1-Antitrypsin is an important protease inhibitor
- Responsible for inhibiting neutrophil elastase
- Also inhibits trypsin, chymotrypsin, and bacterial proteases

Clinical Correlate

α-1-Antitrypsin deficiency is the most common genetic disease requiring liver transplantation in children.

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

G. HEMODYNAMIC LIVER DISEASE

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 → centrilobular fibrosis → cardiac cirrhosis

H. BENIGN 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

I. MALIGNANT LIVER TUMORS

1. **Hepatocellular carcinoma** (HCC)
   a. Most common primary malignant tumor of the liver
   b. Asia and Japan > United States
   c. Etiology: cirrhosis, hepatitis B and C virus, 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
2. **Cholangiocarcinoma**
   a. Uncommon (<10%)
   b. Risk factors
      i. Thorotrast
      ii. *Clonorchis sinensis* (liver fluke)
   c. Micro: adenocarcinoma arising from bile duct epithelium
   d. Discovered late in the course
   e. Poor prognosis (average survival is 6 months)
3. **Angiosarcoma**
   a. Rare, malignant vascular neoplasm
   b. Chemical carcinogens: vinyl chloride, thorotrast, and arsenic
   c. Aggressive tumors with a poor 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, hemorrhoids, caput medusa, hepatic encephalopathy, spider angiomata, palmar erythema, gynecomastia, hypoalbuminemia, decreased clotting factors, and hepatorenal syndrome.

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.

Amebic 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.

(Continued)

Chapter Summary (*continued*)

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.

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.

Benign tumors of the liver include hemangiomas and hepatic adenomas. Malignant tumors include hepatocellular carcinoma, cholangiocarcinoma, angiosarcoma, and metastatic tumors.

Review Questions

1. A 28-year-old intravenous drug user comes to the physician because of a 1-week history of weakness, fatigue, and extreme nausea. He says that he typically uses his own needles to inject drugs, but "money was tight" four months ago, and he had been "forced" to share needles with friends. He has not shared a needle in the past 2 months. Physical examination shows scleral icterus, jaundiced skin, and right upper quadrant abdominal tenderness. Laboratory studies show markedly elevated levels of alanine aminotransferase and aspartate aminotransferase. The diagnosis is suspected to be viral hepatitis. Which of the following markers is most likely to be positive at this stage of the disease?

   A. Anti-HAV IgG
   B. HBcAb IgG
   C. HBsAb IgG
   D. HBsAg

2. An 18-year-old boy is brought to the physician by his mother because of "uncontrollable shaking" of his right hand. The mother says that she is also concerned about some "bizarre behavior" lately. Physical examination shows a resting tremor and golden deposits on his corneas. Laboratory studies are most likely to show which of the following results?

   A. Elevated serum iron
   B. Decreased urinary copper excretion
   C. Decreased serum ceruloplasmin
   D. Decreased serum ferritin
   E. Decreased tissue copper levels

Answers

1. **Answer: D.**
2. **Answer: C.**

Red Blood Cell Pathology

19

A. 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* (drepanocytes) 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.

B. 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 = 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)

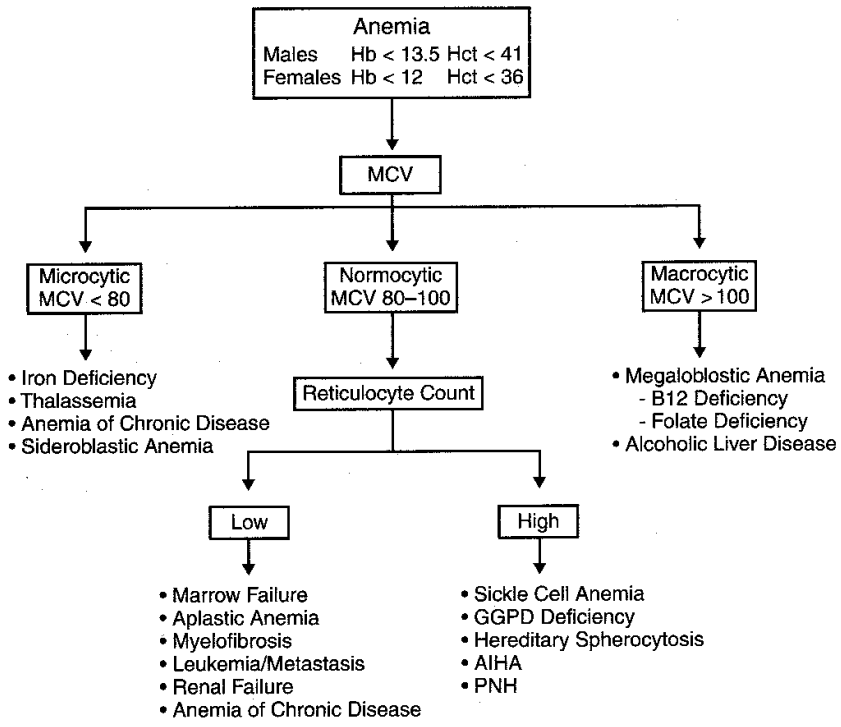


Figure 19-1. Classification of Anemias Based on MCV

2. **Pathogenesis of anemia**
   a. Blood loss
   b. Hemolytic anemias
      i. Hereditary spherocytosis
      ii. G6PD deficiency
      iii. Sickle cell disease
      iv. Hemoglobin C disease
      v. Thalassemia
      vi. Paroxysmal nocturnal hemoglobinuria
      vii. Immunohemolytic 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

C. 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)

Note

Ferritin is an acute phase reactant and may be artificially elevated in inflammatory states.

Table 19-1. Iron Panel for Microcytic Anemias

	Iron Deficiency	AOCD	Thalassemia Minor	Sideroblastic Anemia
Serum iron	↓	↓	Normal	↑
TIBC	↑	↓	Normal	↓
% Saturation	↓	↓	Normal	↑
Serum ferritin	↓	↑	Normal	↑

2. **Anemia of chronic disease (AOCD)**
   a. Characterized by iron being trapped in bone marrow macrophages
   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
      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 (– α/αα), which produces 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 produces 50% α chains
         - Genotype: cis (– –/αα) type is seen in Asians
         - Genotype: trans (–α/–α) 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 Barts (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 (β^0)
   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. Associated with *ring sideroblasts 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

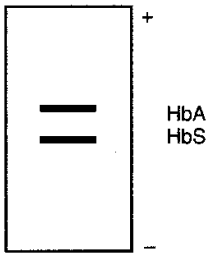
D. NORMOCYTIC ANEMIAS

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
3. **Sickle cell disease**
   a. 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)
   b. 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 increased blood hemoglobin F levels)
      iv. Presence of hemoglobin C (SC: double-heterozygote individual) makes symptoms better
   c. 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
   d. 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)

Note

Hemoglobin electrophoresis takes advantage of the differences in pI values between HbA and HbS (Glu6Val; glutamate at position 6 has been replaced by valine).



Hemoglobin electrophoresis at pH 8.4

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.

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

e. 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)

f. 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. 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

b. X-linked inheritance; patient populations include
i. African Americans (A^- type)
- Hemolysis is secondary to acute oxidative stress, such as oxidative drugs (primaquine, 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 favism 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

c. 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 spectrin* (most commonly) 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)
         - Small lymphocytic lymphoma (WDLL)
         - Drugs (penicillin)
   b. Peripheral blood smear: microspherocytes
   c. Lab: *positive direct Coombs' test* (direct antiglobulin test [DAT])
8. **Paroxysmal nocturnal hemoglobinuria (PNH)**
   a. Abnormality: decreased glycosyl phosphatidyl inositol (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*
   b. Symptoms are episodes (paroxysms) of hemolysis at night.
   c. Acidosis *in vivo*, which occurs during sleep (breathing slowly retains CO_2) and exercise (lactic acidosis), causes activation of complement
   d. PNH is a clonal stem cell disorder that therefore affects all cell lines
   e. Pancytopenia in peripheral blood: anemia, leukopenia, thrombocytopenia
   f. Complications: increased risk for aplastic anemia, leukemia, and venous thrombosis
   g. Lab tests for PNH
      i. Sucrose *in vitro* (sucrose lysis test)
      ii. Acidosis *in vitro* (Ham's test)

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.

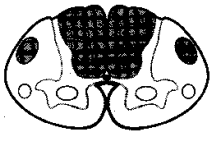
E. MACROCYTIC ANEMIAS

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} 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 breakdown 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 (SCDSD): 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

Note

Normal Sequence of B_{12} Absorption

1. Dietary B_{12} binds to salivary R-binders.
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.



Subacute combined degeneration

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)
      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 SCDSC)
   c. Lab tests
      i. Low serum folate levels and increased serum homocysteine
   d. Treatment: folate

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, anemias of diminished erythropoiesis.

Iron deficiency anemia is a microcytic anemia seen most often in the elderly and poor populations, 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.

(Continued)

Chapter Summary (*continued*)

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.

Paroxysmal nocturnal hemoglobinuria produces episodic hemolysis as a result of increased red-cell sensitivity to the lytic actions of complement.

Megaloblastic anemias occur when there is impaired DNA synthesis, which leads to delayed mitoses. Important causes include vitamin B_{12} deficiency and folate deficiency.

Review Questions

1. A 62-year-old man comes to the physician because he "just can't do as much walking anymore." He used to be able to walk 10 blocks without even "breaking a sweat," but now he is exhausted after only two blocks. He also says that he occasionally gets a "strange" sensation, as if his heart is "leaping out" of his chest. His temperature is 37°C (98.6°F), blood pressure is 110/80 mm Hg, and pulse is 87/min. Physical examination shows pale skin and mucous membranes. A fecal occult blood test is positive. A peripheral blood smear shows small erythrocytes with marked size variability. Laboratory studies are most likely to show which of the following results?

	Serum Iron	Total Iron Binding Capacity	% Saturation	Serum Ferritin
A.	Decreased	Decreased	Increased	Decreased
B.	Decreased	Decreased	Increased	Increased
C.	Decreased	Increased	Decreased	Decreased
D.	Decreased	Increased	Decreased	Increased
E.	Increased	Decreased	Increased	Decreased
F.	Increased	Decreased	Increased	Increased

2. A 14-year-old girl is brought to the emergency department by a camp counselor because of severe leg pain. She knows that she has a "chronic disease," but she is not exactly sure what it is. Physical examination shows a 2-cm ulcer on her lower leg that appears to extend to the bone. An x-ray of her lower leg is normal. A technetium radionuclide scan of her leg shows increased uptake. Cultures of the wound grow Salmonella. A peripheral blood smear shows Howell-Jolly bodies. Which of the following is the most likely underlying condition?

   A. Alpha-thalassemia
   B. Beta-thalassemia
   C. G6PD-deficiency
   D. Hereditary spherocytosis
   E. Sickle cell anemia

Answers

1. **Answer: C.**
2. **Answer: E.**

White Blood Cell Pathology 20

A. REACTIVE PROLIFERATIONS OF 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 endoplastic reticulum [RER]), toxic granulations (prominent granules), and cytoplasmic vacuoles of neutrophils
      v. Increased leukocyte alkaline phosphatase (LAP) is useful to differentiate benign reactions from neoplastic chronic myelocytic leukemia (CML) (which has decreased LAP)
   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
      v. Certain cancers (adenocarcinomas)
   c. Increased monocytes (monocytosis) are seen with
      i. Certain chronic diseases, such as some collagen vascular diseases and inflammatory bowel disease (IBD)
      ii. Certain infections, especially TB
   d. Increased lymphocytes (lymphocytosis) are seen with
      i. Acute (viral) diseases
      ii. Chronic inflammatory processes
   e. **Infectious mononucleosis (IM)** is an example of a virus disease causing lymphocytosis
      i. 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])
      ii. Sequence of events
         - EBV invades B-lymphocytes via CD21 (CR2) receptors
         - Cytotoxic (CD8) T-lymphocytes respond against invaded B-cells and form atypical lymphocytes (Downey cells), which are enlarged lymphocytes that

have abundant cytoplasm that is condensed peripherally ("ballerina skirt" appearance); they are similar in appearance to monocytes, hence the name "mononucleosis"

- Atypical lymphocytes are found in the peripheral blood and T-cell areas of lymph nodes (paracortex) and may cause misdiagnosis as Hodgkin disease histologically (therefore, don't biopsy a lymph node!)

iii. 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).

iv. Clinical infectious monocytosis

- Age groups ("kissing disease") include adolescents and young adults
- 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

v. Complications include hepatic dysfunction, splenic rupture, and rash if treated with ampicillin

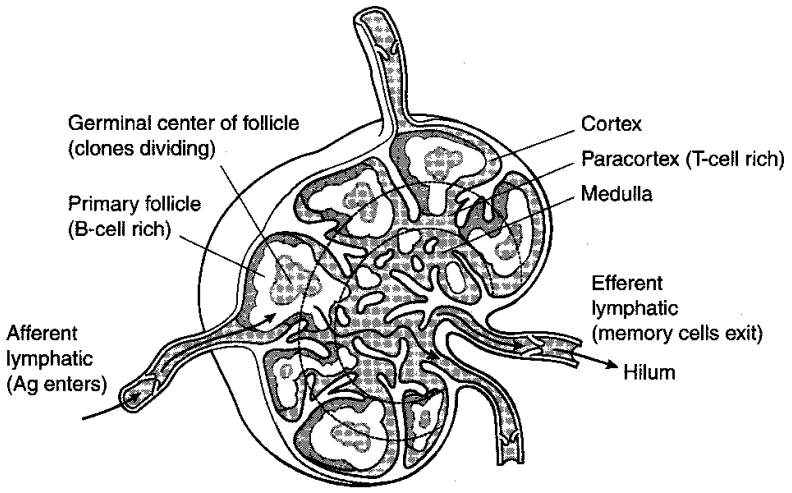


Figure 20-1. Lymph Node

2. **Lymphadenopathy**

a. Acute nonspecific lymphadenitis

i. Tender enlargement of lymph nodes

ii. Focal involvement is seen with bacterial lymphadenitis

- Histology: may see neutrophils within the lymph node
- Note: cat-scratch fever (due to *Afipia felis*) causes stellate microabscesses

iii. Generalized involvement of lymph nodes is seen with viral infections (see reactive T cells immunoblasts 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.

B. 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. **Non-Hodgkin lymphoma 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)
      ii. The *Working Formulation* divides non-Hodgkin lymphomas into three categories based on the prognosis (low-grade, intermediate-grade, and high-grade)

Table 20-1. Working Formulation of Non-Hodgkin Lymphomas

Low Grade	Intermediate Grade	High Grade
Small lymphocytic	Follicular large cell	Large cell immunoblastic
Follicular, small-cleaved cell	Diffuse, small-cleaved cell	Lymphoblastic
Follicular, mixed, small-cleaved and large cell	Diffuse, mixed, small and large cell	Small, noncleaved cell (Burkitt and non-Burkitt type)
	Diffuse, large cell	

      iii. *Rappaport* is an old classification (developed 1966) that is based on the microscopic appearance of tumor cells
         - The size of the tumor cells was classified as either lymphocytic or histiocytic, and the tumor growth pattern was nodular or diffuse
         - Well differentiated cells were similar to lymphocytes; poorly differentiated cells were angulated (cleaved) or had nucleoli

Clinical Correlate

ALL is associated with infiltration of the CNS and testes (*Sanctuary sites*). Prophylactic radiation and/or chemotherapy to the head is recommended because malignant cells in brain are protected from chemotherapy by the blood–brain barrier.

C. PRECURSOR B-CELL AND T-CELL NEOPLASMS

1. **Acute lymphoblastic leukemia (ALL)**
   a. *Lymphoblasts* are positive for terminal deoxytransferase (TdT) (which is determined by using a nuclear stain), PAS, and acid phosphatase
   b. The French-American-British (FAB) classification of ALL (no longer employed)
      i. L1: small homogeneous blasts (85% of cases of ALL)
      ii. L2: larger, heterogeneous (pleomorphic) blasts with nuclear clefts
      iii. L3: (<1% of cases) large blasts with cytoplasmic vacuoles that stain with oil red O (leukemic form of Burkitt lymphoma)
   c. 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 (a.k.a. FAB L3, the leukemic form of Burkitt's lymphoma)
         - Cytoplasmic μ present: pre-B-ALL
         - Early pre B-ALL is the most common type of ALL and is seen primarily in children
         - Symptoms are 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. 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 (WDLL)
      i. If 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 are also 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 of the leukemias
   ii. Mean age at time of diagnosis is 60
   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)

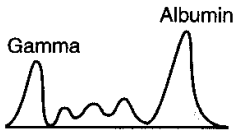
2. **Hairy cell leukemia**
   a. Indolent disease of older men
   b. Lymphocytes have "hairlike" cytoplasmic projections ("dry tap" with bone marrow aspiration)
   c. Diagnostic stain: positive tartrate-resistant acid phosphatase (TRAP)
   d. Physical exam: a markedly enlarged spleen (splenomegaly) due to infiltrate of red pulp by malignant cells
   e. Treatment with 2-chlorodeoxyadenosine (2CDA), which inhibits adenosine deaminase (ADA) and increases levels of toxic deoxyadenosine
3. **Follicular lymphomas**
   a. The most common form of non-Hodgkin's lymphoma (NHL) in the United States
   b. All follicular lymphomas are derived from B-lymphocytes
   c. 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)
   d. 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
   e. Classification
      i. Follicular small cleaved (<20% large cells in follicles)
      ii. Small cleaved cells are also called centrocytes
      iii. Small cleaved cells in peripheral smear are called "buttock cells"
      iv. Follicular mixed small and large cells (20–50% large cells, which are also called centroblasts, in the follicles)
      v. Follicular large cell (>50% large cells in the follicles)
4. **Diffuse large B-cell lymphoma**
   a. The Working Formulation divides the diffuse lymphomas into diffuse small cleaved, diffuse mixed small cleaved and large cell, and diffuse large cell

b. Common features
   i. Composed of large cells with a diffuse growth pattern
   ii. May present at extranodal sites: CNS, stomach, etc.
   iii. Aggressive, rapidly proliferating tumor
   iv. 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. Micro
      i. Medium-sized lymphocytes with a high mitotic rate
      ii. *"Starry-sky" appearance* is 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 nonendemic form
      i. Commonly involves the abdomen (such as bowel, retroperitoneum, or ovaries)
      ii. High incidence in AIDS patients
6. **Mantle cell lymphoma (MCL)**
   a. Synonym: intermediate differentiated lymphocytic lymphoma
   b. MCL is not in the original working classification
   c. Most cases of small-cleaved NHL in the Working Formulation are, in fact, mantle cell lymphoma
   d. The tumor cells arise from mantle zone B-lymphocytes (positive for CD19, CD20, and CD5; negative for CD23)
   e. 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. May arise inside or outside lymph nodes (extranodal)
   b. Associated with mucosa-associated lymphoid tissue: MALTomas
   c. Begins as reactive polyclonal reaction and may be associated with previous autoimmune disorders
   d. Remains localized for long periods of time
8. **Plasma cell neoplasms (multiple myeloma)**
   a. Multiple myeloma is the most common primary tumor arising in bone of adults

b. 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. Twenty percent express Bence-Jones proteins, which are light chains that are small and can be filtered into urine
c. Histology
   i. Bone marrow has increased numbers of plasma cells (>20% is characteristic)
   ii. Peripheral blood may show rouleaux ("stack of coins")
d. Multiple lytic bone lesions due to the osteoclastic activating factor (OAF)
   i. OAF is IL-6 (increased amounts of IL-6 are associated with a poorer prognosis because survival of myeloma cells is dependent on IL-6).
   ii. Lytic bone lesions cause hypercalcemia, bone pain, and increased risk of fracture
e. Complications
   i. Increased risk of infection, the most common cause of death
   ii. Renal disease, such as myeloma nephrosis
   iii. Amyloidosis (10% of patients) due to amyloid light (AL) chains
f. Plasmacytoma: solitary aggregates → plasma cells, which may be located
   i. Within bone: precursor lesions to later develop into myeloma
   ii. Outside bone (extramedullary): usually found within the upper respiratory tract and are not precursor lesions for myeloma
g. **Monoclonal gammopathy of undetermined significance (MGUS)**
   i. Old name was benign monoclonal gammopathy
   ii. M protein is found in 1–3% of asymptomatic individuals over the age of 50 (the incidence increases with increasing age)
   iii. About 20% of these individuals will develop a plasma cell dyscrasia in 10–15 years

9. **Lymphoplasmacytic lymphoma (Waldenström macroglobulinemia)**
   a. Synonym: small lymphocytic lymphoma with plasmacytic differentiation
   b. Waldenström's 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



IgG Myeloma with γ Spike and Reduced Albumin

E. 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-1 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 prognosis 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)

F. HODGKIN DISEASE (HD)

1. **Hodgkin versus non-Hodgkin lymphomas**
   a. Characteristics of HD that are different from NHL
      i. Clinically, HD may present similar to infection (with fever)
      ii. Spread is contiguous to adjacent node groups (unlike non-Hodgkin's lymphomas)
      iii. Classification is based on inflammatory response and not malignant cell
      iv. No leukemic state
      v. Extranodal spread uncommon
2. **Hodgkin disease**
   a. The malignant cell is the *Reed-Sternberg (RS) cell*
      i. "Owl-eye" appearance: symmetric (mirror image) bilobed nucleus with prominent central nucleoli surrounded by clear space
      ii. RS cells are positive for CD15 (Leu-M1) and CD30 (Ki-1)
      iii. Except for lymphocyte predominate HD in which the malignant cells stain for B-cell markers and have negative CD15 and CD30
   b. Classification of HD
      i. LP (lymphocyte predominant) type; has L-H cells (popcorn cells) and are negative for CD15 and CD30
      ii. Mixed cellularity; has eosinophils and plasma cells (increased number of eosinophils is related to IL-5 secretion)
      iii. Lymphocyte depleted (LD); has few lymphocytes, and there are many RS cells

iv. Nodular sclerosis (NS)
- This is the most common subtype
- The only type more common in females
- Lymph node has broad collagen bands
- RS variant: *Lacunar cells* (clear space surrounding cell)

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 and inversely proportional to the number of lymphocytes
v. Survivors of chemotherapy and radiotherapy have increased risk for non-Hodgkin lymphoma or acute leukemia

Chapter Summary

Leukocytosis is a common reactive pattern 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, medicines, 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.

(Continued)

Chapter Summary (*continued*)

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 t(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 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.

Lymphoplasmacytic lymphoma (Waldenstrom 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 CD-15 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.

Review Questions

1. A 28-year-old woman comes to the physician because of a "big lump" on her neck that she found 3 days ago. She says that she is rarely sick and only goes to the doctor every few years for a Pap smear. Her temperature is 38.1°C (100.5°F). Physical examination shows a 2.3-cm nontender cervical lymph node. Excisional biopsy of the lymph node is most likely to show which of the following?

   A. Aggregates of atypical PAS-positive lymphocytes
   B. Cells with bilobed nuclei and central nucleoli surrounded by a clear space
   C. Medium lymphocytes with a starry-sky appearance
   D. Rouleaux formation
   E. Small cleaved "buttock" cells

2. A 68-year-old man comes to the physician because of a 2-day history of confusion, increased urination, decreased food intake, constipation, nausea, and vomiting. He says that he has been feeling "a bit more tired than usual" lately, but he was not seriously concerned until now. An electrocardiogram shows a shortening of the QT interval. A bone marrow biopsy shows 25% plasma cells. A peripheral blood smear shows rouleaux formation. Laboratory studies show:

Sodium	138 mg/dl
Potassium	4 mg/dl
Chloride	100 mg/dl
Bicarbonate	22 mg/dl
Calcium	14 mg/dl

   He is at greatest risk for which of the following conditions?

   A. Adult T-cell lymphoma
   B. Amyloidosis
   C. Burkitt lymphoma
   D. Hodgkin lymphoma
   E. Mycosis fungoides

Answers

1. **Answer: B.**

2. **Answer: B.**

Myeloid Neoplasms

21

A. ACUTE MYELOGENOUS LEUKEMIA (AML)

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 thromboplastic 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)

B. MYELODYSPLASIA

1. **Myelodysplastic syndromes (MDS)**
   a. The classification of myelodysplastic syndromes is based on the number of blasts in the marrow
   b. Dysplastic changes include **Pelger-Huët cells ("aviator glasses" nuclei)**, ring sideroblasts, nuclear budding, and **"pawn ball" megakaryocytes**
   c. MDS patients have an **increased risk of developing acute leukemia** (preleukemias)

C. MYELOPROLIFERATIVE SYNDROMES (MPS)

1. **General**
   a. MPSs are clonal neoplastic proliferations of multipotent myeloid stem cells
   b. Bone marrow is usually markedly hypercellular (hence the name myeloproliferative)
      i. All cell lines are increased in number (erythroid, myeloid, and megakaryocytes)
      ii. Cannot tell the MPSs apart by the histologic appearance of the bone marrow
2. **Chronic myelogenous leukemia (CML)**
   a. Clonal proliferation of pluripotent stem cells
   b. A unique characteristic is the chromosomal translocation
      i. *Philadelphia (Ph) chromosome, which has t(9;22)*
      ii. 9 has c-abl (an oncogene), while 22 has bcr (breakpoint cluster region)
      iii. This translocation forms a new protein P210 that has tyrosine kinase activity
   c. Insidious onset (i.e., chronic) and massive splenomegaly
   d. Micro: hypercellular bone marrow with all cell lines increased in number
   e. Peripheral leukocytosis including
      i. Markedly increased numbers of neutrophils (and bands and metamyelocytes)
      ii. Increased eosinophils and basophils (like the other MPSs)
   f. *Decreased* leukocyte alkaline phosphatase (LAP) activity is diagnostic compared with leukemoid reaction, which has increased LAP
   g. Treatment
      i. Control with hydroxyurea
      ii. Bone marrow transplant
   h. Prognosis
      i. Slow progression (half develop accelerated phase <5 years)
      ii. Then blast crisis (very bad prognosis; doesn't respond to chemotherapy): 2/3 myeloid blasts and 1/3 lymphoid blasts
3. **Polycythemia vera (P. vera)**
   a. Characteristic findings
      i. Increased erythroid precursors with increased red cell mass (primary)
      ii. Increased hematocrit
      iii. Increased blood viscosity
   b. Decreased erythropoietin (EPO), but RBCs have increased sensitivity to EPO and overproliferate
   c. Increased basophils and increased eosinophils (like all of the MPSs)
   d. Histamine release from basophils causes intense pruritus and gastric ulcers (bleeding may cause iron deficiency)
   e. Increased LAP
   f. Clinical characteristics: plethora (redness) and cyanosis (blue)
   g. Complications
      i. Increased blood viscosity can cause deep vein thromboses and infarcts
      ii. High cell turnover can cause hyperuricemia, resulting in gout
      iii. P. vera may develop into a "spent phase" with myelofibrosis
      iv. Increased risk for acute leukemia

4. **Essential thrombocythemia (ET)**
   a. Increased megakaryocytes (and other cell lines) in bone marrow
   b. Peripheral blood smear
      i. Increased number of platelets (>1,000,000), some with abnormal shapes
      ii. Also increased numbers of leukocytes
   c. Clinical signs include excessive bleeding and occlusion of small vessels
5. **Myelofibrosis (MF) with myeloid metaplasia**
   a. Etiology is unknown (agnogenic)
   b. Bone marrow aspiration may be a "dry tap"
   c. Biopsy specimen shows hypocellular marrow with fibrosis (increased reticulin)
      i. Fibroblasts are polyclonal proliferation (not neoplastic)
      ii. Fibrosis is secondary to factors released from megakaryocytes, such as platelet-derived growth factor (PDGF)
   d. Enlarged spleen due to extramedullary hematopoiesis (myeloid metaplasia)
   e. Peripheral smear
      i. Leukoerythroblastosis (immature white cells and nucleated red cells)
      ii. *Teardrop RBCs*
   f. High cell turnover causes hyperuricemia and gout

Note

The spleen is the most common site for extramedullary hematopoiesis.

Chapter Summary

Acute myelogenous leukemia is a proliferation of nonlymphoid leukemic cells within 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.

Review Questions

1. A 68-year-old man comes to the physician because of a 2-month history of "extreme fatigue." He states that he is just not himself lately and it is "really worrisome." He has been leading a very active life since retiring from his job at a rubber factory 3 years ago. His temperature is 38.2°C (100.8°F). Physical examination shows hepatosplenomegaly, diffuse lymphadenopathy, and sternal tenderness. Laboratory studies show:

Hemoglobin	9 g/dl
Hematocrit	37%
Platelets	42,000/mm^3

A bone marrow biopsy shows numerous cytoplasmic granules and cells with intracytoplasmic rods that stain positive with myeloperoxidase. Which of the following is the most likely diagnosis?

A. Acute lymphoblastic leukemia
B. Acute myelogenous leukemia
C. Chronic lymphocytic leukemia
D. Chronic myelogenous leukemia
E. Myelofibrosis with myeloid metaplasia

2. A 49-year-old woman comes to the physician for a periodic health maintenance examination. She has no specific complaints. Physical examination shows massive splenomegaly. Routine laboratory studies show an elevated white blood count with an increased number of immature granulocytes, an elevated platelet count, and normochromic, normocytic anemia. There is decreased leukocyte alkaline phosphatase activity. Which of the following is the most likely chromosomal translocation associated with this condition?

A. t(8;14)
B. t(9;22)
C. t(11;14)
D. t(14;18)
E. t(15;17)

Answers

1. **Answer: B.**

2. **Answer: B.**

Female Genital Pathology

22

A. VULVA

1. **Condyloma acuminatum**
   a. 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. Benign tumor
   b. Occur along the milk line
   c. Histologically similar to an intraductal papilloma of the breast
3. **Extramammary Paget disease of the vulva**
   a. Usually involves labia majora
   b. Gross: erthematous, crusted rash
   c. Micro: intraepidermal malignant cells with pagetoid spread
   d. Not usually associated with underlying tumor

B. 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

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.

C. 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 adhesions

Clinical Correlate

Tubal ectopic pregnancies usually occur in the ampulla of the fallopian tube. Tubal rupture results in severe, acute lower abdominal pain.

Table 22-1. Malignant Tumors of the Female Genital Tract

Incidence	Mortality
1. Endometrial cancer	1. Ovarian cancer
2. Ovarian cancer	2. Endometrial cancer
3. Cervical cancer	3. Cervical cancer

2. **Cervical carcinoma**
   a. Epidemiology
      i. Third most common malignant tumor of the female genital tract in United States
      ii. Peak incidence in the 40s
   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. Immunosuppresion
   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)
      - CIN II (moderate dysplasia)
      - CIN III (severe dysplasia)
      - CIS (carcinoma *in situ*)
      - Invasive squamous-cell carcinoma
e. Clinical presentation
   i. Asymptomatic
   ii. Postcoital vaginal bleeding
   iii. Dyspareunia
   iv. Malodorous discharge
f. Diagnosis
   i. Papanicolaou (Pap) smear: early detection
   ii. Colposcopy with biopsy

D. 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 bladder
      v. Peritoneal cavity
   d. Gross
      i. Red-brown serosal nodules ("powder burns")
      ii. Endometrioma: ovarian "chocolate" cyst
   e. Clinical presentation
      i. Chronic pelvic pain
      ii. Dysmenorrhea and dyspareunia
      iii. Rectal pain and constipation
      iv. Infertility

3. **Leiomyoma (fibroids)**
   a. Most common tumor of the female genital tract
   b. Benign smooth muscle tumor of the myometrium
   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
   h. Malignant variant: leiomyosarcoma
4. **Endometrial carcinoma**
   a. Epidemiology
      i. Most common malignant tumor of the female genital tract
      ii. Most commonly affects postmenopausal women
   b. 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
   c. Gross
      i. Tan polypoid endometrial mass
      ii. Invasion of myometrium is prognostically important
   d. Micro: endometroid adenocarcinoma (most common type)
   e. Clinical presentation: postmenopausal vaginal bleeding

E. OVARY

1. **Polycystic ovarian disease (Stein-Leventhal syndrome)**
   a. Clinical presentation
      i. Young females of reproductive age
      ii. Oligomenorrhea or secondary amenorrhea
      iii. Hirsutism
      iv. Infertility
      v. Obesity
   b. Unknown etiology
   c. Lab
      i. Elevated luteinizing hormone (LH)
      ii. Low follicle stimulating hormone (FSH)
      iii. Elevated testosterone
   d. Gross: bilaterally enlarged ovaries with multiple cysts
   e. Micro: multiple follicle cysts
   f. 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: unilocular, 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 + ascities + pleural effusion

b. **Granulosa cell tumor**
i. Potentially malignant
ii. *Estrogen producing tumor*
iii. Clinical presentation
- 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)

F. GESTATIONAL TROPHOBLASTIC 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 triploid cell 69, XXY (23,X [maternal] + 23X [one sperm] +23Y [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 22-2. Properties of a Partial Mole Versus Those of a Complete Mole

	Partial Mole	Complete Mole
Ploidy	Triploid	Diploid
Number of chromosomes	69	46 (All paternal)
β-HCG	Elevated (+)	Elevated (+++)
Chorionic villi	Some are hydropic	All are hydropic
Trophoblast proliferation	Focal	Marked
Fetal tissue	Present	Absent
Invasive mole	10%	10%
Choriocarcinoma	Rare	2%

2. **Invasive moles:** 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

Chapter Summary

Lesions of the vulva include condyloma acuminatum, papillary hidradenoma, and extramammary Paget disease.

Lesions of the vagina include vaginal adenosis, clear-cell adenocarcinoma, and embryonal rhabdomyosarcoma.

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 in HPV-related areas of CIN.

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.

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.

Review Questions

1. A 27-year-old woman comes to the emergency department because of severe abdominal and pelvic pain for the past 12 hours. She says she has two sexual partners that she has been with for "years." She is not sure if they are involved with any other women. Her last menstrual period was 4 days ago, and it was normal. She denies any rectal pain or change in bowel habits. Physical examination shows cervical motion tenderness, bilateral lower abdominal tenderness, and right-upper quadrant tenderness. Which of the following is the most likely diagnosis?

   A. Endometriosis
   B. Leiomyoma
   C. Pelvic inflammatory disease
   D. Polycystic ovary disease
   E. Torsion of a teratoma

2. A 32-year-old woman comes to the physician with her husband because "she just can't seem to get pregnant." They have been unsuccessfully trying to conceive for the past 14 months, having unprotected sexual intercourse during her "fertile days." Her menstrual periods arrive at regular 28-day intervals, but they are accompanied by severe abdominal cramps. She says that often experiences rectal pain during defecation and pelvic pain during sexual intercourse. She says that she has been to many physicians "over the years" because of "chronic pelvic pain." An explorative laparoscopy is scheduled to determine the cause of her infertility. Which of the following is the most likely finding at laparoscopy?

   A. "Grape-like" soft tissue mass protruding from the uterus into the peritoneal cavity
   B. Multiple well circumscribed subserosal uterine tumors
   C. Red-brown serosal nodules and ovarian "chocolate" cysts
   D. Ruptured ovarian cyst containing hair, teeth, cartilage, thyroid, and greasy material
   E. "Violin-string" adhesions between the fallopian tubes and liver capsule

Answers

1. **Answer: C.**

2. **Answer: C.**

Breast Pathology

23

A. MASTITIS

1. Acute mastitis
   a. Common during lactation
   b. Organism: *Staphylococcus aureus* (most common)
2. Fat necrosis
   a. Often related to trauma or prior surgery
   b. May produce a palpable mass or lesion on mammography

B. FIBROCYSTIC CHANGES

1. Old name: fibrocystic disease
2. Age 20–50
3. Extremely common
4. May produce a palpable mass or nodularity
5. Most often involves the upper outer quadrant

Table 23-1. Nonproliferative Versus Proliferative Fibrocystic Changes

Nonproliferative	Proliferative Changes
Fibrosis Cysts (blue-domed) Apocrine metaplasia Microcalcifications	Ductal hyperplasia ± Atypia Sclerosing adenosis Small duct papillomas

Table 23-2. Relative Risk of Developing Breast Cancer with Fibrocystic Change

Relative Risk	Fibrocystic Change
No increase	Fibrosis, cysts, apocrine metaplasia, adenosis
1.5–2×	Sclerosing adenosis, ductal hyperplasia, papillomas
4–5×	Atypical ductal or lobular hyperplasia

Note

Most Common Causes of Breast Lumps

- Fibrocystic changes
- Normal breast, no disease
- Cancer
- Fibroadenoma

Table 23-3. Features That Distinguish Fibrocystic Change from Breast Cancer

Fibrocystic Change	Breast Cancer
Often bilateral	Often unilateral
May have multiple nodules	Usually single
Menstrual variation	No menstrual variation
Cyclic pain and engorgement	No cyclic pain or engorgement
May regress during pregnancy	Does not regress during pregnancy

C. BENIGN NEOPLASMS

1. **Fibroadenoma**
   a. Most common benign breast tumor in women <35
   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

D MALIGNANT NEOPLASMS

1. **Carcinoma of the breast**
   a. Epidemiology
      i. Most common cancer in females (1 in 9 women in the US!)
      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 chromosome 17q21
         • BRCA2 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 Malignancies)

b. Invasive (infiltrating) ductal carcinoma
i. Most common (>80%)
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 invasion by tumor

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)
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

E. OTHER MALIGNANCIES

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

Chapter Summary

Acute mastitis commonly occurs during lactation and is usually due to *Staphylococcus aureus*.

Fibrocystic change is an extremely common condition of women aged 20 to 50 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.

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 in the breast with an underlying invasive or in situ ductal carcinoma.

Cystosarcoma phyllodes is a large tumor involving both stroma and glands that behaves malignantly in 10–20% of cases.

Review Questions

1. A 32-year-old woman comes to the physician because of "breast lumps" that she noticed while performing her self-breast examination in the shower 1 week ago. She thinks that she may have felt them during her breast examination in the previous month, but they were slightly smaller then. She says that she performs this examination each month, 3 days before she is due to get her menstrual period. She has mild breast tenderness each month before her period and sometimes has to wear a larger bra during this time because her breasts are "swollen." Physical examination shows 6 to 8-cm and 0.3 to 0.9-cm, tender nodules in the upper outer quadrant of each breast. Excisional biopsy of a few of these nodules is most likely to show which of the following?

   A. Blue-domes cysts, fibrosis, and apocrine metaplasia
   B. Clusters of bland cells within pools of mucin
   C. Papillary growths within lactiferous ducts and sinuses
   D. Proliferation of stroma, ducts, and lobules
   E. Small cells forming a single-line pattern

2. A 56-year-old woman comes to the physician for a health maintenance examination. She has no physical complaints, but she is concerned about her risk for breast cancer. She had menarche at age 9, a bilateral hysterectomy with oophorectomy because of leiomyomas at age 39, has been pregnant four times, and has been "slightly anorexic" for the past 25 years. Her mother's great-grandmother was diagnosed with breast cancer at age 94. Which of the following factors in this patient's history increases her breast cancer risk the most?

   A. Age of menarche
   B. Age of menopause
   C. Family history
   D. Parity
   E. Weight

Answers

1. **Answer: A.**

2. **Answer: A.**

Male Pathology 24

A. 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 fibromatosis 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

B. 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

C. 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

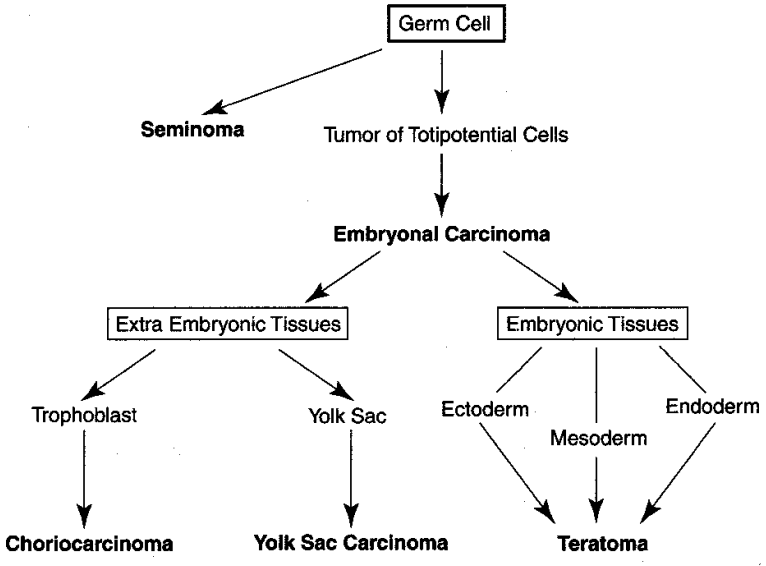


Figure 24-1. Germ Cell Malignancies

Table 24-1. Seminomas Versus Nonseminomatous Germ-Cell Tumors

Seminomas	Nonseminomatous Germ Cell Tumors
Seminoma	Embryonal, yolk sac, choriocarcinoma, teratoma
Radiosensitive	Not radiosensitive
Chemosensitive	Chemosensitive
Late metastasis	Early metastases to retroperitoneal lymph nodes
Excellent prognosis	More aggressive

4. **Germ-cell tumors**
   a. **Seminoma**
      i. Most common germ-cell tumor in adults age 15–35
      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, granulomas, 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 20s–40s
      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 then 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
      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 ectoderm, endoderm, 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 then 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
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
b. Non-Hodgkin lymphoma, diffuse large-cell type

7. **Scrotal squamous cell carcinoma** (SCC) is associated with exposure to soot (chimney sweeps)

D. PROSTATE

Note

The H in BPH more accurately represents hyperplasia than hypertrophy, although you may see either term used.

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 = 70%, age 70 = 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 peri-urethral 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

Bridge to Anatomy

Hyperplasia → transitional/periurethral zones

Carcinoma → peripheral zone

iv. Urgency, frequency, nocturia, dysuria
v. Prostate specific antigen (PSA) may be elevated but is usually <10 ng/ml

g. Complications
i. UTIs
ii. Bladder trabeculation and diverticula formation
iii. Hydronephrosis and renal failure (rare)

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 cancer**

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

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 U/S 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

Clinical Correlate

An elderly man with osteoblastic metastasis visible on x-ray should be considered as having prostate carcinoma until proven otherwise.

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.

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. Orchitis or testicular inflammation can be caused by mumps.

Testicular torsion is a twisting of the spermatic cord that may cause painful hemorrhagic infarction.

Testicular cancers tend to cause firm, painless masses, and, like ovarian cancers, 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.

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.

Benign prostatic hypertrophy 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.

Review Questions

1. A 26-year-old man comes to the physician because of a 3-month history of a painless testicular mass. He says that it was the size of a pea when he first noticed it, and it has been growing for the past few months. He is sexually active, but denies ever having a sexually transmitted disease. He does not have dysuria or penile discharge. Physical examination shows a 2-cm, firm mass in the left testes. An ultrasound shows a hypoechoic intratesticular mass. Laboratory studies show elevated levels of placental alkaline phosphatase. A radical orchiectomy is performed, and the mass is sent to pathology for evaluation. Gross examination shows a 2.3-cm gray-tan mass. Microscopic examination is the most likely to show which of the following?

   A. Ectoderm, endoderm, and mesodermal tissue in a haphazard arrangement
   B. Large, primitive cells with hemorrhage and necrosis
   C. Polygonal germ cells with clear cytoplasm and round nuclei arranged in lobules
   D. Proliferation of syncytiotrophoblasts and cytotrophoblasts
   E. Schiller-Duval bodies

2. A 59-year-old man comes to the physician because of a 6-month history of "difficulty stopping and starting urinary flow." He says that the most troubling part is that he "dribbles" after he urinates, and he should not be doing this because he is not "an old man." Digital examination shows nodules in the transitional and periurethral zones of the prostate. A prostate specific antigen test is 4.2 ng/ml. This condition puts this patient at increased risk for which of the following complications?

   A. Carcinoma of the seminal vesicles
   B. Lung and liver metastases
   C. Osteoblastic bony metastases
   D. Testicular carcinoma
   E. Urinary tract infections

Answers

1. **Answer: C.**

2. **Answer: E.**

Endocrine Pathology 25

A. THYROID GLAND

1. **Multinodular goiter (nontoxic goiter)**
   a. Presentation
      i. Females > males
      ii. Frequently asymptomatic
      iii. Typically euthyroid
      iv. Goiter
      v. Plummer syndrome: development of hyperthyroidism (toxic multinodular goiter) late in the course
   b. Gross: enlarged thyroid gland with multiple colloid nodules
   c. Microscopic
      i. Nodules of varying sizes composed of colloid follicles
      ii. Calcification, hemorrhage, cystic degeneration, and fibrosis
   d. Lab: normal T4, T3, and TSH

B. HYPERTHYROIDISM

1. **General features of hyperthyroidism**
   a. Clinical features
      i. Tachycardia and palpitations
      ii. Nervousness and diaphoresis
      iii. Heat intolerance
      iv. Weakness and tremors
      v. Diarrhea
      vi. Weight loss despite a good appetite
   b. Lab
      i. Elevated free T4
      ii. 1° hyperthyroidism: decreased TSH
      iii. 2° and 3° hyperthyroidism: elevated TSH
2. **Graves disease**
   a. Definition: autoimmune disease characterized by production of IgG autoantibodies to the TSH receptor
   b. Clinical features
      i. Females > males; age 20–40

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

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)

C. HYPOTHYROIDISM

1. **General features of hypothyroidism**
   a. Clinical features
      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
   b. Lab
      i. Decreased free T4
      ii. 1° hypothyroidism: elevated TSH
      iii. 2° and 3° 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 (endemic cretinism)

4. **Endemic goiter**
   a. Uncommon in the United States
   b. Etiology: dietary deficiency of iodine

D. 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
      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 "Hürthle cell" changes
   f. May be associated with other autoimmune diseases (SLE, RA, SS [Sjögren syndrome], etc.)
   g. Complication: increased risk of non-Hodgkin lymphoma (NHL) 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
      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.

E. 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
      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%
3. **Follicular carcinoma**
   a. Accounts for 15% of malignant thyroid tumors
   b. Females > males; age 40–60
   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
      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

F. PARATHYROID GLANDS

1. **Primary hyperparathyroidism**
   a. Etiology
      i. Parathyroid adenoma (80%); may be associated with MEN I
      ii. Parathyroid hyperplasia (15%)
         • Diffuse enlargement of four glands
         • 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's and Trousseau's 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.

G. PITUITARY GLAND

1. **Pituitary adenomas**
   a. **Prolactinoma**
      i. Most common type
      ii. Galactorrhea, amenorrhea, and infertility
      iii. Decreased libido and impotence
   b. **Growth-hormone–producing adenoma**
      i. Lab
         - Elevated growth hormone
         - Elevated somatomedin C (insulin-like growth factor)

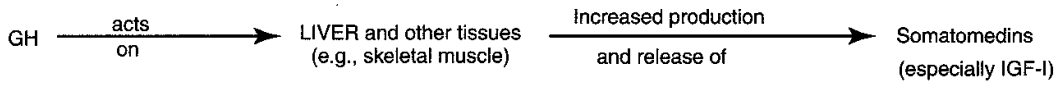


Figure 25-1

      ii. Gigantism
         - Children and adolescents
         - Prior to fusion of the growth plates
         - Tall stature and long extremities
      iii. Acromegaly
         - Adults
         - Prominent jaw
         - Flat, broad forehead
         - Enlarged hands and feet
         - Visceral abnormalities
   c. Corticotrope adenomas produce ACTH, causing Cushing disease
   d. Thyrotrope adenomas produce TSH, causing hyperthyroidism
   e. Gonadotrope adenomas produce LH and FSH
   f. 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: ADH deficiency resulting 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: excessive production of ADH, resulting in oliguria, water retention, hyponatremia, and cerebral edema
   b. Etiology: paraneoplastic syndrome, head trauma, other

Clinical Correlate

Any pituitary tumor that destroys more than 75% of the pituitary may result in panhypopituitarism, which is characterized by abnormalities of the thyroid, adrenal gland, and reproductive organs.

Common Causes of Panhypopituitarism

- Pituitary adenomas
- Sheehan syndrome
- Craniopharyngiomas

H. ADRENAL GLAND

1. **Cushing syndrome**
   a. Definition: disease characterized by increased levels of glucocorticoids

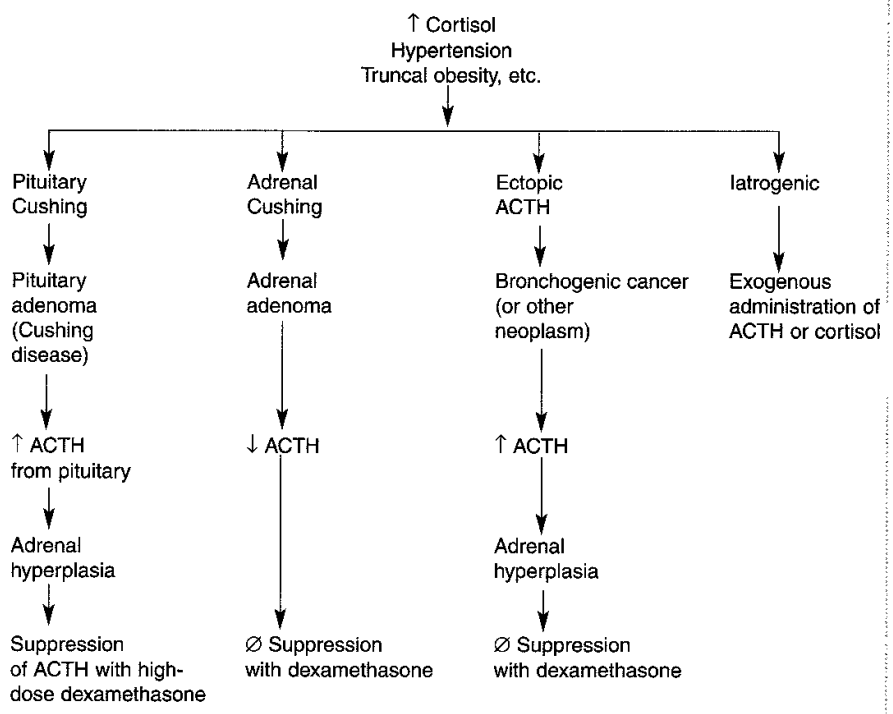


Figure 25-2. Summary of Cushing Syndrome and Its Effects

2. **Primary hyperaldosteronism (Conn syndrome)**
   a. Definition: adrenocortical adenoma producing aldosterone
   b. Clinical feature: hypertension
   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* infection in a child

Note

Dexamethasone suppression test: Administration of dexamethasone (a cortisol analog) normally will suppress pituitary ACTH production, resulting in suppression of adrenal cortisol production and a decrease in urinary free cortisol.

b. Clinical features
   i. Disseminated intravascular coagulation (DIC)
   ii. Hypotension and shock
   iii. Acute adrenal insufficiency
   iv. Often fatal
c. Treatment: antibiotics and steroid replacement

5. **Addison disease (chronic adrenocortical insufficiency)**
   a. Definition: destruction of the adrenal cortex, leading to a deficiency of glucocorticoids, mineralocorticoids, and androgens
   b. Etiology
      i. Autoimmune adrenalitis
      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

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.

6. **Pheochromocytoma**
   a. Definition: uncommon tumor of the adrenal medulla, which produces catecholamines
   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)

I. MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES (MEN)

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
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
4. **MEN III (IIb)**
   a. Features medullary carcinoma of the thyroid, pheochromocytoma, and mucocutaneous neuromas
   b. Genetic mutation of RET proto-oncogene

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.

(Continued)

Chapter Summary (*continued*)

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, hypernatremia, and dehydration. SIADH is excessive production of ADH, resulting in oliguria, water retention, hyponatremia, and cerebral edema.

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* 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.

Review Questions

1. A 39-year-old man comes to the physician because of "facial changes" that relatives at a family reunion recognized. He says that he does not think that there is anything different about him, but his cousins that he had not seen in 10 years made him promise that he would get a "complete physical." On further questioning, he recalls that he has had to buy bigger shoes and gloves in the past few months. Physical examination shows a prominent jaw and a flat, broad forehead. Laboratory studies are most likely to show which of the following?

   A. Decreased thyroid stimulating hormone
   B. Decreased thyroxine
   C. Elevated ACTH
   D. Elevated parathyroid hormone
   E. Elevated somatomedin C

2. A 32-year-old woman undergoes a thyroidectomy because of papillary carcinoma. She is given thyroid replacement therapy to avoid the development of hypothyroidism. She returns to the physician a month after the surgery complaining of "sadness," generalized weakness, and muscle spasms. Gentle tapping over the facial nerve shows a facial twitch. Inflation of a blood pressure cuff above her systolic pressure for 3 minutes shows a carpopedal spasm. An electrocardiogram shows an increased QT interval. None of these findings were present before the surgery. Laboratory studies will most likely show which of the following?

   A. Hypercalcemia
   B. Hyperkalemia
   C. Hypermagnesemia
   D. Hypocalcemia
   E. Hypokalemia

Answers

1. **Answer: E.**

2. **Answer: D.**

Bone Pathology 26

A. NORMAL BONE

1. **Composition**
   a. Organic matrix
      i. Cells
      ii. Type I collagen (90% of bone protein)
      iii. Osteocalcin
      iv. Glycoproteins, proteoglycans, etc.
   b. Inorganic matrix
      i. Calcium hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$
      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's 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.

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.

B. 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)
   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 (OGI) ("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 26-1. 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 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 palsies
      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

C. 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
   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

7. 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
8. Complications
   a. AV shunts within marrow may result in high-output cardiac failure.
   b. Osteosarcoma
   c. Other sarcomas

D. 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's 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
   b. Weight-bearing exercise
   c. Calcium and vitamin D
   d. Biphosphonate (alendronate)
   e. Calcitonin

E. OSTEOMALACIA AND RICKETS

Note

Rickets and osteomalacia are disorders of osteoid mineralization; osteoid is produced in normal amounts but is not calcified properly.

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 undermineralized
   c. Enchondral bone formation is affected, leading to *skeletal deformities*
      i. Craniotabes 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. 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)

Clinical Correlate

The laboratory findings help distinguish osteomalacia from osteoporosis.

d. Lab
   i. Low serum calcium and phosphorus
   ii. High alkaline phosphatase

F. 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. *Involucrum:* 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. Intraosseous (Brodie) abscess
      iii. 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. Vertebral compression fracture
      ii. Psoas abscesses
      iii. Amyloidosis

G. 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

H. 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 growths 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 require 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

I. 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)
      iii. Patients with familial retinoblastoma have a high risk
   c. Clinical features: localized pain and swelling
   d. Classic x-ray findings
      i. *Codman's triangle* (periosteal elevation)
      ii. "Sunburst" pattern
      iii. Bone destruction
   e. Grossly
      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
   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. **Giant-cell tumor of bone ("osteoclastoma")**
   a. Uncommon malignant neoplasm containing multinucleated giant cells admixed with stromal cells
   b. Females > males; age 20–50
   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. Micro: 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
4. **Ewing sarcoma**
   a. 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)
   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). Cell 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, 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 pre-existing 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.

Osteomalacia (adults) and rickets (children) are both 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*) which may reach bone via blood, direct inoculation, or spread from nearby infection.

(Continued)

Chapter Summary (*continued*)

Complications include ischemic necrosis of bone, sequestrum formation, fracture, intraosseous abscess, 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.

Osteitis fibrosa cystica is the name for the generalized bone resorption with accompanying histologic changes seen in hyperparathyroidism; hemorrhage 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.

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).

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's 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 preexisting enchondroma, exostosis, or Paget disease. Giant-cell tumor of bone is an uncommon malignant 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." 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.

Review Questions

1. A 2-year-old boy is brought to the physician by his mother because she thinks he may have trouble hearing. She says he is having difficulty learning to speak because he probably cannot hear "a word anyone says to him." His aunt is deaf. The physician reviews the boy's chart and realizes that this patient has been in many times before due to multiple fractures. Physical examination shows small, discolored teeth, thin sclera with a blue hue, and multiple ecchymoses. Which of the following is the most likely diagnosis?

   A. Achondroplasia
   B. Child abuse
   C. Osteitis deformans
   D. Osteogenesis imperfecta
   E. Osteopetrosis

2. A 5-year-old boy is brought to the physician by his foster mother for a physical examination. She says that the boy moved into her house last week, and she just wants "to make sure that he receives the proper medical attention that a young child deserves." Physical examination shows an outward protrusion of the sternum and curvatures of the tibia and femur of both lower extremities, leading to a "bowing" appearance. Which of the following is the most likely cause of this patient's condition?

   A. Abnormal synthesis of type I collagen
   B. Deficiency of calcium
   C. Deficiency of vitamin D
   D. Mutation in fibroblast growth factor receptor 3
   E. Slow virus infection with paramyxovirus

Answers

1. **Answer: D.**

2. **Answer: C.**

Joint Pathology 27

Table 27-1. Osteoarthritis (OA) Versus Rheumatoid Arthritis (RA)

Osteoarthritis (OA)	Rheumatoid Arthritis (RA)
"Wear and tear"	Systemic autoimmune disease (+) Rheumatoid factor (+) Rheumatoid nodules
Degeneration of articular cartilage	Synovial proliferation
Weight-bearing joints • Knees, hips, spine	Small joints • Hands and feet
Asymmetrical	Symmetrical and migratory

A. OSTEOARTHRITIS (DEGENERATIVE JOINT DISEASE)

1. 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
2. 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
3. X-ray
   a. Narrowing of the joint space due to loss of cartilage
   b. Osteosclerosis and bone cysts
   c. *Osteophytes (osteophytic lipping)*
4. 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*

5. Pathology
   a. Weight-bearing joints → 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

B. 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
   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 cyst 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 pneumonoconiosis
   g. Amyloidosis

C. 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

Bridge to Biochemistry

Uric acid is the end product of purine metabolism.

In a Nutshell

Lesch-Nyhan Syndrome

- X-linked
- Deficiency of hypoxanthine-guanine phosphoribosyltransferase (HPRT)
- Mental retardation
- Spasticity
- Self-mutilating behaviors
- Hyperuricemia

D. 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. Age > 50
   b. Deposition of *calcium pyrophosphate crystals*
   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

E. INFECTIOUS 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's 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 chronica migrans*)
   d. Migratory arthritis involving the knees, shoulders, and elbows
   e. Histologically similar to rheumatoid arthritis
   f. CNS and cardiac involvement

Chapter Summary

Osteoarthritis 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 (osteophytes, called Heberden's nodes if they involve the DIP joints and Bouchard's 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, 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 which 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 chronica migrans) and may be accompanied or followed by CNS and cardiac involvement.

Review Questions

1. A 51-year-old man comes to the emergency department because of excruciating pain in his right knee. He describes the pain as so severe that it woke him from a deep sleep. He denies any similar episodes in the past. He has hypothyroidism and takes thyroid replacement therapy. He admits to a few "drinking binges" over the past 2 weeks. His temperature is 38.1°C (100.5°F), blood pressure is 130/90 mm Hg, and pulse is 80/min. Examination shows an erythematous, warm, swollen, and exquisitely tender right knee. Blood cultures are negative. Synovial fluid analysis shows positively birefringent, rhomboid-shaped crystals. Which of the following is the most likely diagnosis?

   A. Gonococcal arthritis
   B. Gout
   C. Lyme arthritis
   D. Pseudogout
   E. Psoriatic arthritis

2. A 21-year-old college student comes to the student health clinic with a 3-day history of fever, chills, a rash, and pain in her hips, hands, wrist, feet, and ankles. Severe knee pain and swelling began 24 h after the other joint pain. Her menstrual period began 2 days prior to the onset of this condition. Her temperature is 38.3°C (101°F). Physical examination shows hemorrhagic pustules on the trunk and extensor surfaces of the distal extremities and a swollen red left knee with a decreased range of motion. Joint fluid analysis shows:

Leukocyte count	90,000/μl
Neutrophils	90%

   Which of the following is the most likely diagnosis?

   A. Gonococcal arthritis
   B. Gout
   C. Lyme arthritis
   D. Pseudogout
   E. Reiter syndrome

Answers

1. **Answer: D.**

2. **Answer: A.**

Skeletal Muscle and Peripheral Nerve Pathology

28

A. SKELETAL MUSCLE

Table 28-1. Type I (Slow Twitch) Versus Type II (Fast Twitch) Muscles

	Type I	Type II
Twitch Rate	Slow twitch	Fast twitch
Function	Postural weight bearing Sustained tension	Purposeful movement Short, quick bursts
Metabolism	Aerobic (Krebs cycle)	Anaerobic (glycolysis)
Energy source	Fatty acids	Glycogen
Mitochondria	Many	Few
Color	Red	White
Fatigue	Slow fatigue	Rapid fatigue

Note

Skeletal muscle fiber type is determined by innervation.

B. INFLAMMATORY MYOPATHIES

1. **Polymyositis**
   a. Clinical presentation
      i. Adults
      ii. Bilateral proximal muscle weakness
   b. Micro
      i. Endomysial lymphocytic inflammation (mostly cytotoxic T8)
      ii. Skeletal muscle fiber degeneration and regeneration
2. **Dermatomyositis**
   a. Clinical presentation
      i. Children or adults
      ii. Bilateral proximal muscle weakness
      iii. Skin rash of the upper eyelids
      iv. Periorbital edema
   b. Micro
      i. Perimysial and vascular lymphocytic inflammation
      ii. *Perifascicular fiber atrophy*
      iii. Skeletal muscle fiber degeneration and regeneration
   c. Increased risk of lung, stomach, and ovarian cancers

3. **Inclusion body myositis**
   a. Clinical presentation
      i. Adults > age 50
      ii. Asymmetrical distal muscle weakness
   b. Micro: cytoplasmic vacuoles with basophilic granules and amyloid
   c. EM: filamentous inclusions

C. MYASTHENIC SYNDROMES

1. **Myasthenia gravis**
   a. Definition: autoimmune disease characterized by autoantibodies against the neuromuscular junction, resulting in muscular weakness

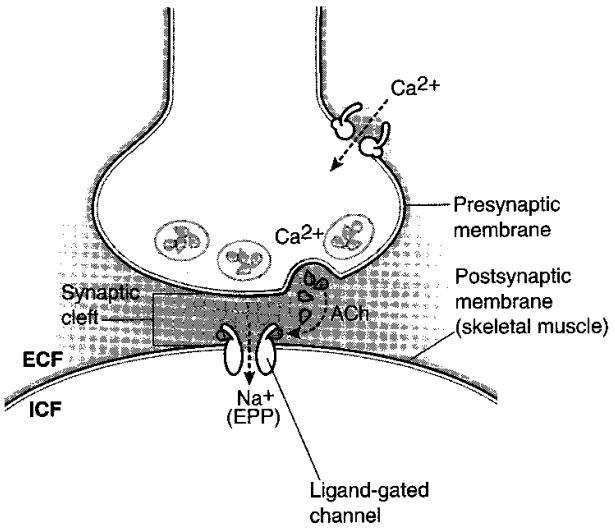


Figure 28-1. Neuromuscular Transmission

   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. 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 channel

D. MUSCULAR DYSTROPHY

1. **Duchenne muscular dystrophy**
   a. Most common and severe form of muscular dystrophy
   b. 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
   c. Clinical presentation
      i. Normal at birth with onset of symptoms by age 5
      ii. Progressive muscular weakness
      iii. Proximal weakness of shoulder and pelvic girdles
      iv. Calf pseudohypertrophy
      v. Heart failure and arrhythmias may occur
      vi. Respiratory insufficiency and pulmonary infections
   d. Lab: elevated serum creatine kinase
   e. Micro
      i. Muscle fibers of various sizes
      ii. Necrosis, degeneration, and regeneration of fibers
      iii. Fibrosis
      iv. Fatty infiltration
   f. Diagnosis
      i. Muscle biopsy: immunostains show decreased dystrophin protein
      ii. DNA analysis by PCR
2. **Becker muscular dystrophy**
   a. Less common and not as severe as Duchenne muscular dystrophy
   b. Mutation produces an altered dystrophin protein
   c. Later onset with variable progression
   d. Cardiac involvement is rare
   e. May have a relatively normal life span

E. INFLAMMATORY NEUROPATHY

1. **Guillain-Barré syndrome**
   a. Clinical presentation
      i. Preceded by a viral illness
      ii. Muscular weakness with an *ascending paralysis*
      iii. Loss of deep tendon reflexes
   b. Pathology: inflammation and demyelination of peripheral nerves and spinal nerve roots, resulting in muscular weakness
   c. Diagnosis
      i. Nerve conduction studies
      ii. Lumbar puncture: elevated protein
   d. Prognosis: fatal in 5% because of respiratory paralysis

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 2 (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 T8 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.

Review Questions

1. A previously healthy 39-year-old woman comes to the physician because she has been feeling "very weak lately." She says she is having difficulty brushing her hair and climbing stairs. She denies any change in vision or facial weakness. Physical examination shows bilateral proximal muscle weakness. A muscle biopsy shows endomysial lymphocytic inflammation. Which of the following is the most likely diagnosis?

   A. Dermatomyositis
   B. Eaton-Lambert syndrome
   C. Guillain Barré syndrome
   D. Myasthenia gravis
   E. Polymyositis

2. A 22-year-old woman comes to the physician because of a reddish-purple rash on her eyelids. She says that she has also been experiencing "arm weakness," which has forced her to quit her job as a hairdresser. Physical examination shows periorbital edema, a reddish-purple rash on her eyelids, and proximal muscle weakness. A muscle biopsy shows perifascicular fiber atrophy, perimysial and vascular lymphocytic inflammation, and skeletal muscle fiber degeneration and regeneration. This patient is at greatest risk for which of the following conditions?

   A. Endometritis
   B. Hepatitis
   C. Ovarian cancer
   D. Ovarian cysts
   E. Thymoma

Answers

1. **Answer: E.**

2. **Answer: C.**

Central Nervous System Pathology

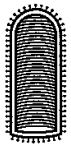
29

A. 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 29-1. CSF Parameters in Different Forms of Meningitis

Condition	Cells/μl	Glucose (μg/dl)	Proteins (mg/dl)	Pressure (mm H_2O)
Normal values	<5 lymphocytes	45–85 (50–70% glycemia)	15–45	70–180
Purulent (bacterial)	Up to 90,000 neutrophils	Decreased (<45)	Increased (>50)	Markedly elevated
Aseptic (viral)	100–1,000 most lymphocytes	Normal	Increased (>50)	Slightly elevated
Granulomatous (mycobacterial/ fungal)	100–1,000 most lymphocytes	Decreased (<45)	Increased (>50)	Moderately elevated



Rhabdovirus

3. **Viral encephalitides**
   a. Common features: perivascular cuffs, microglial nodules, neuron loss, and neuronophagia
   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 *vacuolar myelopathy:* similar to vitamin B12 deficiency–associated *subacute combined degeneration*
   d. *Progressive multifocal leukoencephalopathy* (PML)
      i. Related to *JC virus* (a polyomavirus)
      ii. JC virus causes PML in immunocompromised patients (especially AIDS)
      iii. Histopathology: demyelination, lymphohistiocytic, and astrogliosis
      iv. Astrocytes acquire bizarre shapes
      v. Oligodendrocytes in active lesions contain 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 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. **Creutzfeldt-Jacob Disease (CJD)**
   a. 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^c
      iv. In disease states, PrP^c changes to a β-pleated sheet conformation: PrP^{sc}
      v. Low spontaneous change results in sporadic cases of CJD
      vi. Mutations of PrP result in hereditary cases of CJD
      vii. PrP^{sc} facilitates conformational change of other PrP^c molecules into PrP^{sc}
      viii. PrP^{sc} is responsible for cerebral pathologic changes
   b. 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
   c. What are the clinical manifestations of spongiform encephalopathies?
      i. CJD: 85% cases are sporadic; 15% are familial
      ii. Middle-aged 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 29-2. Prion Diseases

Disease	Infectious Agent	Host	Comments
Kuru	Prion	Human	Subacute Spongiform Encephalopathy (SSE); Fore Tribe - New Guinea; consuming infected brains
Creutzfeldt-Jakob Disease	Prion	Human	SSE Genetic predisposition
Gerstmann-Straussler	Prion	Human	SSE
Fatal Familial Insomnia	Prion	Human	SSE
Scrapie	Prion	Sheep	SSE—scraping their wool off on fences

B. 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**
      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, 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. ***Infarction:*** **85% of all stroke cases**
      i. Thrombosis of cerebral artery (atherosclerosis-related)
      ii. Cardiogenic embolism
      iii. Small-vessel disease: arteriolosclerosis, amyloid angiopathy, etc.
   d. ***Hemorrhage:*** **15% of all stroke cases**
      i. Intracerebral
      ii. Subarachnoid
3. **Infarction**
   a. Thrombotic occlusion
      i. Due to atherosclerosis
      ii. Leads to *anemic* (white) infarct
   b. Embolic occlusion
      i. Often due to thromboemboli from cardiac chambers
      ii. Less frequently due to atheroemboli
      iii. Leads to *hemorrhagic* infarct
   c. Small-vessel disease
      i. Related to hypertension, resulting in hyaline arteriolosclerosis
      ii. Leads to *lacunar* infarcts or lacunae
   d. Pathology (ie, morphological features of brain infarcts)

Clinical Correlate

Strokes frequently occur in the middle cerebral artery territory.

Table 29-3. Gross and Microscopic Changes Associated with Cerebral Infarction

Time	Gross Changes	Microscopic Changes
0–12 h	No changes	Minimal or no changes
12–24 h	Minimal changes	Red (hypereosinophilic) neurons with pyknotic nuclei
24–48 h	Indistinct gray-white matter junction	Neutrophilic infiltration
2–10 d	Friable tissue with marked edema	Histiocytic infiltration; neurons disappear
2–3 wk	Tissue liquefies	Liquefactive necrosis; histiocytes filled with products of myelin breakdown
3 wk–mo	Fluid-filled cavity demarcated by gliotic scar	Fluid-filled cavity; reactive astrocytes and lipid-laden macrophages (gitter cells)
Years	Old cyst surrounded by gliotic scar	Astrogliosis surrounding a cyst

Note: Hemorrhagic infarct leads to erythrocyte degradation and hemosiderin deposition.

e. Clinical manifestations depend on affected artery

f. Common *neurovascular syndromes*

i. Anterior cerebral artery (ACA)
- Weakness and sensory loss in contralateral leg
- Transient expressive aphasia
- Abulia

ii. Middle cerebral artery (MCA)
- Contralateral hemiplegia (face and arm) and gaze palsy
- Contralateral sensory loss
- Aphasia if dominant hemisphere affected

iii. Posterior cerebral artery (PCA)
- Contralateral hemianopia or total cortical blindness if bilateral
- Alexia without agraphia
- Thalamic syndrome

iv. Dementia: due to recurrent infarcts or small vessel disease

4. **Hemorrhage**

a. Causes 15% of strokes

b. ***Intracerebral* (intraparenchymal) hemorrhage**

i. Hypertension: most frequent predisposing condition; involves basal ganglia, cerebellum, pons, and centrum semiovale

ii. Other causes: vascular malformations, especially *arteriovenous malformations* (AVMs), cerebral amyloid angiopathy, neoplasms, vasculitides, abnormal hemostasis, hematological malignancies, and infections

iii. Symptoms: severe headache, frequent nausea/vomiting, steady progression of symptoms over 15–20 minutes, and coma

c. ***Epidural* hemorrhage**
   i. Virtually always traumatic
   ii. Usually associated with skull fracture
   iii. Tear of dural arteries, most frequently *middle meningeal artery*
   iv. Leads to cerebral herniation (usually subfalcine) if not promptly evacuated
   v. Lucid interval before loss of consciousness ("*talk and die syndrome*")

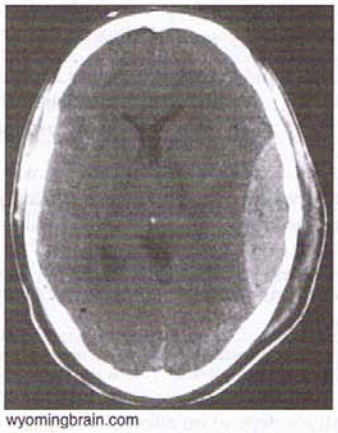


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Figure 29-1. Epidural Hematoma

d. ***Subdural* hemorrhage**
   i. Usually traumatic
   ii. Caused by rupture of *bridging veins* (from cerebral convexities to sagittal sinus)
   iii. Predisposing conditions: brain atrophy and abnormal hemostasis
   iv. Headache, drowsiness, focal neurological deficits, sometimes dementia
   v. Recurs frequently

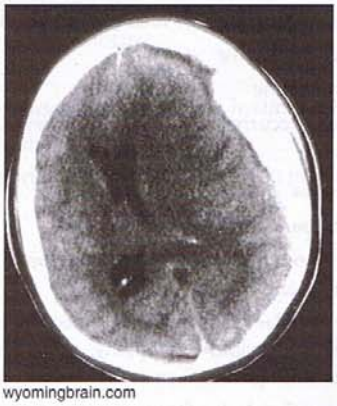

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Figure 29-2. Subdural Hematoma

e. **Subarachnoid hemorrhage**
   i. Most frequent cause: ruptured berry aneurysms
   ii. Less frequent causes: extension of an intracerebral or subdural hematoma, vascular malformations, trauma, abnormal hemostasis, and tumors
   iii. Sudden (*"thunderclap"*) headache, nuchal rigidity, neurological deficits on one side, and stupor

5. **Berry aneurysms**
   a. Thin-walled saccular outpouchings, consisting of intima and adventitia only
   b. Most frequent cause of subarachnoid hemorrhage
   c. Most frequent sites: anterior circle of Willis at branching points
   d. Pathogenesis: congenital focal weakness of artery; not identifiable at birth
   e. Associated disorders: Marfan syndrome, Ehlers-Danlos type 4, and adult polycystic kidney disease
   f. Hypertension and cigarette smoking predispose to formation
   g. Rupture is precipitated by sudden increase in blood pressure
   h. Prognosis after rupture: 1/3 die, 1/3 recover, and 1/3 rebleed

C. CNS TRAUMA

1. **Cranial cavity and brain**
   a. ***Concussion***
      i. Change in the momentum of the head (impact against a rigid surface)
      ii. Loss of consciousness and reflexes, temporary respiratory arrest, and amnesia for the event
      iii. Pathogenesis uncertain
      iv. Parenchymal injuries may or may not be evident at autopsy
   b. ***Contusions***
      i. Impact of parts of brain against inner calvarial surfaces
      ii. Bruising to the brain resulting from tissue and vessel disruption
      iii. Sites of injury: crests of orbital gyri in frontal and temporal poles
      iv. *Coup* (site of injury) and *contrecoup* (site diametrically opposite)
      v. Coup and contrecoup develop when the head is *mobile* at the time of impact
      vi. *Acute:* hemorrhage of brain tissue in a wedge-shaped area
      vii. *Subacute:* necrosis and liquefaction of brain
      viii. *Remote:* depressed area of cortex with yellow discoloration (*"plaque jaune"*)
   c. ***Diffuse axonal injury***
      i. Injury to the white matter due to acceleration/deceleration
      ii. Damage to axons at nodes of Ranvier with impairment of axoplasmic flow
      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. *Histopathology:* axonal swellings appreciable in the white matter

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. Cingulate gyrus is displaced underneath the falx to the opposite side
      ii. Compression of anterior cerebral artery
   b. **Transtentorial (uncal)**
      i. Uncus of the temporal lobe is displaced over the free edge of the tentorium
      ii. Compression of the third nerve
         • Pupillary dilatation on the same side
         • Infarct in dependent territory
      iii. Advanced stages: *Duret hemorrhage* within the central pons and midbrain
   c. **Cerebellar tonsillar**
      i. Displacement of cerebellar tonsils through the foramen magnum
      ii. Compression of medulla: cardiorespiratory arrest

D. 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. *Myelocele:* 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. Downward displacement of cerebellar tonsils
   b. Type 2
      i. Most often symptomatic

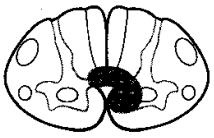
Note

Open neural tube defects (not spina bifida occulta) lead to increased alfa-fetoprotein during pregnancy, which, in conjunction with ultrasound, allows prenatal diagnosis.

ii. Faulty craniospinal junction, resulting in small posterior fossa, with
- Downward displacement of cerebellar vermis and medulla
- Compression of the fourth ventricle
- Obstructive hydrocephalus
- Frequent lumbar meningomyelocele

iii. Frequent association with syringomyelia

3. **Syringomyelia**
   a. Ependymal-lined, CSF-filled channel parallel to and connected with central canal (*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* enlarges progressively and destroys the spinal parenchyma
   e. Symptomatology: paralysis and loss of sensory functions



Syringomyelia

4. **Perinatal brain injury**
   a. 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

E. 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
      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, 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 deficits
ii. Chronic plaque: slower nerve conduction, allowing for partial recovery
iii. Recurrent attacks: progressive neurological deterioration

f. Clinical course
i. 85% 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 (brainstem 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. 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

F. 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 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. Autosomal dominant disorder characterized pathologically by degeneration of GABA-*nergic* 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
   iii. Pathophysiology: loss of caudate nucleus *GABA-nergic* neurons removes inhibitory influences on extrapyramidal circuits, thus leading to chorea
e. Clinical manifestations
   i. The disease manifests between age 20 and 40.
   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 29-4. The Dementias

Frequent Causes	Less Frequent Causes
Alzheimer disease	Pick disease
Dementia with Lewy bodies	Primary subcortical degenerations: Parkinson disease, multiple system atrophy, Huntington disease, progressive supranuclear palsy
Vascular dementia	Prion diseases (Creutzfeldt-Jacob)
Mixed Alzheimer and vascular	Normal pressure hydrocephalus dementia

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: epiphenomenon, 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 29-5. 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 allelelic 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. *Senile plaques:* 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
      - Granulovacuolar 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 SP-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. Aphasia (loss of language skills) and apraxia (loss of learned motor skills)
vi. Within 5–10 years, patients become mute and bedridden

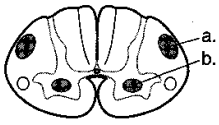
e. Treatment
i. No effective treatment available
ii. Mild improvement with inhibitors of acetylcholinesterase (e.g., *tacrine*)

4. **Dementia with Lewy bodies**
a. Etiopathogenesis: obscure, no known risk factors
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. Treatment: possible benefit from cholinesterase inhibitors
e. Clinical manifestations: memory loss, parkinsonism, and visual hallucinations

5. **Amyotrophic lateral sclerosis**
a. 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. Autosomal recessive disorder with onset in early childhood
b. Due to expansion of an unstable triplet nucleotide repeat in the *frataxin* gene
c. Degeneration involves the following groups of neurons
i. Dorsal root ganglia
ii. Clarke's column (origin of spinocerebellar tract)
iii. Neurons of posterior column of spinal cord
iv. Cranial nerve nuclei of VII, X, and XII



Amyotrophic lateral sclerosis (ALS)
a. Primary lateral sclerosis (corticospinal tract)
b. Progressive spinal muscular atrophy (ventral horn)

v. Dentate nucleus and Purkinje cells of cerebellum
vi. Betz neurons of primary motor cortex

d. 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.

G. 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 29-6. Differences Between Primary and Metastatic Tumors

Primary	Metastatic
Poorly circumscribed	Well circumscribed
Usually single	Often multiple
Location varies according to specific type	Usually located at the junction between gray and white matter

4. **Astrocytomas**
   a. Originate from astrocytes and exhibit
      i. Fibrillary background
      ii. Immunoreactivity for glial *f*ibrillary *a*cidic *p*rotein (GFAP)
      iii. Diffuse (ill-demarcated) pattern of growth
   b. ***Fibrillary astrocytomas***
      i. *Grading* is important for both prognosis and treatment. Most frequent systems in the United States and Europe: *Daumas-Duport* and *WHO*
      ii. Both systems identify four grades based on nuclear atypia (pleomorphism), mitoses, necrosis, and vascular endothelial hyperplasia (VEH)

Note

Glioblastoma multiforme has a tendency to cross the midline by involving the corpus callosum ("Butterfly glioma")

iii. Grade 1–2 astrocytomas are well differentiated astrocytomas
iv. Grade 3 astrocytomas are anaplastic astrocytomas
v. Grade 4 astrocytomas are called ***glioblastoma multiforme*** (GBM)
- GBM is the most common CNS primary malignancy
- Histology: marked nuclear atypia, mitoses, necrosis, and VEH
- Characteristic histopathological feature: areas of necrosis surrounded by rows of neoplastic cells (*pseudopalisading necrosis*)
- VEH is often florid, giving rise to *glomeruloid formations*

vi. Most common location: white matter, commonly in the centrum semiovale
vii. Well differentiated: affect younger patients and grow slowly
viii. Anaplastic astrocytomas and GBM: aggressive, affect older patients

c. **Pilocytic astrocytoma**
i. Benign astrocytic tumor of children and young adults
ii. Locations: posterior fossa (cerebellum) and diencephalon
iii. Often presents as a cystic lesion with a mural nodule
iv. 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
v. Favorable prognosis for posterior fossa tumors

5. **Oligodendroglioma**
a. 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 chickenwire 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. 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. 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 (*syncytial*)
      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 location may not be amenable to complete resection
8. **Primitive neuroectodermal tumors (PNET)**
   a. Highly undifferentiated; 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. 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
   e. Good prognosis after surgical resection
10. **Craniopharyngioma**
    a. 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,* the most common tumor of the tooth
    e. Benign but tends to recur after resection

Note

Bilateral acoustic schwannomas are pathognomonic of neurofibromatosis type 2.

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 streptococci 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 atypicals such as MAI, particularly in AIDS patients) meningoencephalitis causes tuberculomas of the basal surface of the brain and dura matter.

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 I (predilection for hemorrhagic necrosis of temporal lobes with viral inclusions), rabies (rare, Negri bodies in hippocampal and Purkinje neurons), and HIV (AIDS-dementia complex with microglial nodules and multinucleated giant cells, vacuolar myelopathy 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 abscess that may be seen on MRI/CT as ring-enhancing lesions. Cerebral abscess due to bacteria can complicate a variety of medical conditions (acute bacterial endocarditis, chronic pulmonary abscess, cyanotic heart disease with right to left shunt, mastoiditis, sinusitis, otitis, open fracture, prior neurosurgery) and causes increased intracranial pressure, focal neurologic defects, and a ring-enhancing lesion on CT/MRI.

Creutzfeldt-Jacob disease is caused by a conformational change in a prion protein that leads to spongiform change with kuru plaques in the neuropil; rapidly 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 clinicopathological 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 (reversible focal neurologic symptoms due to small platelet thrombi or atheroemboli), infarction (85% of strokes), and hemorrhage (15% of strokes).

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 hemianopia or total cortical blindness, alexia, thalamic syndrome), and dementia (secondary to recurrent infarcts or small vessel disease).

(Continued)

Chapter Summary (*continued*)

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 recurs), 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 to 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 contrecoup pattern, can cause local infarction), and diffuse axonal injury (sudden acceleration/deceleration stretches and "pops" axons, producing little gross injury, but coma from which recovery often never occurs). 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 Duret hemorrhage in brainstem), 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), meningomyelocele (with outpouching meninges, spinal cord, and spinal roots), and myelocele (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 meningomyelocele and syringomyelia (CSF-filled channel near central canal; most often related to Arnold-Chiari type 2).

Perinatal brain injury (risk factor prematurity) can cause cerebral palsy, germinal matrix hemorrhage, periventricular leukomalacia, and multicystic encephalopathy.

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 myelinosis is a rare, potentially fatal, focal demyelination of the basis pontis possibly related to over-rapid correction of hyponatremia in malnourished patients and alcoholics.

(Continued)

Chapter Summary (*continued*)

Parkinson disease is one of the degenerative and dementing 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 GABAergic neurons of the caudate nucleus, and clinically by chorea and dementia.

Alzheimer disease (60% of all cases of dementia) has increasing incidence with older age, is characterized by gross and microscopic brain abnormalities (atrophic brain with particular involvement of the hippocampus and temporal lobes, senile 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 bed-ridden 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 multiple areas of degeneration in the cerebellum, brain stem, and spinal cord, clinically producing gait ataxia, leading to a wheelchair-bound state by age five.

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 brain; subtype fibrillary with grade 1–2 being well differentiated, grade 3 being anaplastic, and grade 4 being aggressive glioblastoma multiforme; subtype pilocytic astrocytoma involving cerebellum or diencephalon of children and young adults and having a particularly good prognosis), oligodendroglioma (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, whorled cells, psammoma bodies, usually good prognosis), primitive neuroectodermal tumors (aggressive but therapy-responsive small basophilic 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).

Review Questions

1. An 18-year-old girl comes to the emergency department because of a severe headache and a stiff neck. She says that she has been studying for college finals over the past few days, and assumed that the headache was due to "all of the intense cramming," but when the neck pain started, she realized that this might be "a bit more serious." Her temperature is 39.4°C (103°F). Physical examination shows nuchal rigidity. A lumbar puncture is performed. Analysis of cerebrospinal fluid shows:

Neutrophils	90,000 /ml
Glucose	40 mg/dl
Protein	55 mg/dl
Pressure	200 mm H_2O

Which of the following is the most likely diagnosis?

A. Acute purulent meningitis
B. Cryptococcal meningitis
C. Rabies encephalitis
D. Enterovirus meningitis
E. Mycobacterial meningoencephalitis

2. A 54-year-old man with polycystic kidney disease comes to the emergency department because of the "most excruciating headache." He says that all he remembers is that he was at work, yelling at a "bratty teenager" while serving food in the local high school cafeteria, and then he woke up on the floor of the cafeteria kitchen. He says that he must have "passed out" because he would never lie down on "that dirty floor" by choice. Physical examination shows nuchal rigidity. A lumbar puncture is performed and shows xanthochromasia. Which of the following is the most likely diagnosis?

A. Acute purulent meningitis
B. Concussion
C. Intracerebral hemorrhage
D. Subarachnoid hemorrhage
E. Transient ischemic attack

Answers

1. **Answer: A.**

2. **Answer: D.**

Skin Pathology 30

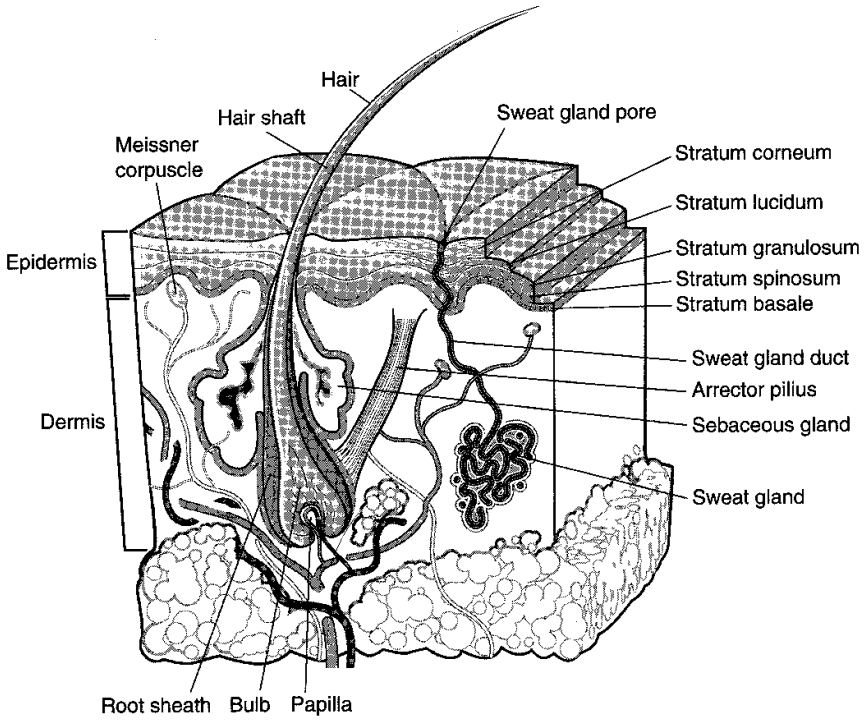


Figure 30-1. Skin

A. DISORDERS OF PIGMENTATION

1. **Vitiligo**
   a. 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. 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. Common in fair-skinned children
   b. Light brown macules on face, shoulders, and chest
   c. Darken and fade with the seasons (exposure to sunlight)
   d. Micro
      i. Increased melanin deposition in the basal cell layer of the epidermis
      ii. Normal number of melanocytes
4. **Benign lentigo**
   a. Benign, localized proliferation of melanocytes
   b. Small, oval, light brown macules
   c. Micro: linear melanocytic hyperplasia

B. MELANOCYTIC TUMORS

1. **Congenital nevi (birthmarks)**
   a. Present at birth
   b. Giant congenital nevi have increased risk of melanoma
2. **Nevocellular nevus (mole)**
   a. Benign tumor of melanocytes (nevus cells)
   b. Clearly related to sun exposure
   c. Types: 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. 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. Incidence
      i. Increasing at a rapid rate
      ii. Melanoma peaks in ages 40–70
   b. Risk factors
      i. Chronic sun exposure, sunburns

ii. Fair-skinned individuals
iii. Dysplastic nevus syndrome

c. Gross
i. Asymmetric, irregular borders, variegated color, large diameter, enlarging, macule, papule, or nodule
ii. Males: upper back; females: back and legs

d. Lentigo maligna melanoma
i. Older age; usually on the face or neck
ii. Best prognosis

e. Superficial spreading melanoma
i. Overall, most common type
ii. Primarily horizontal growth pattern

f. Acral-lentiginous melanoma
i. Most common melanoma in dark-skinned individuals
ii. Affects palms, soles, and subungual area

g. Nodular melanoma
i. Nodular tumor with a vertical growth pattern
ii. Worst prognosis of the melanomas

h. Prognosis
i. Staging is by depth of invasion (vertical growth)
- Breslow's thickness
- Clark's levels

i. Treatment
i. Wide surgical excision
ii. Systemic disease is treated with chemotherapy or immunotherapy
iii. May resolve spontaneously

C. BENIGN EPIDERMAL AND DERMAL LESIONS

1. **Acanthosis nigricans**
a. Thickened, hyperpigmented skin in axillae and groin
b. Associated with internal malignancy

2. **Seborrheic keratoses**
a. Benign squamoproliferative 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-Trélat (paraneoplastic syndrome): sudden development of multiple lesions may accompany an underlying malignancy

3. **Psoriasis**
   a. Epidemiology
      i. Affects 1% of the U.S. population
      ii. Most common form is psoriasis vulgaris
      iii. Unknown etiology
      iv. Clear genetic component
      v. May be associated with arthritis, enteropathy, and myopathy
   b. Gross
      i. Common sites: knees, elbows, and scalp
      ii. Gross: well demarcated *erythematous plaques with a silvery scale*
      iii. Auspitz sign: removal of scale results in pinpoint bleeding
      iv. Nail beds show pitting and discoloration
   c. Pathogenesis: increased epidermal turnover
   d. 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*
   e. Treatment
      i. Topical steroids and ultraviolet irradiation
      ii. Severe systemic disease may be treated with methotrexate

D. 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 UV-B)
      ii. Fair complexion
      iii. Chronic skin ulcers or sinus tracts
      iv. Long-term exposure to hydrocarbons, arsenic, burns, radiation
      v. Immunosuppression
      vi. Xeroderma pigmentosa
   c. Precursors
      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. Nests 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 United States
   b. Most common in middle-aged or elderly individuals
   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 basaloid 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. 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
   d. Electron microscopy: cytoplasmic ***Birbeck granules*** (tennis-racket–shaped)

4. **Mycosis fungoides (cutaneous T-cell lymphoma)**
   a. Adults (age >40); M > F
   b. Gross: rash of scaly red patches, plaques, or nodules
   c. Common sites: trunk, extremities, face
   d. Micro
      i. Superficial dermal infiltrate of T lymphocytes
      ii. *Epidermotropism:* tendency to invade the epidermis
      iii. *Pautrier microabscesses:* collections of lymphocytes within the epidermis
   e. *Sézary syndrome:* blood involvement

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 lentigos (like freckles but not under control of sun exposure).

Melanocytic tumors include congenital nevi (birth marks, giant ones have increased risk of melanoma), nevocellular nevi (common moles with proliferating nevus cells; subclassified as junctional, compound, and intradermal), dysplastic nevi (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 asymmetric, 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-lentiginous 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 axillae and groin that may be associated with internal malignancy), seborrheic keratoses (very common benign squamo-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).

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 metastasize but may be locally aggressive), histiocytosis X (proliferation of Birbeck granule-containing Langerhans cells of skin; unifocal variant: eosinophilic granuloma, multifocal variant: Hand-Schuller-Christian disease, acute disseminated: Letterer-Siwe syndrome), and mycosis fungoides (cutaneous T-cell lymphoma with superficial dermal infiltrate of T lymphocytes and epidermotropism with Pautrier microabscesses; rash, plaques, or nodules; can have blood involvement know as Sezary syndrome).

Review Questions

1. A 72-year old man comes to the physician because of a lesion on the side of his forehead. He has had the lesion for "a long time," but he came to the office today because his youngest son is getting married in a few months, and his son's fiancée asked him to get it removed so she does not have to see the "ugly growth" in her wedding pictures. On physical examination, the lesion is a 1.5-cm brown plaque with an adherent greasy scale. It appears to be "stuck-on." Histologic evaluation shows "horn cysts." Which of the following is the most likely diagnosis?

   A. Acanthosis nigricans
   B. Actinic keratoses
   C. Basal cell carcinoma
   D. Malignant melanoma
   E. Seborrheic keratoses
   F. Squamous cell carcinoma

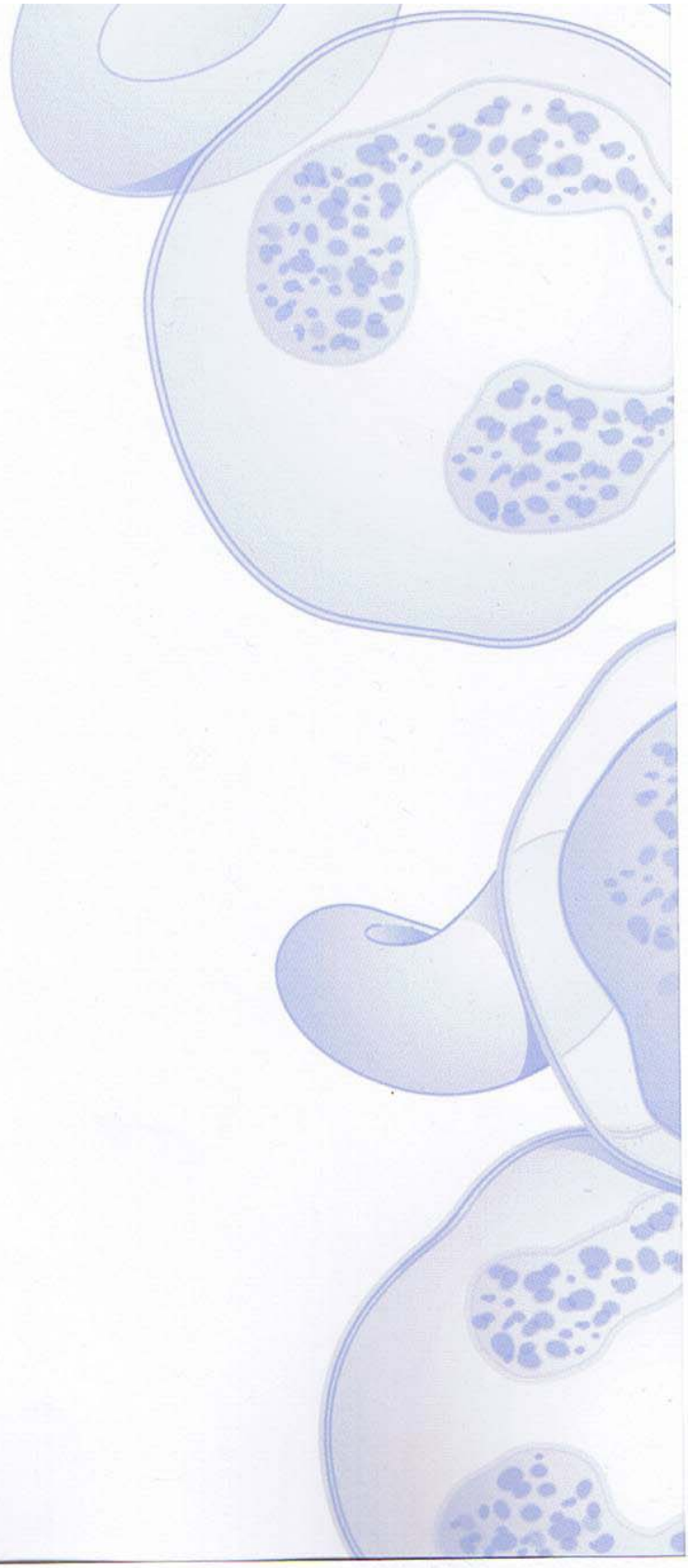
2. A 58-year-old man comes the physician because of an ulcer on his lower lip. The lesion has been there for about 6 months, but lately it has been very "crusty." It started bleeding last week, and his wife scheduled this appointment. Physical examination shows a 1.3-cm hyperkeratotic and eroded plaque on his lower lip. Microscopic evaluation will most likely show which of the following?

   A. Basaloid epidermal hyperplasia and keratin-filled epidermal pseudocysts
   B. Epidermal hyperplasia, elongation of rete ridges, and Munro microabscesses
   C. Invasive nests of basaloid cells with a palisading growth pattern
   D. Nests of atypical keratinocytes, keratin pearls, and intercellular bridges
   E. Pautrier microabscesses and superficial dermal infiltrate of T lymphocytes

Answers

1. **Answer: E.**

2. **Answer: D.**



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