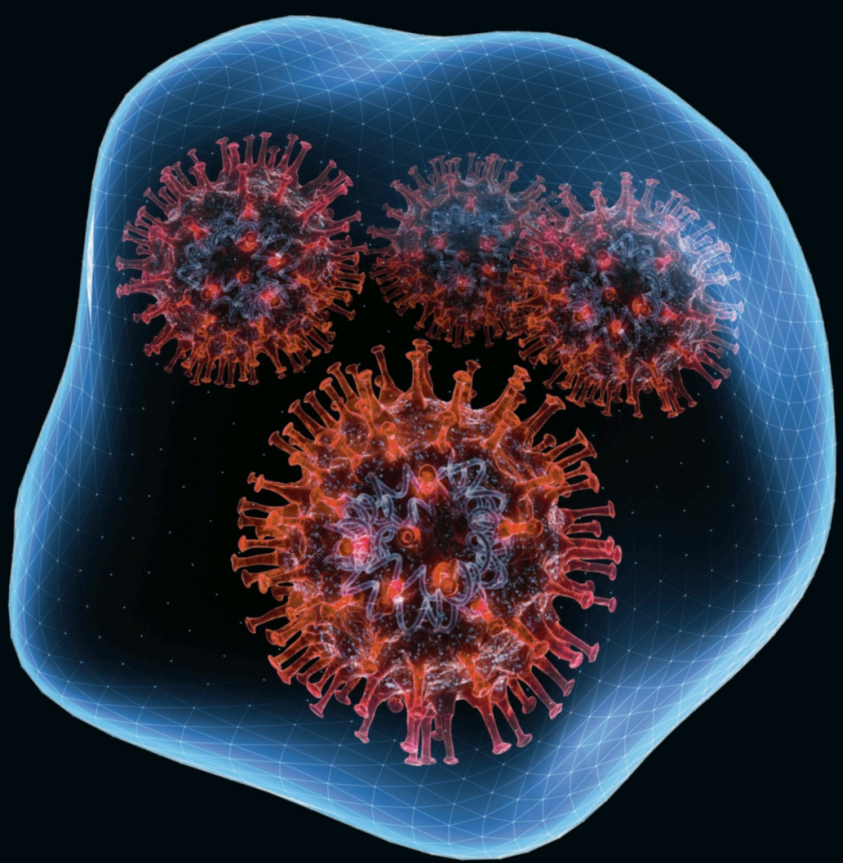
KAPLAN MEDICAL

PRECLINICAL PATHOLOGY REVIEW 2023



FOR USMLE® STEP 1 AND COMLEX-USA® LEVEL 1

USMLE® and United States Medical Licensing Examination® is a joint program of the National Board of Medical Examiners (NBME) and the Federation of State Medical Boards (FSMB), which are not affiliated with Kaplan and were not involved in the production of, and do not endorse, this product. COMLEX-USA® is a registered trademark of the National Board of Osteopathic Medical Examiners, Inc. (NBOME), which is not affiliated with Kaplan and was not involved in the production of, and does not endorse, this product.

KAPLAN MEDICAL

PRECLINICAL PATHOLOGY REVIEW 2023

FOR USMLE® STEP 1 AND COMLEX-USA® LEVEL 1

USMLE® and United States Medical Licensing Examination® is a joint program of the National Board of Medical Examiners (NBME) and the Federation of State Medical Boards (FSMB), which are not affiliated with Kaplan and were not involved in the production of, and do not endorse, this product.
COMLEX-USA® is a registered trademark of the National Board of Osteopathic Medical Examiners, Inc. (NBOME), which is not affiliated with Kaplan and was not involved in the production of, and does not endorse, this product.

USMLE® and United States Medical Licensing Examination® is a joint program of the National Board of Medical Examiners (NBME) and the Federation of State Medical Boards (FSMB), which are not affiliated with Kaplan and were not involved in the production of, and do not endorse, this product.

COMLEX-USA® is a registered trademark of the National Board of Osteopathic Medical Examiners, Inc. (NBOME), which is not affiliated with Kaplan and was not involved in the production of, and does not endorse, this product.

This publication is designed to provide accurate information in regard to the subject matter covered as of its publication date, with the understanding that knowledge and best practice constantly evolve. The publisher is not engaged in rendering medical, legal, accounting, or other professional service. If medical or legal advice or other expert assistance is required, the services of a competent professional should be sought. This publication is not intended for use in clinical practice or the delivery of medical care. To the fullest extent of the law, neither the Publisher nor the Editors assume any liability for any injury and/or damage to persons or property arising out of or related to any use of the material contained in this book.

© 2023 by Kaplan North America, LLC

Published by Kaplan Medical, a division of Kaplan North America, LLC.
1515 W Cypress Creek Road
Fort Lauderdale, FL 33309

All rights reserved. The text of this publication, or any part thereof, may not be reproduced in any manner whatsoever without written permission from the publisher.

10 9 8 7 6 5 4 3 2 1

Course ISBN: 978-1-5062-8454-5

All rights reserved under International and Pan-American Copyright Conventions. By payment of the required fees, you have been granted the non-exclusive, non-transferable right to access and read the text of this eBook on screen. No part of this text may be reproduced, transmitted, downloaded, decompiled, reverse engineered, or stored in or introduced into any information storage and retrieval system, in any form or by any means, whether electronic or mechanical, now known or hereinafter invented, without the express written permission of the publisher.

Editors

John Barone, MD
Anatomic and Clinical Pathologist
Beverly Hills, CA

Manuel A. Castro, MD, AAHIVS
Diplomate of the American Board of Internal Medicine
Certified by the American Academy of HIV Medicine
Wilton Manors, FL

The editors would like to acknowledge ***Henry Sanchez, MD*** *(UCSF, San Francisco),* ***Alexis Peedin, MD,*** *and* ***Mona Wood, MD*** *for their invaluable contributions.*

KP00710.indb 3 13/10/22 1:51 PM

We want to hear what you think. What do you like or not like about the Notes?
Please email us at **medfeedback@kaplan.com**.

KP00710.indb 4 13/10/22 1:51 PM

Table of Contents

CHAPTER 1: Fundamentals of Pathology 1

CHAPTER 2: Cellular Injury and Adaptation 5

CHAPTER 3: Inflammation 15

CHAPTER 4: Tissue Repair 23

CHAPTER 5: Circulatory Pathology 27

CHAPTER 6: Genetic Disorders and Disorders of Sexual Development 39

CHAPTER 7: Immunopathology 53

CHAPTER 8: Amyloidosis 63

CHAPTER 9: Principles of Neoplasia 65

CHAPTER 10: Skin Pathology 75

CHAPTER 11: Red Blood Cell Pathology: Anemias 87

CHAPTER 12: Vascular Pathology 97

CHAPTER 13: Cardiac Pathology 105

CHAPTER 14: Pulmonary Pathology 119

CHAPTER 15: Renal Pathology 137

CHAPTER 16: Gastrointestinal Tract Pathology 155

CHAPTER 17: Pancreatic Pathology 167

CHAPTER 18: Gallbladder and Biliary Tract Pathology 171

CHAPTER 19: Liver Pathology 175

CHAPTER 20: Central Nervous System Pathology 185

KP00710.indb 5 13/10/22 1:51 PM

CHAPTER 21: Hematopoietic Pathology: White Blood Cell Disorders & Lymphoid and Myeloid Neoplasms 205

CHAPTER 22: Female Genital Pathology 219

CHAPTER 23: Breast Pathology 231

CHAPTER 24: Male Pathology 237

CHAPTER 25: Endocrine Pathology 243

CHAPTER 26: Bone Pathology 253

CHAPTER 27: Joint Pathology 263

CHAPTER 28: Soft Tissue and Peripheral Nerve Pathology 269

INDEX 277

KP00710.indb 6 13/10/22 1:51 PM

Fundamentals of Pathology

1

LEARNING OBJECTIVES

- ❑ Define the etiology, pathogenesis, morphology, and clinical significance of disease
- ❑ List techniques for staining pathologic specimens
- ❑ Understand the stains used to identify specific structures

Pathology is the study of all aspects of disease, i.e. symptoms/signs, pathogenesis, complications, and morphologic consequences (including structural, functional and molecular alterations in cells, tissues, and organs).

Morphologic changes of the disease process include both gross changes and microscopic changes.

NOTE

The **etiology** (cause) of a disease may be genetic or environmental. The **pathogenesis** of a disease defines the temporal sequence and patterns of cellular injury lead to disease. The **clinical significance** of a disease relates to its signs and symptoms, disease course including complications, and prognosis.

DIAGNOSTIC TECHNIQUES

Gross examination of organs (on exam questions) is done in 2 steps: identify the organ and then identify the pathologic abnormality (e.g., nodules in a cirrhotic liver, necrotic tumor in a lung).

Gross features that may contribute to making a diagnosis include size, shape, consistency, and color of the tissue/organ. Tissue sections from the organ are submitted for microscopic examination to make the ultimate diagnosis.

The following techniques are used to help examine microscopic sections of tissue. A single specimen may require multiple slides so that various stains/ techniques can be applied and help to confirm the diagnosis.

- Histochemical stains, which use chemical reactions to highlight various structures or pathogens
- Hematoxylin & eosin (H&E) stain (**gold standard for histological evaluation**), in which hematoxylin binds nucleic acids and calcium salts, while eosin stains both extracellular and intracellular proteins)
- Immunohistochemical (antibody) stains (**usually dark brown = positive**)
  - Cytokeratin (stains epithelial cells)
  - Vimentin (stains cells of mesenchymal origin except the 3 muscle types; stains many sarcomas)
  - Desmin (stains smooth, cardiac, and skeletal myosin), prostate specific antigen, and many others

NOTE

The term "eosinophilic" is often used in pathology to refer to cells that are very pink.

NOTE

Reticulin and trichrome help to identify nodules of fibrosis in the cirrhotic liver.

KP00710.indb 1 13/10/22 1:51 PM

- Ancillary studies used on tissue sections
  - Immunofluorescence microscopy (IFM), used for renal and autoimmune disease
  - Transmission electron microscopy (EM), used for renal disease, neoplasms, infections, and genetic disorders
- Molecular techniques used on fresh and formalin-fixed tissue
  - Protein electrophoresis
  - Southern and Western blots
  - Polymerase chain reaction (PCR)
  - Next-generation sequencing (NGS)
  - Cytogenetic analysis (karyotyping, in situ hybridization studies)

HISTOCHEMICAL STAINS

Table 1-1. Structures Stained by H&E

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

KP00710.indb 2 13/10/22 1:51 PM

Table 1-2. Histochemical Stains and Select Diseases in which they might be Positive

Stain	Target	Select Associated Disease States
Prussian Blue	Iron	Hemochromatosis, hemosiderosis
Congo Red	Amyloid	Amyloidosis
Acid fast (Ziehl-Neelsen, Fite)	Acid-fast bacilli	*M. tuberculosis*, MAC infections
Periodic acid-Schiff (PAS)	Molecules with high-carbohydrate content	Candida, α1-antitrypsin deficiency (hepatocytes), glycogen storage diseases, diabetic nephropathy (Kimmelstiel-Wilson nodules)
Trichrome	Connective tissue, type IV collagen	Cirrhosis, crescentic glomerulonephritis
Reticulin	Type III collagen	Cirrhosis, myelofibrosis

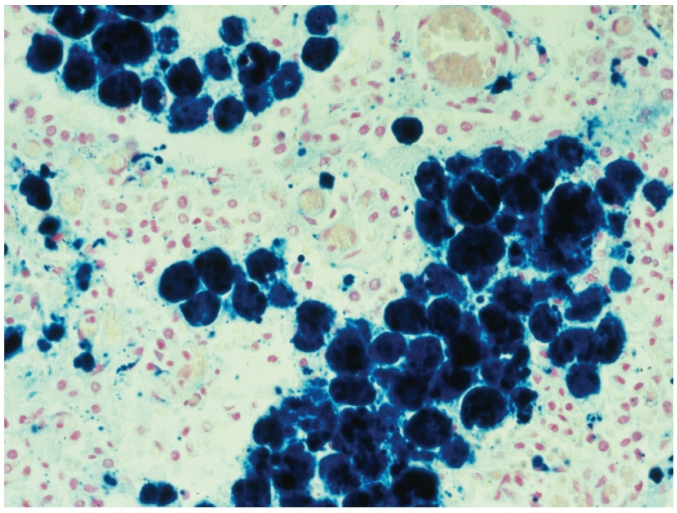


Figure 1-1. Prussian Blue Stain Shows Hemosiderin Caused by RBC Breakdown within Macrophages

KP00710.indb 3 13/10/22 1:51 PM

Cellular Injury and Adaptation

2

LEARNING OBJECTIVES

- ❑ Explain causes of cellular injury
- ❑ Demonstrate understanding of cellular changes during injury and cell death
- ❑ Answer questions about cellular adaptive responses to injury
- ❑ Describe cellular alterations during injury

CELLULAR INJURY

Causes of Cellular Injury

- **Hypoxia** (**most common**) occurs when lack of oxygen prevents the cell from synthesizing sufficient ATP by aerobic oxidation. Major mechanisms of hypoxia are ischemia, cardiopulmonary failure, and decreased O_2-carrying capacity of the blood (e.g., anemia). **Ischemia**, due to a loss of blood supply, is the most common cause of hypoxia and is typically related to a decrease in arterial flow or venous outflow (e.g., atherosclerosis, thrombus, thromboembolus).
- **Pathogens** (viruses, bacteria, parasites, fungi, and prions) can injure the body by direct infection of cells, production of toxins, or host inflammatory response.
- **Immunologic dysfunction** includes hypersensitivity reactions and autoimmune diseases.
- **Genetic abnormalities** cause congenital disorders, e.g., lysosomal storage disorders, which cause intracellular accumulations of proteins, triggering cell death.
- **Chemical injury** can occur with drugs, poisons (cyanide, arsenic, mercury, etc.), pollution, occupational exposure (CCl4, asbestos, carbon monoxide, etc.), and social/lifestyle choices (alcohol, smoking, IV drug abuse, etc.).
- **Physical injury** includes trauma (blunt/penetrating/crush injuries, gunshot wounds, etc.), burns, frostbite, radiation, and pressure changes.
- **Nutritional or vitamin imbalance**
  - **Inadequate calorie/protein intake** can cause marasmus (decrease in total caloric intake causes adipose stores to be depleted so skeletal muscles is used, leading to muscle wasting i.e. cachexia) and kwashiorkor (decrease in total protein intake, leading to edema and abdominal distension).

KP00710.indb 5 13/10/22 1:51 PM

- **Excess caloric intake** can cause obesity (**second leading cause of premature preventable death in the United States**) and atherosclerosis.
- **Vitamin deficiencies** can be seen with vitamin A (night blindness, squamous metaplasia, immune deficiency), vitamin C (scurvy), vitamin D (rickets and osteomalacia), vitamin K (bleeding diathesis), vitamin B12 (megaloblastic anemia, neuropathy, and spinal cord degeneration), folate (megaloblastic anemia and neural tube defects), and niacin (pellagra [diarrhea, dermatitis, and dementia]).
- **Hypervitaminosis** (uncommon) can result in tissue-specific abnormalities.

NOTE

Risk factors for vitamin K deficiency include prematurity (neonates) and fat malabsorption syndromes (cystic fibrosis, celiac disease)



Figure 2-1. Radiograph of a Child with Rickets Shows Bowed Legs

Cellular Changes During Injury

Cellular responses to injury include adaptation (hypertrophy or atrophy; hyperplasia or metaplasia), reversible injury, and irreversible injury and eventual cell death (necrosis, apoptosis, or necroptosis).

The cellular response to injury depends on several important factors, including type of cell injured and the cell's ability to adapt.

KP00710.indb 6 13/10/22 1:51 PM

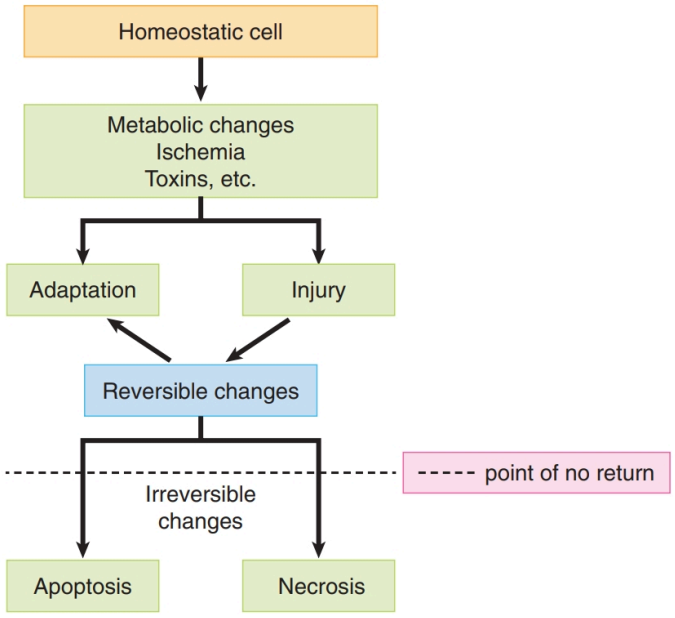


Figure 2-2. Cellular Response to Stress and Injurious Stimuli

Important intracellular targets and their mechanisms of cell injury are as follows:

- Damage to DNA, proteins, lipid membranes, and circulating lipids (LDL) can be caused by oxygen-derived free radicals, including superoxide anion ($O_2^{\bullet -}$), hydroxyl radical (•OH), and hydrogen peroxide (H_2O_2).
- Several key biochemical pathways are dependent on ATP. Disruption of Na^+/K^+ or Ca^{++} pumps cause imbalances in solute concentrations. Additionally, ATP depletion increases anaerobic glycolysis that leads to a decrease in cellular pH. Chronic ATP depletion causes morphological and functional changes to the ER and ribosomes.
- Several defects can lead to movement of fluids into the cell, including formation of the membrane attack complex via complement, breakdown of Na^+/K^+ gradients (i.e., causing sodium to enter or potassium to leave the cell), etc.
- Influx of calcium can cause problems because calcium is a second messenger, which can activate a wide spectrum of enzymes. These enzymes include proteases (protein breakdown), ATPases (contributes to ATP depletion), phospholipases (cell membrane injury), and endonucleases (DNA damage).
- Mitochondrial dysfunction causes decreased oxidative phosphorylation and ATP production, formation of mitochondrial permeability transition (MPT) channels, and release of cytochrome c (a trigger for apoptosis).

NOTE

Protective factors against free radicals include:

- Antioxidants

  (vitamins A, E, C)
- Superoxide dismutase (converts superoxide → hydrogen peroxide)
- Glutathione peroxidase (converts hydroxyl ions or hydrogen peroxide → water)
- Catalase (converts hydrogen peroxide → oxygen and water)

KP00710.indb 7 13/10/22 1:51 PM

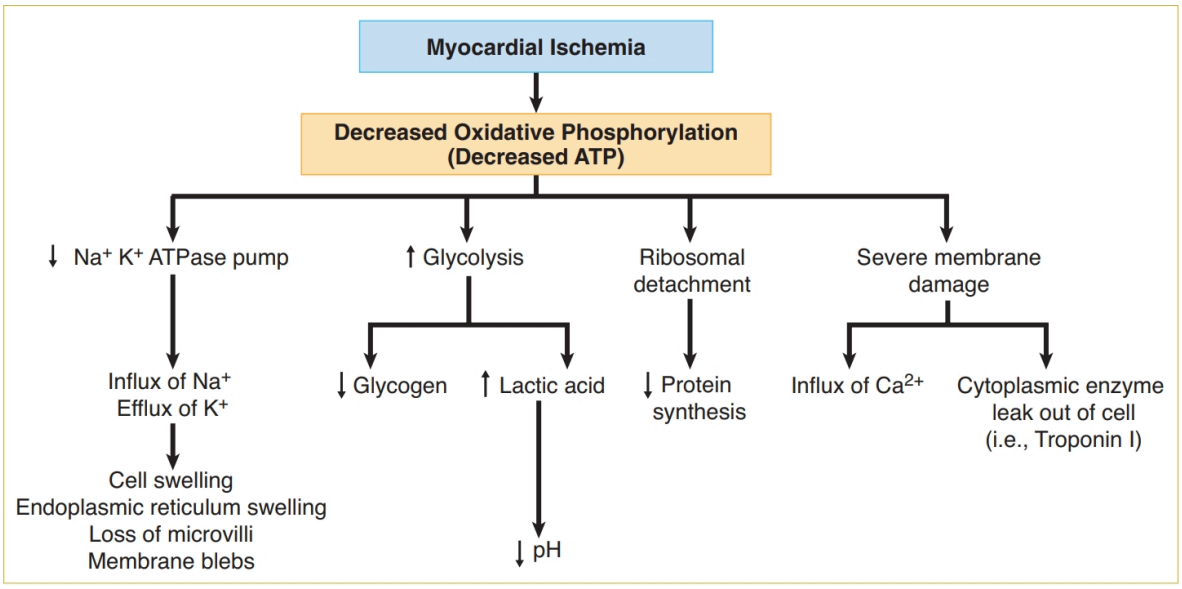


Figure 2-3. Classic Example of Cellular Injury Caused by Hypoxia

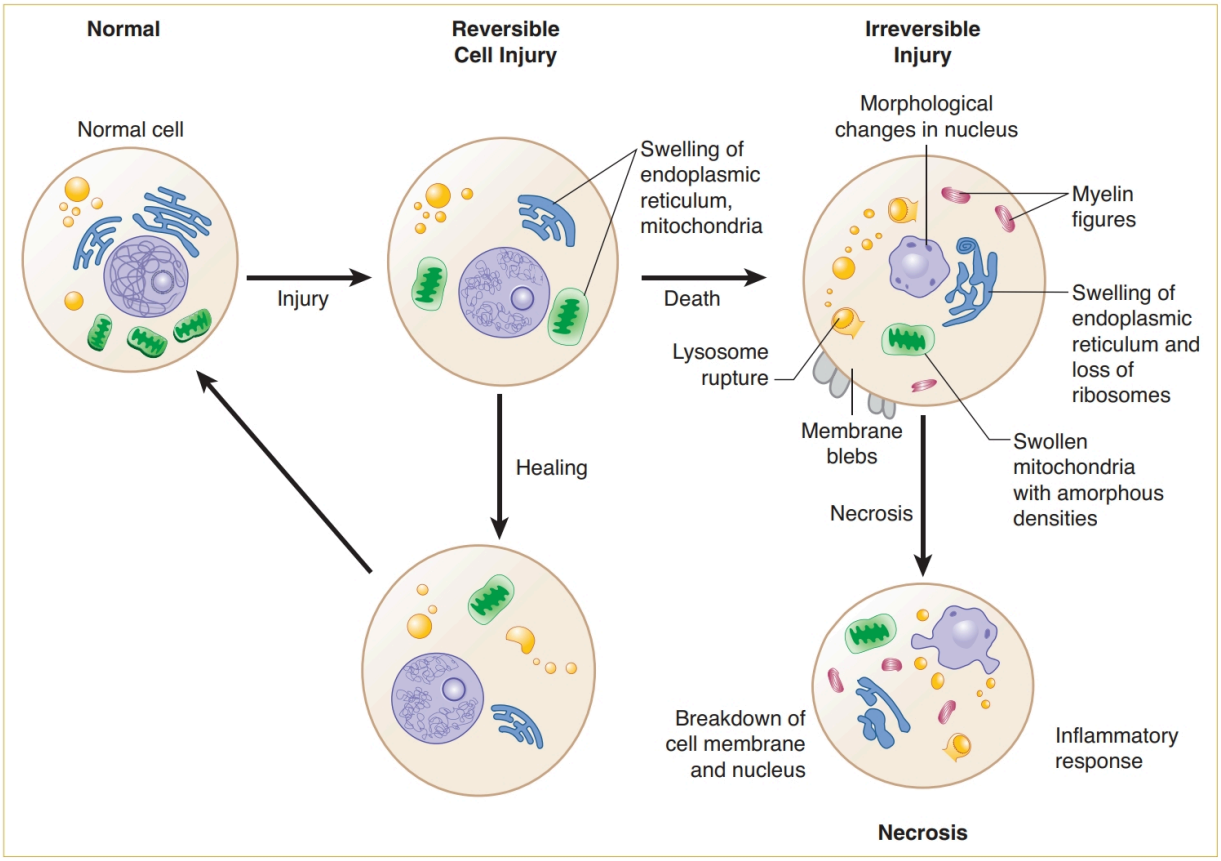


Figure 2-4. Cell Injury

KP00710.indb 8 13/10/22 1:51 PM

Reversible cell injury:

- **Decreased synthesis of ATP** by oxidative phosphorylation.
- **Decreased function of Na^+K^+ ATPase membrane pumps**, which in turn causes influx of Na^+ and water, efflux of K^+, cellular swelling (hydropic swelling), and swelling of the endoplasmic reticulum.
- The **switch to anaerobic glycolysis** results in depletion of cytoplasmic glycogen, increased lactic acid production, and decreased intracellular pH.
- **Decreased protein synthesis** leads to detachment of ribosomes from the rough endoplasmic reticulum.
- **Plasma-membrane blebs and myelin figures** may be seen.

Irreversible cell injury:

- **Severe membrane damage** plays a critical role in irreversible injury, allows a massive influx of calcium into the cell, and allows efflux of intracellular enzymes and proteins into the circulation.
- **Marked mitochondrial dysfunction** produces mitochondrial swelling, large densities seen within the mitochondrial matrix, irreparable damage of the oxidative phosphorylation pathway, and an inability to produce ATP.
- **Rupture of the lysosomes** causes release of lysosomal digestive enzymes into the cytosol and activation of acid hydrolases followed by autolysis.
- **Nuclear changes** can include pyknosis (degeneration and condensation of nuclear chromatin), karyorrhexis (nuclear fragmentation), and karyolysis (dissolution of the nucleus).

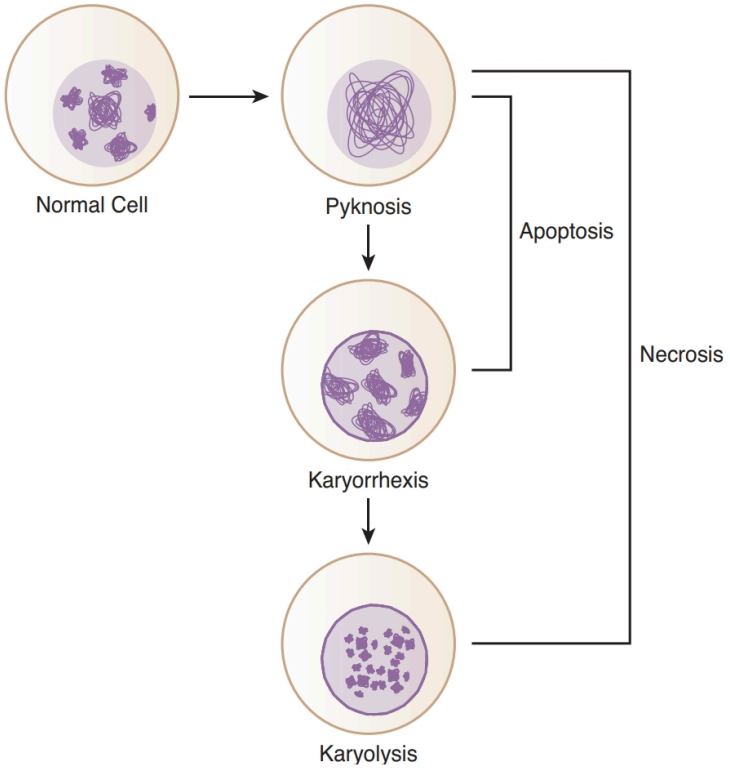


Figure 2-5. Nuclear Changes in Irreversible Cell Injury

NOTE

Reversible and irreversible changes represent a spectrum, and any reversible change can become irreversible.

CLINICAL CORRELATE

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

- Myocardial injury: troponin (**most specific**), CPK-MB, lactate dehydrogenase (LDH)
- Hepatitis: transaminases (aspartate transaminase [AST], alanine transaminase [ALT])
- Pancreatitis: amylase and lipase
- Hepatobiliary injury: alkaline phosphatase, gamma-glutamyltransferase (GGT)

KP00710.indb 9 13/10/22 1:51 PM

CELL DEATH

Cell Death with an Inflammatory Response

Morphologic types of necrosis (cell death in living tissue, often with an inflammatory response) are as follows:

- **Coagulative necrosis** (**most common**) results from ischemic injury (infarct). It is caused by the denaturing of proteins within the cytoplasm.
  - Microscopic examination shows loss of nucleus but preserved cellular shape
  - Common in most organs, including the heart, liver, and kidney, but not the brain
- **Liquefaction necrosis** results from cellular destruction by hydrolytic enzymes.
  - Leads to autolysis (release of proteolytic enzymes from injured cells) and heterolysis (release of proteolytic enzymes from inflammatory cells)
  - Common in abscesses, brain infarcts, and pancreatic necrosis
- **Caseous necrosis** is a combination of coagulation and liquefaction necrosis.
  - Gross appearance is soft, friable, and "cheese-like"
  - Characteristic of granulomatous diseases, including TB
- **Fat necrosis** is caused by the action of lipases on adipocytes.
  - Gross appearance is chalky and white
  - Characteristic of acute pancreatitis
- **Fibrinoid necrosis** is a form of necrotic connective tissue that histologically resembles fibrin.
  - Microscopic examination shows eosinophilic (pink) homogeneous appearance
  - Often caused by acute immunologic injury (e.g., hypersensitivity type reactions II and III) and vascular hypertensive damage
- **Gangrenous necrosis** is a gross term used to describe dead tissue.
  - Commonly seen in lower limbs, gallbladder, GI tract, testes
  - Microscopically, **dry gangrene** is associated with coagulative necrosis, while **wet gangrene** is associated with liquefactive necrosis.

NOTE

Liquefaction by leukocyte enzymes is called "suppuration," and the resultant fluid is called "purulent material" (or pus).

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), which are chalky white on gross examination.

KP00710.indb 10 13/10/22 1:51 PM



© Richard P. Usatine, MD Used with permission.

Figure 2-6. Gangrenous Necrosis Affects the First and Third Toes of a Diabetic Foot

Cell Death without an Inflammatory Response

Apoptosis is a specialized form of programmed cell death without an inflammatory response. It is an active process regulated by proteins, and often affects only single cells or small groups of cells.

- In **morphologic appearance,** the cell shrinks in size and has dense eosinophilic cytoplasm. Next, nuclear chromatin condensation (pyknosis) is seen that is followed by fragmentation of the nucleus (karyorrhexis). Cytoplasmic membrane blebs form next, leading eventually to a breakdown of the cell into fragments (apoptotic bodies). Macrophages then phagocytose the apoptotic bodies.
- **Stimuli for apoptosis include:**
  - Cell injury and DNA damage (radiation causing irreparable DNA damage)
  - Physiologic reduction in hormone or growth factor (progesterone level falls in late luteal phase, causing apoptosis of endometrial cells)
  - 'Death signals' delivered via the Fas receptor-ligand interaction (self-reactive T lymphocytes undergo apoptosis)
- **Apoptosis is regulated by proteins.**
  - The protein bcl-2 (which inhibits apoptosis) prevents release of cytochrome c from mitochondria and binds pro-apoptotic protease activating factor (Apaf-1).
  - The protein p53 (which stimulates apoptosis) is elevated by DNA injury and arrests the cell cycle.
  - If DNA repair is impossible, p53 stimulates apoptosis.
- **Execution of apoptosis** is mediated by a cascade of caspases (cysteine aspartic acid proteases). The caspases digest nuclear and cytoskeletal proteins, and also activate endonucleases.

NOTE

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

CLINICAL CORRELATE

If the cells in the interdigital space fail to undergo apoptosis, the fetus will be born with webbed hands and/or webbed feet (**syndactyly**).

CLINICAL CORRELATE

Graft-versus-host disease (GVHD) is a complication of allogeneic hematopoietic stem cell transplant. The transplanted marrow (the 'graft') contains cytotoxic T-cells that recognize the new host proteins (usually HLA) as foreign and attack the host tissue, triggering apoptosis of host cells. The skin, mucosa, liver, and GI tract are often involved; biopsy of the affected organs would demonstrate apoptosis.

KP00710.indb 11 13/10/22 1:51 PM

- **Physiologic examples of apoptosis** include embryogenesis (organogenesis and development), hormone-dependent apoptosis (menstrual cycle), thymus (selective death of lymphocytes).
- **Pathologic examples of apoptosis** include viral diseases (viral hepatitis [Councilman body]), graft-versus-host disease, and cystic fibrosis (duct obstruction and pancreatic atrophy).

ADAPTATION TO CELLULAR INJURY

In general, cellular adaptation is a potentially reversible change in response to the environment.

Atrophy

Atrophy is a decrease in cell/organ size and functional ability. Causes include decreased workload/disuse (immobilization); ischemia (atherosclerosis); lack of hormonal or neural stimulation, malnutrition, and aging.

Light microscopic examination shows small shrunken cells with lipofuscin granules. Electron microscopy shows decreased intracellular components and autophagosomes.

Hypertrophy

Hypertrophy is an increase in cell size and functional ability due to increased synthesis of intracellular components.

Causes of hypertrophy include:

- Increased mechanical demand can be physiologic (striated muscle of weight lifters) or pathologic (cardiac muscle in hypertension).
- Increased endocrine stimulation plays a role in puberty (growth hormone (GH), androgens/estrogens, etc.), gravid uterus (estrogen), and lactating breast (prolactin and estrogen).

Hypertrophy is mediated by growth factors, cytokines, and other trophic stimuli and leads to increased expression of genes and increased protein synthesis.

Hyperplasia

Hyperplasia is an increase in the number of cells in a tissue or organ. Some cell types are unable to exhibit hyperplasia (e.g., nerve, cardiac, skeletal muscle cells).

- Physiologic causes of hyperplasia include compensatory mechanisms (e.g., after partial hepatectomy), hormonal stimulation (e.g., breast development at puberty), and antigenic stimulation (e.g., lymphoid hyperplasia).
- Pathologic causes of hyperplasia include endometrial hyperplasia and prostatic hyperplasia of aging.

Hyperplasia is mediated by growth factors, cytokines, and other trophic stimuli; increased expression of growth-promoting genes (proto-oncogenes); and increased DNA synthesis and cell division.

CLINICAL CORRELATE

Living at a high altitude—where the oxygen content of air is relatively low—can lead to compensatory hyperplasia of red blood cell (RBC) precursors in the bone marrow and an increased number of circulating RBCs (secondary polycythemia).

KP00710.indb 12 13/10/22 1:51 PM

Metaplasia

Metaplasia is a reversible change of one fully differentiated cell type to another, usually in response to irritation. It has been suggested that the replacement cell is better able to tolerate the environmental stresses. For example, bronchial epithelium (normally ciliated columnar) undergoes squamous metaplasia in response to the chronic irritation of tobacco smoke.

The proposed mechanism is that 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.

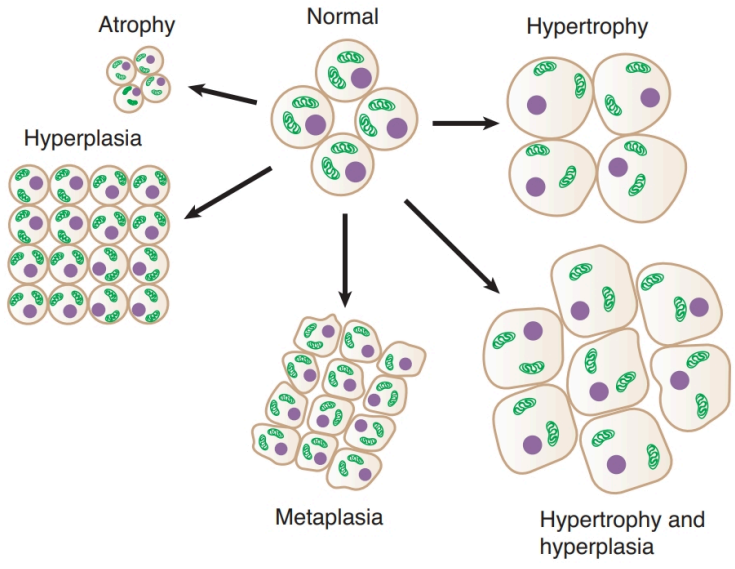


Figure 2-7. Cellular Adaptive Responses to Cell Injury

CLINICAL CORRELATE

Barrett esophagus is a classic example of metaplasia. The esophageal epithelium is normally squamous, but it undergoes a change to intestinal epithelium (columnar) when it is under constant contact with gastric acid.

OTHER MANIFESTATIONS OF CELLULAR INJURY

Pathologic Accumulations

- **Lipids** can accumulate intracellularly; they include triglycerides (e.g., fatty change in liver cells), cholesterol (e.g., atherosclerosis, xanthomas), and complex lipids (e.g., sphingolipid accumulation).
- **Proteins** can accumulate in proximal renal tubules in proteinuria and can form Russell bodies (intracytoplasmic accumulation of immunoglobulins) in plasma cells of patients with multiple myeloma.
- **Glycogen storage diseases** are genetic disorders in enzymes of glycogen metabolism causing accumulation of cytotoxic molecules, leading to cell death.
- **Hyaline** describes any intracellular or extracellular alteration that has a pink, glassy, homogenous appearance on H&E stain. Examples include hyaline arteriolosclerosis, amyloid, and hyaline membrane disease of the newborn.

KP00710.indb 13 13/10/22 1:51 PM

- **Calcium**
  - Dystrophic calcification is the precipitation of calcium phosphate in dying or necrotic tissues. Examples include fat necrosis (saponification), psammoma bodies (laminated calcifications that occur in meningiomas and papillary carcinomas of the thyroid and ovary), Monckeberg medial calcific sclerosis in arterial walls, and atherosclerotic plaques.
  - Metastatic calcification is the precipitation of calcium phosphate in normal tissue due to hypercalcemia (supersaturated solution). The many causes include hyperparathyroidism, parathyroid adenomas, renal failure, paraneoplastic syndrome, vitamin D intoxication, milk-alkali syndrome, sarcoidosis, Paget disease, multiple myeloma, metastatic cancer to the bone. The calcifications develop in the interstitial tissues of the stomach, kidneys, lungs, and blood vessels.
- **Exogenous pigments**
  - Anthracotic pigmentation of the lung (secondary to the inhalation of carbon dust)
  - Tattoos
  - Lead that has been ingested (e.g., gingival lead line, renal tubular lead deposits)
- **Endogenous pigments**
  - **Lipofuscin**, a wear-and-tear pigment that is seen as perinuclear yellow-brown pigment; it is caused by indigestible material within lysosomes and is common in the liver and heart
  - **Melanin**, a black-brown pigment derived from tyrosine found in melanocytes and substantia nigra
  - **Hemosiderin**, a golden yellow-brown granular pigment found in areas of hemorrhage or bruises
    - Systemic iron overload can lead to hemosiderosis (increased total body iron stores without tissue injury) or hemochromatosis (increased total body iron stores with tissue injury)
    - Prussian blue stain can identify the iron in the hemosiderin
  - Bilirubin, which accumulates in the basal ganglia of newborns, causing permanent damage (kernicterus)

Serum Enzyme Changes

Serum enzyme markers of cell damage include AST (liver injury), ALT (liver injury), creatine kinase (CK-MB) (heart injury), and amylase and lipase (pancreatic injury; amylase also rises with salivary gland injury).

KP00710.indb 14 13/10/22 1:51 PM

Inflammation 3

LEARNING OBJECTIVES

- ❑ Solve problems concerning acute and chronic inflammation
- ❑ Describe tissue responses to infectious agents

ACUTE INFLAMMATION

Acute inflammation is an immediate response to injury or infection, which is part of innate immunity.

- Short duration in normal host
- Cardinal signs of inflammation include rubor (redness); calor (heat); tumor (swelling); dolor (pain); functio laesa (loss of function).

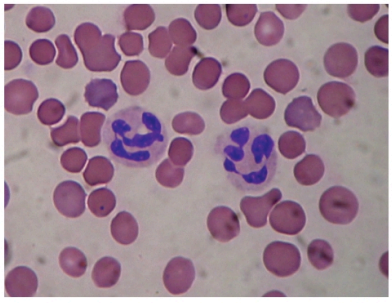
The important components of acute inflammation are **hemodynamic changes, neutrophils**, and **chemical mediators**.

Hemodynamic Changes

- Initial transient vasoconstriction
- Massive vasodilatation mediated by histamine, bradykinin, and prostaglandins
- Increased vascular permeability
  - Chemical mediators of increased permeability include vasoactive amines (histamine and serotonin), bradykinin (an end-product of the kinin cascade), leukotrienes (e.g., LTC4, LTD4, LTE4).
  - The mechanism of increased vascular permeability involves endothelial cell and pericyte contraction; direct endothelial cell injury; and leukocyte injury of endothelium.
- Blood flow slows (stasis) due to increased viscosity, allows neutrophils to marginate

Neutrophils

- **Life span** in tissue 1–2 days
- **Synonyms:** segmented neutrophils, polymorphonuclear leukocytes (PMN)
- **Primary (azurophilic) granules** contain myeloperoxidase, phospholipase A2, lysozyme (damages bacterial cell walls by catalyzing hydrolysis of 1,4-beta-linkages), and acid hydrolases. Also present are elastase, defensins (microbicidal peptides active against many gram-negative and gram-positive bacteria, fungi, and enveloped viruses), and bactericidal/permeability-increasing protein (BPI).



Source: commons.wikimedia.org (Mgiganteus)

Lobed nucleus, small granules
Neutrophil

CLINICAL CORRELATE

- A normal mature neutrophil has a segmented nucleus (3–4 segments).
- Hypersegmented neutrophils (>5 segments) are thought to be pathognomonic of the class of anemias called megaloblastic anemias (vitamin B12 or folate deficiencies).

KP00710.indb 15 13/10/22 1:51 PM

- **Secondary (specific) granules** contain phospholipase A2, lysozyme, leukocyte alkaline phosphatase (LAP), collagenase, lactoferrin (chelates iron), and vitamin B12-binding proteins.

Neutrophil margination and adhesion. Adhesion is mediated by complementary molecules on the surface of neutrophils and endothelium.

NOTE

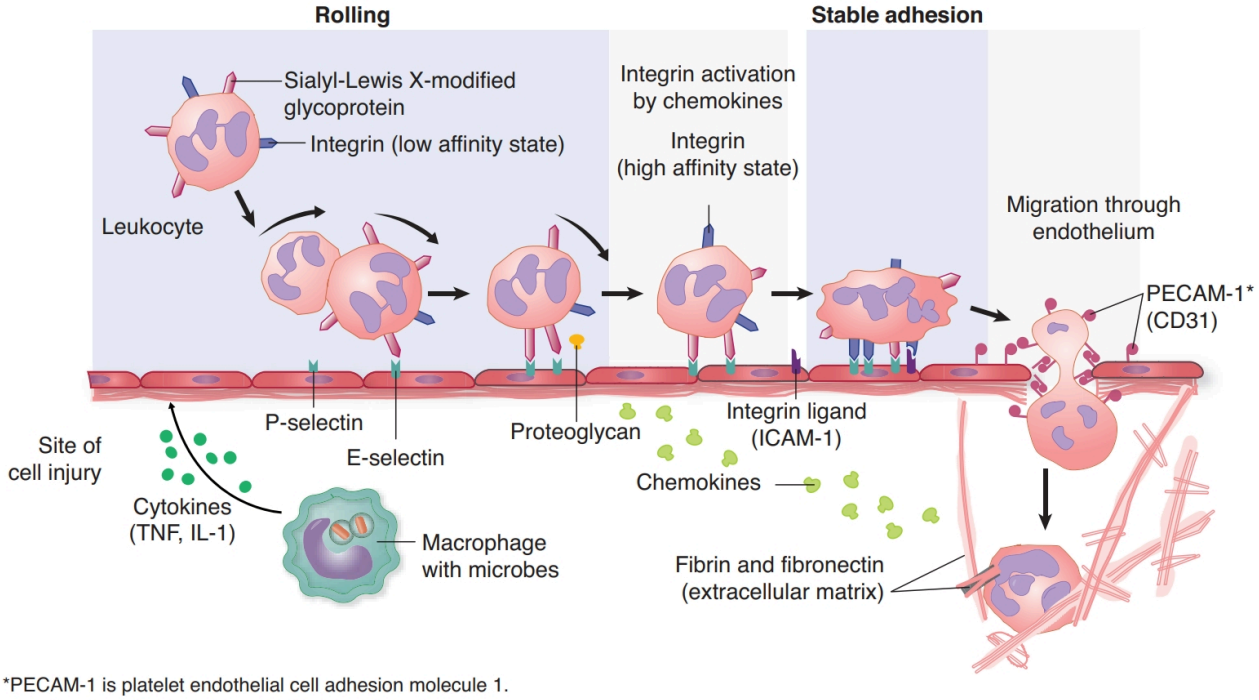
Selectins: weak binding; initiate rolling

Integrins: stable binding and adhesion

- In **step 1**, the endothelial cells at sites of inflammation have increased expression of *E-selectin* and *P-selectin*, due to elaboration of cytokines by resident tissue macrophages.
- In **step 2**, neutrophils weakly bind to the endothelial selectins and roll along the surface.
- In **step 3**, neutrophils are stimulated by chemokines to express their integrins.
- In **step 4**, binding of the integrins to cellular adhesion molecules (ICAM-1 and VCAM-1) allows the neutrophils to firmly adhere to the endothelial 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



*PECAM-1 is platelet endothelial cell adhesion molecule 1.

Figure 3-1. Adhesion and Migration

KP00710.indb 16 13/10/22 1:51 PM

Modulation of adhesion molecules in inflammation occurs as follows. The fastest step involves redistribution of adhesion molecules to the surface; for example, P-selectin is normally present in the Weibel-Palade bodies of endothelial cells and can be mobilized to the cell surface by exposure to inflammatory mediators such as histamine and thrombin.

- Additionally, synthesis of adhesion molecules occurs. For example, proinflammatory cytokines IL-1 and TNF induce production of E-selectin, ICAM-1, and VCAM-1 in endothelial cells.
- There can also be increased binding affinity, as when chemotactic agents cause a conformational change in the leukocyte integrin LFA-1, which is converted to a high-affinity binding state.

Defects in adhesion can be seen in diabetes mellitus, corticosteroid use, acute alcohol intoxication, and leukocyte adhesion deficiency (autosomal recessive condition with recurrent bacterial infections).

In **emigration (diapedesis)**, leukocytes emigrate from the vasculature (postcapillary venule) by extending pseudopods between the endothelial cells. They then move between the endothelial cells, migrating through the basement membrane toward the inflammatory stimulus.

Chemotaxis is the attraction of cells toward a chemical mediator that is released in the area of inflammation. Important chemotactic factors for neutrophils include bacterial products such as *N*-formyl-methionine and host-derived molecules such as leukotriene B4 (LTB4), complement system product C5a, and α-chemokines (IL-8).

Phagocytosis and degranulation. Opsonins coat microbes to enhance their detection and phagocytosis. Important opsonins include the Fc portion of IgG isotypes, complement system product C3b, and plasma proteins such as collectins (which bind to bacterial cell walls).

Engulfment occurs when the neutrophil sends out cytoplasmic processes that surround the bacteria. The bacteria are then internalized within a phagosome. The phagosome fuses with lysosomes (degranulation).

Defects in phagocytosis and degranulation include Chédiak-Higashi syndrome, an autosomal recessive condition characterized by neutropenia. The neutrophils have giant granules (lysosomes) and there is a defect in chemotaxis and degranulation.

Intracellular killing can occur in either the presence or absence of oxygen.

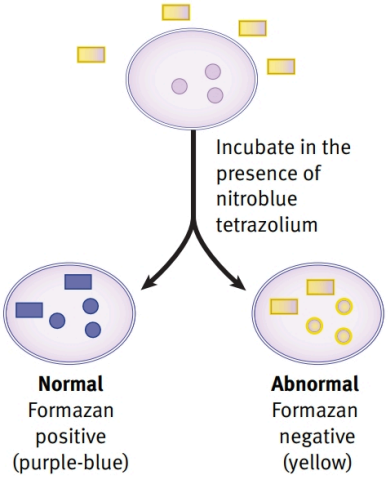
In **oxygen-dependent killing**, respiratory burst requires oxygen and NADPH oxidase and produces superoxide, hydroxyl radicals, and hydrogen peroxide. Myeloperoxidase requires hydrogen peroxide and halide (Cl^-) and produces HOCl (hypochlorous acid).

CLINICAL CORRELATE

Leukocyte adhesion deficiency type I

- Autosomal recessive
- Deficiency of β2 integrin subunit (CD18)
- Recurrent bacterial infection
- Delay in umbilical cord sloughing

KP00710.indb 17 13/10/22 1:51 PM



Nitroblue Tetrazolium Reduction

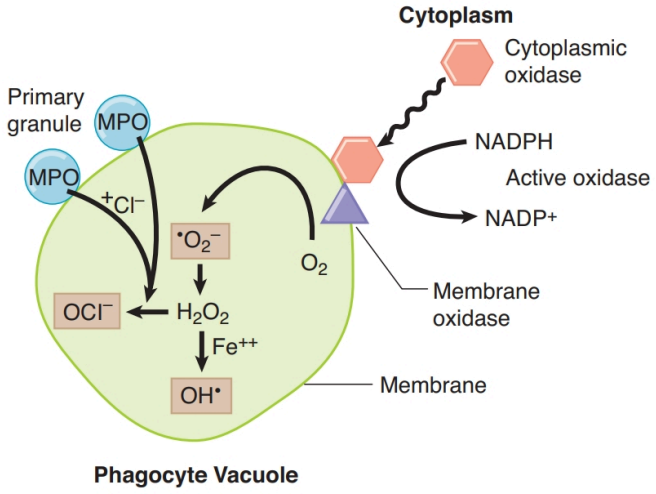


Figure 3-2. Oxygen-Dependent Killing

Oxygen-independent killing involves lysozyme, lactoferrin, acid hydrolases, BPI, and defensins.

Deficiencies of oxygen-dependent killing include:

- Chronic granulomatous disease of childhood can be X-linked or autosomal recessive. It is characterized by a deficiency of NADPH oxidase, lack of superoxide and hydrogen peroxide, and recurrent bacterial infections with catalase-positive organisms (*S. aureus*). The nitroblue tetrazolium test will be negative.
- Myeloperoxidase deficiency is an autosomal recessive condition characterized by infections with *Candida*. In contrast to chronic granulomatous disease, the nitroblue tetrazolium test will be positive.

Chemical Mediators of Inflammation

Vasoactive amines

- **Histamine** is produced by basophils, platelets, and mast cells. It causes vasodilation and increased vascular permeability. Triggers for release include IgE-mediated mast cell reactions, physical injury, anaphylatoxins (C3a and C5a), and cytokines (IL-1).
- **Serotonin** is produced by platelets and causes vasodilation and increased vascular permeability.

Kinin system

- Activated Hageman factor (factor XII) converts prekallikrein → kallikrein
- Kallikrein cleaves high-molecular-weight-kininogen (HMWK) → bradykinin
- Effects of bradykinin include increased vascular permeability, pain, vasodilation, bronchoconstriction, and pain

KP00710.indb 18 13/10/22 1:51 PM

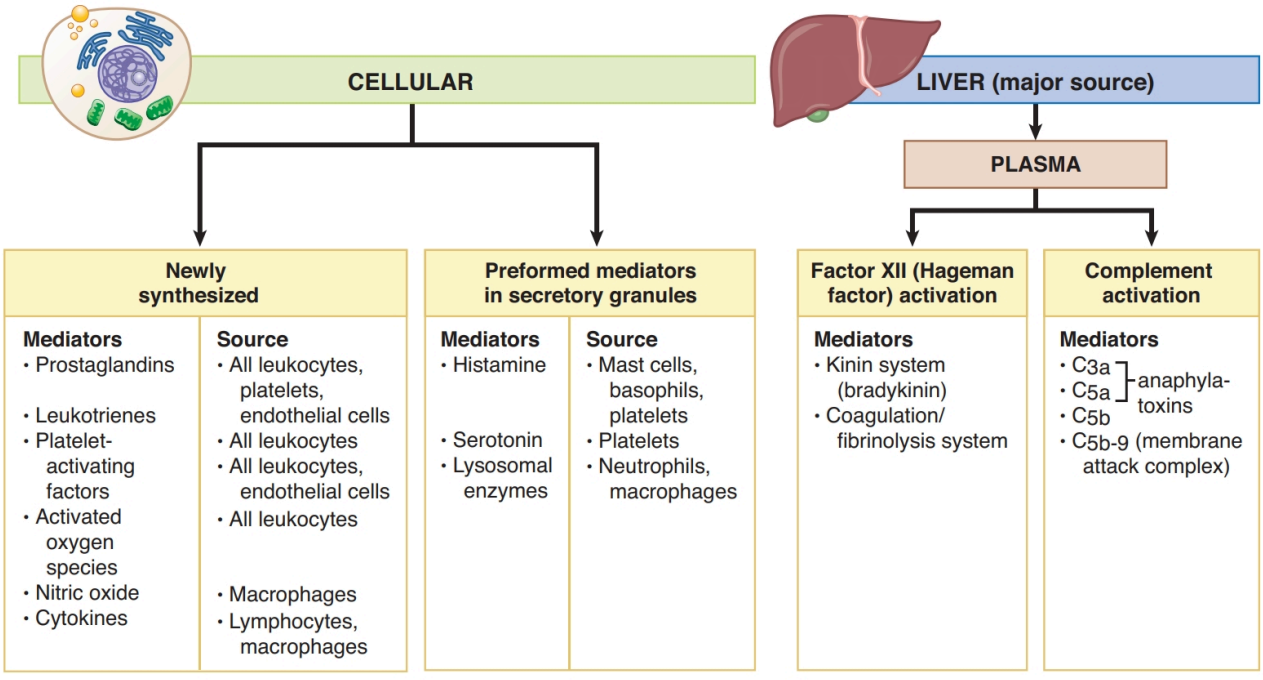


Figure 3-3. Sources of Chemical Mediators of Inflammation

Arachidonic acid products

- **Cyclooxygenase pathway**
  - Thromboxane A2 is produced by platelets and causes vasoconstriction and platelet aggregation.
  - Prostacyclin (PGI2) is produced by vascular endothelium and causes vasodilation and inhibition of platelet aggregation.
  - Prostaglandin E_2 causes pain.
  - Prostaglandins PGE2, PGD2, and PGF2 cause vasodilatation.

Lipoxygenase pathway

- Leukotriene B4 (LTB4) causes neutrophil chemotaxis, while leukotriene C4, D4, E4 cause vasoconstriction. Lipoxins are antiinflammatory products which inhibit neutrophil chemotaxis.

Important products in the complement cascade include C5b-C9 (membrane attack complex), C3a, C5a (anaphylatoxins stimulate the release of histamine), C5a (leukocyte chemotactic factor), and C3b (opsonin for phagocytosis).

Cytokines

- IL-1 and TNF cause fever and induce acute phase reactants; enhance adhesion molecules; and stimulate and activate fibroblasts, endothelial cells, and neutrophils.
- IL-8 is a neutrophil chemoattractant produced by macrophages.

NOTE

Mediators of Pain

- Bradykinin
- Prostaglandins (E_2)

NOTE

Mediators of Fever

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

KP00710.indb 19 13/10/22 1:51 PM

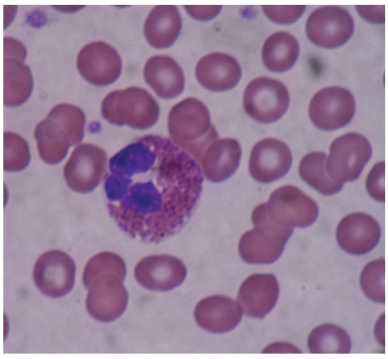
Four Outcomes of Acute Inflammation

- Complete resolution with regeneration
- Complete resolution with scarring
- Abscess formation
- Transition to chronic inflammation

CHRONIC INFLAMMATION

Causes of Chronic Inflammation

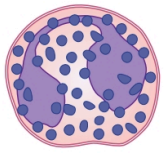
- Following bout of acute inflammation
- Persistent infections
- Infections with certain organisms, including viral infections, mycobacteria, parasitic infections, and fungal infections
- Autoimmune disease
- Response to foreign material
- Response to malignancy



Source: commons.wikimedia.org (Bobjgalindo)

Bilobed nucleus, large granules (pink)

Eosinophil



Bilobed nucleus, large granules (blue)

Basophil

Cells of Chronic Inflammation

- **Macrophages** are derived from blood monocytes. Tissue-based macrophages (life span in connective tissue compartment is 60–120 days) are found in connective tissue (histiocyte), lung (pulmonary alveolar macrophages), liver (Kupffer cells), bone (osteoclasts), and brain (microglia). During inflammation circulating monocytes emigrate from the blood to the periphery and differentiate into macrophages.
  - Respond to chemotactic factors: C5a, MCP-1, MIP-1α, PDGF, TGF-β
  - Secrete a wide variety of active products (monokines)
  - May be modified into epithelioid cells in granulomatous processes
- **Lymphocytes** include B cells and plasma cells, as well as T cells. Lymphotaxin is the lymphocyte chemokine.
- **Eosinophils** play an important role in parasitic infections and IgE-mediated allergic reactions. The eosinophilic chemokine is eotaxin. Eosinophil granules contain major basic protein, which is toxic to parasites.
- **Basophils** contain similar chemical mediators as mast cells in their granules. Mast cells are present in high numbers in the lung and skin. Both basophils and mast cells play an important role in IgE-mediated reactions (allergies and anaphylaxis) and can release histamine.

KP00710.indb 20 13/10/22 1:51 PM

Granulomatous Inflammation

Chronic granulomatous inflammation is a specialized form of chronic inflammation characterized by small aggregates of modified macrophages (epithelioid cells and multinucleated giant cells) usually populated by CD4+ Th1 lymphocytes.

Composition of a granuloma is as follows:

- **Epithelioid cells,** located centrally, form when IFN-γ transforms macrophages to epithelioid cells. They are enlarged cells with abundant pink cytoplasm.
- **Multinucleated giant cells,** located centrally, are formed by the fusion of epithelioid cells. Types include Langhans-type giant cell (peripheral arrangement of nuclei) and foreign body type giant cell (haphazard arrangement of nuclei).
- **Lymphocytes and plasma cells** are present at the periphery.
- **Central necrosis** occurs in granulomata due to excessive enzymatic breakdown and is commonly seen in *Mycobacterium tuberculosis* infection as well as fungal infections and a few bacterial infections. Because of the public health risk of tuberculosis, necrotizing granulomas should be considered tuberculosis until proven otherwise.

CLINICAL CORRELATE

Patients who are to be placed on tumor necrosis factor (TNF) inhibitors such as infliximab must undergo a PPD test before starting therapy. The PPD checks for latent tuberculosis infection, which can be reactivated by the TNF alpha inhibitor.

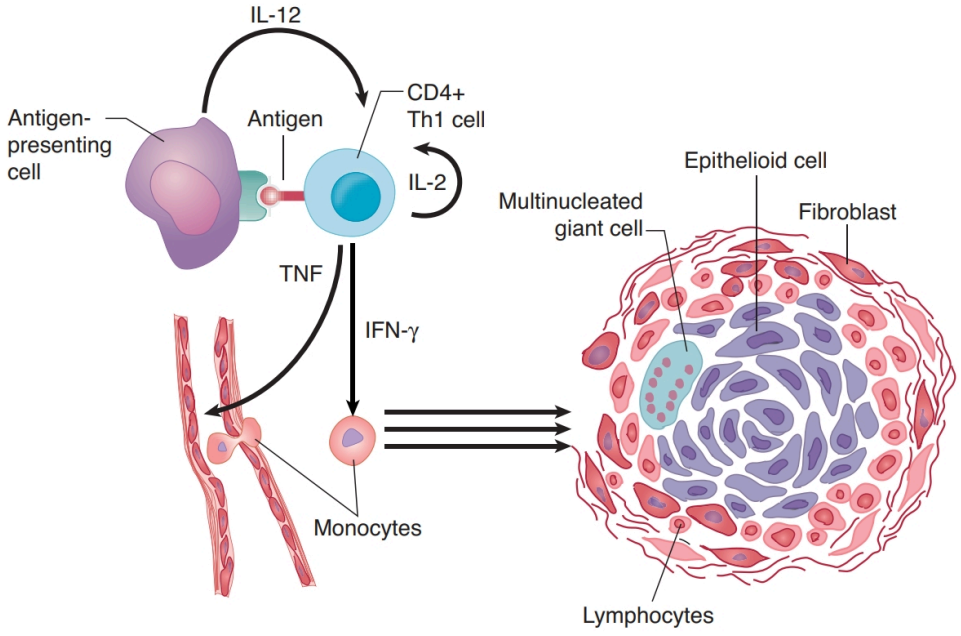
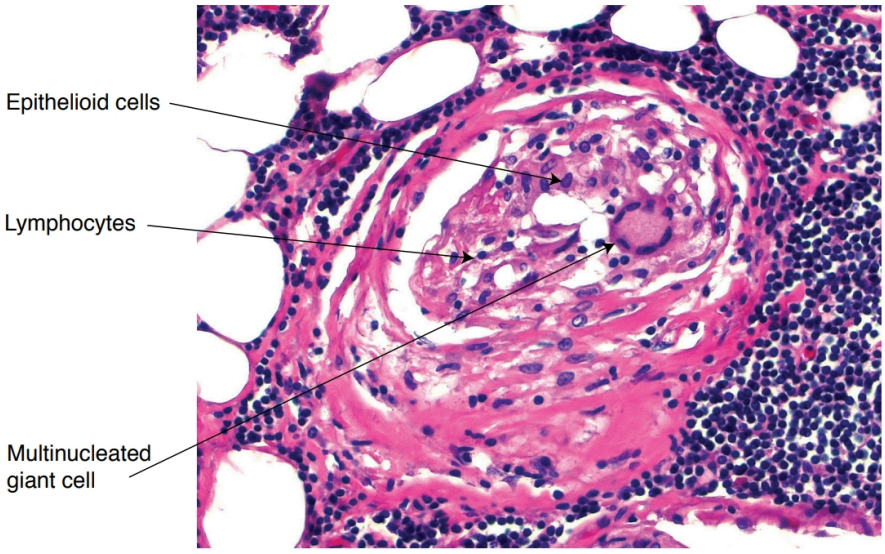


Figure 3-4. Granuloma Formation

Granulomatous diseases include tuberculosis (caseating granulomas), cat-scratch fever, syphilis, leprosy, fungal infections (e.g., coccidioidomycosis), parasitic infections (e.g., schistosomiasis), foreign bodies, beryllium, and sarcoidosis.

KP00710.indb 21 13/10/22 1:51 PM



© Henry Sanchez, MD. Used with permission.

Figure 3-5. A Granuloma Is Seen in the Large, Poorly Circumscribed Nodule in the Center of the Field

TISSUE RESPONSES TO INFECTIOUS AGENTS

General Concepts

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

6 Major Histologic Patterns

- **Exudative inflammation** is acute inflammatory response with neutrophils. Examples include bacterial meningitis, bronchopneumonia, and abscess.
- **Necrotizing inflammation** occurs when a virulent organism produces severe tissue damage and extensive cell death. Examples include necrotizing fasciitis and necrotizing pharyngitis.
- **Granulomatous inflammation.** Granulomatous response predominates with slow-growing organisms such as mycobacteria, fungi, and parasites.
- **Interstitial inflammation** is a diffuse mononuclear interstitial infiltrate that is a common response to viral infectious agents. Examples include myocarditis (Coxsackie virus) and viral hepatitis.
- **Cytopathic/cytoproliferative** inflammation refers to inflammation in which the infected/injured cell is altered. The changes may include intranuclear/cytoplasmic inclusions (cytomegalic inclusion disease, rabies [Negri body]); syncytia formation (respiratory syncytial virus and herpes virus); and apoptosis (Councilman body in viral hepatitis).
- **No inflammation.** An inflammatory response to microbes cannot occur in severely immunosuppressed individuals due to primary immunodeficiencies or acquired immunodeficient states (e.g., AIDS).

KP00710.indb 22 13/10/22 1:51 PM

Tissue Repair 4

LEARNING OBJECTIVES

- ❑ Demonstrate understanding of regeneration and healing
- ❑ Answer questions about aberrations in wound healing

REPAIR AND HEALING

General Concepts

Repair and healing of damaged cells and tissues start almost as soon as the inflammatory process begins. **Tissue repair** involves 5 overlapping processes:

- Hemostasis (coagulation, platelets)
- Inflammation (neutrophils, macrophages, lymphocytes, mast cells)
- Regeneration (stem cells and differentiated cells)
- Fibrosis (macrophages, granulation tissue [fibroblasts, angiogenesis], type III collagen)
- Remodeling (macrophages, fibroblasts, converting collagen III to I)

The **extracellular matrix (ECM)** is an important tissue scaffold with 2 forms, the interstitial matrix and the basement membrane (type IV collagen and laminin). There are 3 ECM components:

- Collagens and elastins
- Gels (proteoglycans and hyaluronan)
- Glycoproteins and cell adhesion molecules

Repair by Tissue Regeneration

Different tissues have different regenerative capacities.

- **Labile cells** (primarily stem cells) regenerate throughout life. Examples include surface epithelial cells (skin and mucosal lining cells), hematopoietic cells, stem cells, etc.
- **Stable cells** (stem cells and differentiated cells) replicate at a low level throughout life and have the capacity to divide if stimulated by some initiating event. Examples include hepatocytes, proximal tubule cells, endothelium, etc.
- **Permanent cells** (few stem cells and/or differentiated cells with the capacity to replicate) have a very low level of replicative capacity. Examples include neurons and cardiac muscle.

KP00710.indb 23 13/10/22 1:51 PM

Repair by Scar Formation

Scar formation occurs in a series of steps when repair cannot be brought about by regeneration.

- First, angiogenesis is promoted by vascular endothelial growth factor (VEGF) and the fibroblast growth factor (FGF) family of growth factors.
- Next, platelet-derived growth factor (PDGF), fibroblast growth factor 2 (FGF-2), and transforming growth factor β (TGF-β) drive fibroblast activation for the formation of granulation tissue.
- Then, TGF-β, PDGF, and FGF drive ECM deposition. Cytokines IL-1 and IL-13 stimulate collagen production for scar formation.

WOUND HEALING

Types of Wound Healing

Primary union (healing by first intention) occurs when wounds are closed physically with sutures, metal staples, dermal adhesive, etc.

Secondary union (healing by secondary intention) occurs when wounds are allowed to heal by wound contraction and is mediated by myofibroblasts at the edge of the wound.

NOTE

Clinicians make decisions about wound healing techniques based on clinical information and the size of the tissue defect.

Repair in specific organs occurs as follows:

- **Liver:** Mild injury is repaired by regeneration of hepatocytes, sometimes with restoration to normal pathology. Severe or persistent injury causes formation of regenerative nodules that may be surrounded by fibrosis, leading to hepatic cirrhosis.
- In the **brain**, neurons do not regenerate, but microglia remove debris and astrocytes proliferate, causing gliosis.
- Damaged **heart muscle** cannot regenerate, so the heart heals by fibrosis.
- In the **lung**, type II pneumocytes replace type I pneumocytes after injury.
- In **peripheral nerves**, the distal part of the axon degenerates while the proximal part regrows slowly, using axonal sprouts to follow Schwann cells to the muscle.

Aberrations in Wound Healing

- **Delayed wound healing** may be seen in wounds complicated by foreign bodies, infection, ischemia, diabetes, malnutrition, scurvy, etc.
- **Hypertrophic scar** results in a prominent scar that is localized to the wound, due to excess production of granulation tissue and collagen. It is common in burn patients.

KP00710.indb 24 13/10/22 1:51 PM

- **Keloid formation** is a genetic predisposition that is common in African Americans. It tends to affect the earlobes, face, neck, sternum, and forearms, and it may produce large tumor-like scars extending beyond the injury site. There is excess production of collagen that is predominantly type III.



© Richard P. Usatine, MD. Used with permission.

Figure 4-1. Keloid on Posterior Surface of Ear (Auricle)

KP00710.indb 25 13/10/22 1:51 PM

Circulatory Pathology

5

LEARNING OBJECTIVES

- ❑ Use knowledge of edema, hemostasis, and bleeding disorders to solve problems
- ❑ Answer questions about thrombosis, embolism, and infarction
- ❑ Solve problems concerning shock

EDEMA

Edema is the presence of excess fluid in the intercellular space.

Causes of Edema

- **Increased hydrostatic pressure** causes edema in congestive heart failure (generalized edema), portal hypertension, renal retention of salt and water, and venous thrombosis (local edema).
- **Hypoalbuminemia and decreased colloid osmotic pressure** cause edema in liver disease, nephrotic syndrome, and protein deficiency (e.g., kwashiorkor).
- **Lymphatic obstruction** (lymphedema) causes edema in tumor, following surgical removal of lymph node drainage, and in parasitic infestation (filariasis → elephantiasis).
- **Increased endothelial permeability** causes edema in inflammation, type I hypersensitivity reactions, and with some drugs (e.g., bleomycin, heroin, etc.).
- **Increased interstitial sodium** causes edema when there is increased sodium intake, primary hyperaldosteronism, and renal failure.
- Specialized forms of tissue swelling due to **increased extracellular glycosaminoglycans** also occur, notably in pretibial myxedema and exophthalmos (Graves disease).

Clinical Types

- **Anasarca** is severe generalized edema.
- **Effusion** is fluid within the body cavities.
- **Pulmonary edema** is fluid in the lung.

NOTE

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

KP00710.indb 27 13/10/22 1:51 PM

Composition of Edema Fluid

- **Transudate** is edema fluid with low protein content.
- **Exudate** is edema fluid with high protein content and cells. Types of exudates include purulent (pus), fibrinous, eosinophilic, and hemorrhagic.
- **Lymphedema** related to lymphatic obstruction leads to accumulation of protein-rich fluid which produces a non-pitting edema.
- **Glycosaminoglycan-rich** edema fluid shows increased hyaluronic acid and chondroitin sulfate, and causes myxedema.

Active hyperemia versus congestion (passive hyperemia): an excessive amount of blood in a tissue or organ can accumulate secondary to vasodilatation (active, e.g., inflammation) or diminished venous outflow (passive, e.g., hepatic congestion).

COAGULATION

NOTE

Clotting is a balance between 2 opposing forces: those favoring the formation of a stable thrombus versus those factors causing fibrinolysis of the clot.

Hemostasis

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

BRIDGE TO PHARMACOLOGY

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

Vascular wall injury. Transient vasoconstriction is mediated by endothelin-1. Thrombogenic factors include a variety of processes:

- Changes in blood flow cause turbulence and stasis favor clot formation.
- Release of tissue factor from injured cells activates factor VII (extrinsic pathway).
- Exposure of thrombogenic subendothelial collagen activates factor XII (intrinsic pathway).
- Release of von Willebrand factor (vWF) binds to exposed collagen and facilitates platelet adhesion.
- Decreased endothelial synthesis of antithrombogenic substances (prostacyclin, nitric oxide [NO_2], tissue plasminogen activator, and thrombomodulin)

Platelets are derived from megakaryocytes in the bone marrow. They form a thrombus through a series of steps.

- **Step 1: Platelet adhesion** occurs when vWF adheres to subendothelial collagen and then platelets adhere to vWF by glycoprotein Ib.
- **Step 2: Platelet activation** occurs when platelets undergo a shape change and degranulation occurs. Platelets synthesize thromboxane A2. Platelets also show membrane expression of the phospholipid complex, which is an important substrate for the coagulation cascade.
- **Step 3: Platelet aggregation** occurs when additional platelets are recruited from the bloodstream. ADP and thromboxane A2 are potent mediators of aggregation. Platelets bind to each other by binding to fibrinogen using GPIIb-IIIa.

KP00710.indb 28 13/10/22 1:51 PM

Laboratory tests for platelets include platelet count (normal 150,000–400,000 mm3) and platelet aggregometry.

Bernard-Soulier syndrome and Glanzmann thrombasthenia present as mucocutaneous bleeding in childhood.

Table 5-1. 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)	

NOTE

Bernard-Soulier Syndrome

- Usually autosomal recessive
- Defects of the GPIb IX-V
- Defective platelet adhesion

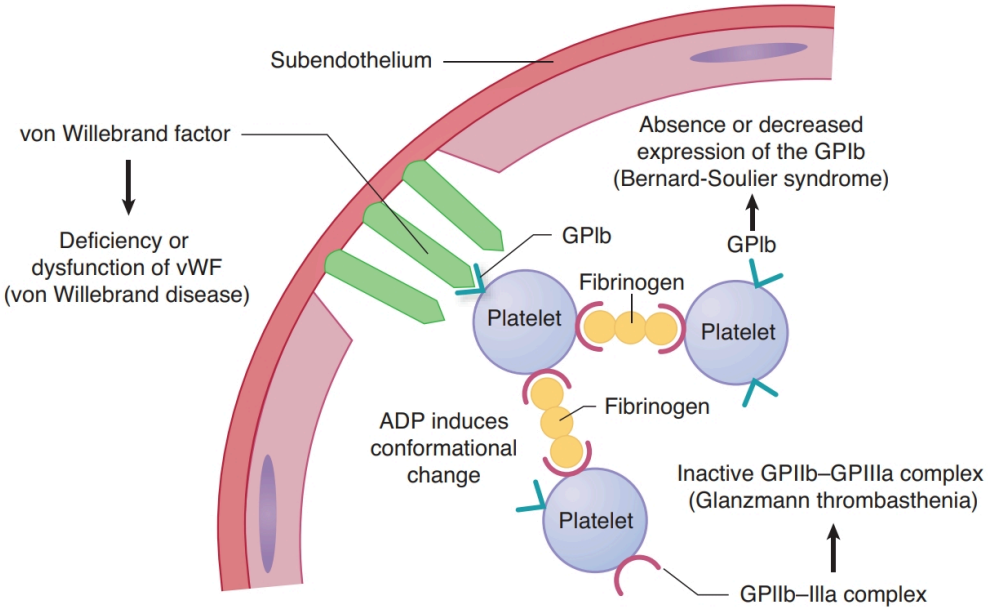


Figure 5-1. Platelet Aggregation

Coagulation factors. The majority of the clotting factors are produced by the liver. The factors are proenzymes that must be converted to the active form. Some conversions occur on a phospholipid surface, and some conversions require calcium.

- The **intrinsic coagulation pathway** is activated by the contact factors, which include contact with subendothelial collagen, HMWK, and kallikrein.
- The **extrinsic coagulation pathway** is activated by the release of tissue factor.

NOTE

- Patients on warfarin therapy should be monitored using prothrombin time (WEPT = warfarin, extrinsic PT).
- Patients on heparin therapy should be monitored using partial thromboplastin time (HIPTT = heparin, intrinsic PTT).

KP00710.indb 29 13/10/22 1:51 PM

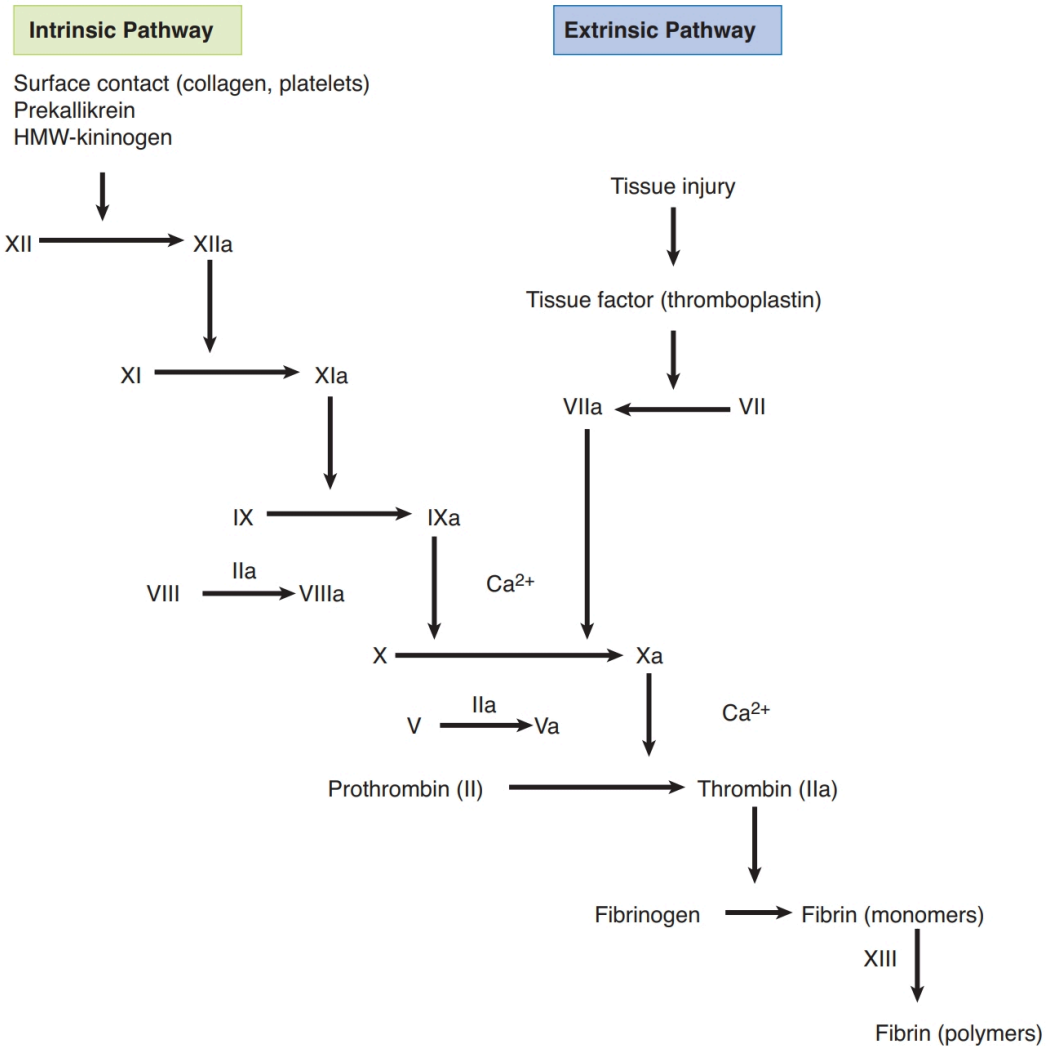


Figure 5-2. Coagulation Cascade

Laboratory Tests

- Prothrombin time (PT), which tests the extrinsic and common coagulation pathways (more specifically, it tests factors VII, X, V, prothrombin, and fibrinogen). The international normalized ratio (INR) standardizes the PT test so that results throughout the world can be compared. A longer time means blood takes longer to clot.
- Partial thromboplastin time (PTT), which tests the intrinsic and common coagulation pathways (more specifically, it tests factors XII, XI, IX, VIII, X, V, prothrombin, and fibrinogen).
- Thrombin time (TT), which tests for adequate fibrinogen levels.
- Fibrin degradation products (FDP), which tests the fibrinolytic system (increased with DIC).

KP00710.indb 30 13/10/22 1:51 PM

Bleeding Disorders

Bleeding disorders caused by platelet abnormalities include immune thrombocytopenia purpura and thrombotic thrombocytopenic purpura.

Immune thrombocytopenia purpura (ITP) is an immune-mediated attack (usually IgG antiplatelet antibodies) against platelets leading to decreased platelets (thrombocytopenia) which result in petechiae, purpura (bruises), and a bleeding diathesis (e.g., hematomas).

The etiology involves **antiplatelet antibodies** against platelet antigens such as GPIIb-IIIa and GPIb-IX (type II hypersensitivity reaction). The antibodies are made in the spleen, and the platelets are destroyed peripherally in the spleen by macrophages, which have Fc receptors that bind IgG-coated platelets.

Forms of ITP include:

- Acute ITP, seen in children following a viral infection and is a self-limited disorder.
- Chronic ITP, usually seen in women in their childbearing years and may be the first manifestation of systemic lupus erythematosus (SLE). Clinically, it is characterized by petechiae, ecchymoses, menorrhagia, and nosebleeds.

Lab studies usually show decreased platelet count and prolonged bleeding time but normal prothrombin time and partial thromboplastin time. Peripheral blood smear shows thrombocytopenia with enlarged immature platelets (megathrombocytes). Bone marrow biopsy shows increased numbers of megakaryocytes with immature forms.

Treatment is corticosteroids, which decrease antibody production; immunoglobulin therapy, which floods Fc receptors on splenic macrophages; and/or splenectomy, which removes the site of platelet destruction and antibody production.

Thrombotic thrombocytopenic purpura (TTP) is a rare disorder of hemostasis in which there is widespread **intravascular formation of fibrin-platelet thrombi**. It is sometimes associated with an acquired or inherited deficiency of the enzyme ADAMTS13, responsible for cleaving large multimers of von Willebrand factor.

Clinically, TTP most often affects adult women. The inclusion criteria are microangiopathic hemolytic anemia and thrombocytopenia, with or without renal failure or neurologic abnormalities. Pathology includes widespread formation of platelet thrombi with fibrin (hyaline thrombi) leading to intravascular hemolysis (thrombotic microangiopathy).

Lab studies typically show decreased platelet count and prolonged bleeding time but normal prothrombin time and partial thromboplastin time. Peripheral blood smear shows thrombocytopenia, schistocytes, and reticulocytosis. Treatment is plasma exchange.

Another cause of bleeding disorders is **endothelial damage**.

Hemolytic uremic syndrome (HUS) is a form of thrombotic microangiopathy due to endothelial cell damage. It occurs mostly in children, typically after a gastroenteritis (typically due to Shiga toxin-producing *E. coli* 0157:H7).

KP00710.indb 31 13/10/22 1:51 PM

Typical HUS presents with abdominal pain, diarrhea (an atypical variant is diarrhea-negative), microangiopathic **hemolytic anemia**, **thrombocytopenia**, and **renal failure**. Renal involvement is seen more commonly than in TTP. The kidney shows fibrin thrombi in the glomeruli. Renal glomerular endothelial cells are targeted by the bacterial toxin. Glomerular scarring may ensue.

Treatment is supportive (fluid management, dialysis, erythrocyte transfusions); plasma exchange is only used for atypical cases.

A number of disorders are related to coagulation factors, as follows:

Table 5-2. 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 thrombocytopenic purpura (TTP) • Disseminated intravascular coagulation (DIC) • Hypersplenism	

NOTE

Glanzmann Thrombasthenia

- Autosomal recessive
- Defective GPIIb-IIIa receptor
- Defective platelet aggregation

- **Hemophilia A (classic hemophilia)** is an X-linked recessive condition resulting from a deficiency of factor VIII. Clinically, hemophilia A predominately affects males. Symptoms vary depending on the degree of deficiency. Newborns may develop bleeding at the time of circumcision. Other problems include spontaneous hemorrhage into joints **(hemarthrosis)**, easy bruising and hematoma formation after minor trauma, and severe prolonged bleeding after surgery or lacerations. Laboratory studies typically show normal platelet count and normal bleeding time, normal PT and prolonged PTT. Treatment is factor VIII concentrate.
- **Hemophilia B (Christmas disease)** is an X-linked recessive condition resulting from a deficiency of factor IX that is clinically identical to hemophilia A. Treatment is recombinant factor IX.
- **Acquired coagulopathies** include vitamin K deficiency (decreased synthesis of factors II, VII, IX, X, and protein C & S) and liver disease (decreased synthesis of virtually all clotting factors).
- **Von Willebrand disease** is an autosomal dominant bleeding disorder characterized by a deficiency or qualitative defect in von Willebrand factor. vWF is normally produced by endothelial cells and megakaryocytes. Clinical features include spontaneous bleeding from mucous membranes, prolonged bleeding from wounds, and menorrhagia in young females. Hemarthrosis is uncommon. Lab studies show normal platelet count, a prolonged bleeding time, normal PT, and often prolonged PTT.

KP00710.indb 32 13/10/22 1:51 PM

Abnormal platelet response to ristocetin (adhesion defect) is an important diagnostic test. Treatment for mild classic cases (type I) is desmopressin (an antidiuretic hormone analog), which releases vWF from Weibel-Palade bodies of endothelial cells.

- **Disseminated intravascular coagulation (DIC)** is always secondary to another disorder.
  - Causes are diverse. Obstetric complications can cause DIC because placental tissue factor activates clotting. Gram-negative sepsis can cause DIC because TNF activates clotting. Other causes include microorganisms (especially meningococcus and rickettsiae), AML M3 (cytoplasmic granules in neoplastic promyelocytes activate clotting), and adenocarcinomas (mucin activates clotting).
  - Clinical features of DIC include widespread microthrombi with consumption of platelets and clotting factors, causing hemorrhage. Laboratory studies show decreased platelet count, prolonged PT/PTT, decreased fibrinogen, and elevated fibrin split products (D dimers). Treat the underlying disorder.

NOTE

Von Willebrand disease is the most common inherited bleeding disorder.

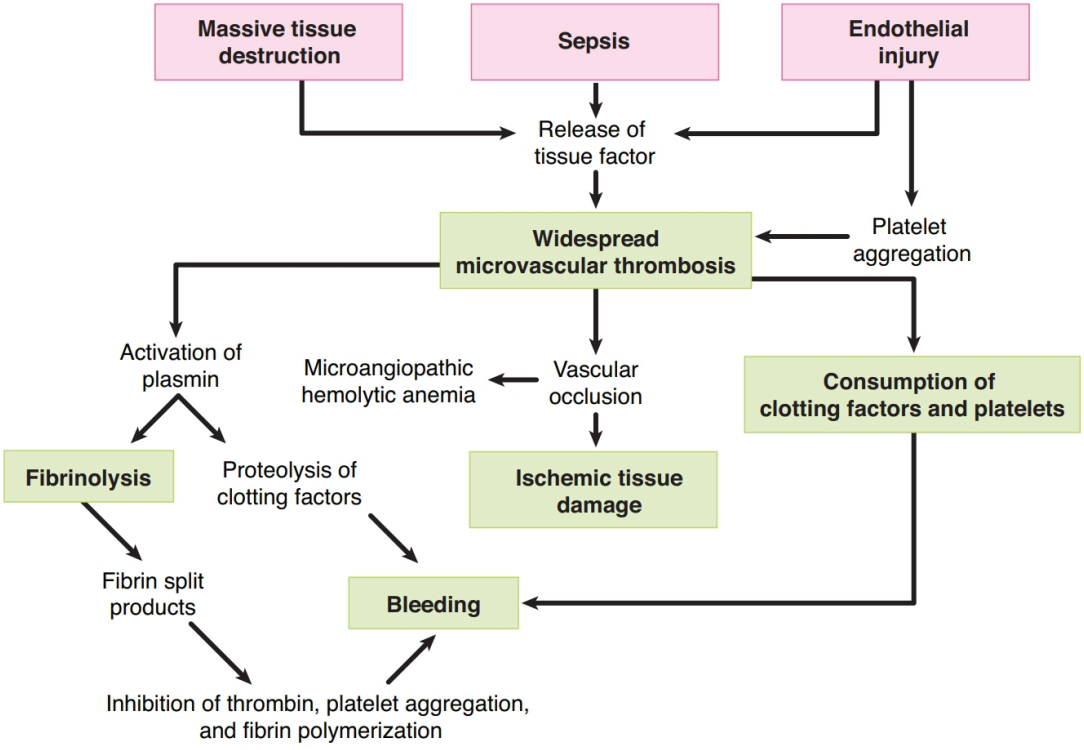


Figure 5-3. Disseminated Intravascular Coagulation

KP00710.indb 33 13/10/22 1:51 PM

THROMBOSIS, EMBOLISM, AND INFARCTION

Thrombosis

Thrombosis is the pathologic formation of an intravascular fibrin-platelet thrombus during life. Factors involved in thrombus formation (**Virchow's triad**) include:

- Endothelial injury due to atherosclerosis, vasculitis, or many other causes
- Alterations in laminar blood flow predisposing for DIC occur with stasis of blood (e.g., immobilization); turbulence (e.g., aneurysms); and hyperviscosity of blood (e.g., polycythemia vera)
- Hypercoagulability of blood can be seen with clotting disorders (factor V Leiden; deficiency of antithrombin III, protein C, or protein S); tissue injury (postoperative and trauma); neoplasia; nephrotic syndrome; advanced age; pregnancy; and oral contraceptives (estrogen increases synthetic activity of the liver, including clotting factors)

Table 5-3. Comparison of a Thrombus with a Blood Clot

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

Common locations of thrombus formation include coronary and cerebral arteries; heart chambers in atrial fibrillation or post-MI (mural thrombus); aortic aneurysms; heart valves (vegetations); and deep leg veins (DVTs).

Outcomes of thrombosis include vascular occlusion and infarctions; embolism; thrombolysis; and organization and recanalization.

Embolism

An embolism is any intravascular mass that has been carried down the bloodstream from its site of origin, resulting in the occlusion of a vessel. There are many types of emboli:

- **Thromboemboli**: most common (98%)
- Atheromatous emboli (severe atherosclerosis)
- Fat emboli (bone fractures and soft tissue trauma)
- Bone marrow emboli (bone fractures and cardiopulmonary resuscitation [CPR])

BRIDGE TO ANATOMY

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

KP00710.indb 34 13/10/22 1:51 PM

- Gas emboli cause decompression sickness ("the bends" and caisson disease) when rapid ascent results in nitrogen gas bubbles in the blood vessels
- Amniotic fluid emboli are a complication of labor that may result in DIC; fetal squamous cells are seen in the maternal pulmonary vessels
- Tumor emboli (metastasis)
- Talc emboli (IV drug abuse)
- Bacterial/septic emboli (infectious endocarditis)

Pulmonary emboli (PE) are often clinically silent and are the most commonly missed diagnosis in hospitalized patients. They are found in almost 50% of all hospital autopsies. Most PE (95%) arise from deep leg vein thrombosis (DVT) in the leg; other sources include the right side of the heart and the pelvic venous plexuses of the prostate and uterus.

Diagnosis of a PE can be established when V/Q lung shows a scan V/Q mismatch. Doppler ultrasound of the leg veins can be used to detect a DVT. Additionally, plasma D-dimer ELISA test is elevated.

Most cases are clinically silent and resolve.

Infarction is more common in patients with cardiopulmonary compromise. Symptoms include shortness of breath, hemoptysis, pleuritic chest pain, and pleural effusion. On gross examination there is typically a hemorrhagic wedge-shaped infarct. The infarction heals by regeneration or scar formation.

- Sudden death can occur when large emboli lodge in the bifurcation (saddle embolus) or large pulmonary artery branches.
- Chronic secondary pulmonary hypertension is caused by recurrent PEs, which increase pulmonary resistance and lead to secondary pulmonary hypertension.

CLINICAL CORRELATE

The classic presentation of pulmonary embolism, which occurs in <20% of patients, includes hemoptysis, dyspnea, and chest pain.

Infarction

Infarction is a localized area of necrosis secondary to ischemia. Common sites of infarction include heart, brain, lungs, intestines, kidneys. Infarcts have multiple causes.

- Most infarcts (99%) result from thrombotic or embolic occlusion of an artery or vein.
- Less common causes include vasospasm and torsion of arteries and veins (e.g., volvulus, ovarian, and testicular torsion).

On gross examination infarctions typically have a wedge shape, with the apex of the wedge tending to point to the occlusion.

- **Anemic infarcts (pale or white color)** occur in solid organs with a single blood supply such as the spleen, kidney, and heart.
- **Hemorrhagic infarcts (red color)** occur in organs with a dual blood supply or collateral circulation, such as the lung and intestines, and can also occur with venous occlusion (e.g., testicular torsion).

KP00710.indb 35 13/10/22 1:51 PM

- Microscopic pathology of infarction can show either coagulative necrosis (most organs) or liquefactive necrosis (brain). The general sequence of tissue changes after infarction is as follows:

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

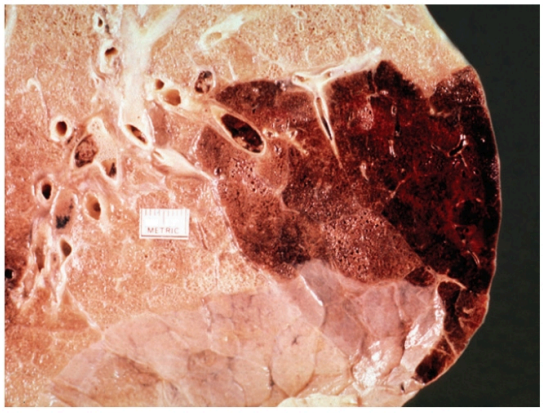


Figure 5-4. Wedge-Shaped Pulmonary Infarction

SHOCK

Shock is characterized by vascular collapse and widespread hypoperfusion of cells and tissue due to reduced blood volume, cardiac output, or vascular tone. The cellular injury is initially reversible; if the hypoxia persists, the cellular injury becomes irreversible, leading to the death of cells and the patient.

Major Causes of Shock

- **Cardiogenic shock** (pump failure) can be due to myocardial infarction, cardiac arrhythmias, pulmonary embolism, and cardiac tamponade.
- **Hypovolemic shock** (reduced blood volume) can be due to hemorrhage, fluid loss secondary to severe burns, and severe dehydration.
- **Septic shock** (viral or bacterial infection) causes cytokines to trigger vasodilatation and hypotension, acute respiratory distress syndrome (ARDS), DIC, and multiple organ dysfunction syndrome. Mortality rate is 20%.
- **Neurogenic shock** (generalized vasodilatation) can be seen with anesthesia and brain or spinal cord injury.
- **Anaphylactic shock** (generalized vasodilatation) is a type I hypersensitivity reaction.

KP00710.indb 36 13/10/22 1:51 PM

Stages of Shock

The stages of shock are arbitrarily defined as follows.

- **Stage I: compensation**

  Perfusion to vital organs is maintained by reflex mechanisms. Compensation is characterized by increased sympathetic tone, release of catecholamines, and activation of the renin-angiotensin system.

- **Stage II: decompensation**

  There is a progressive decrease in tissue perfusion, leading to potentially reversible tissue injury with development of a metabolic (lactic) acidosis, electrolyte imbalances, and renal insufficiency.

- **Stage III: irreversible tissue injury and organ failure**

  This ultimately results in death.

The organs show various manifestations of shock:

- Kidneys show fibrin thrombi in glomeruli and ultimately, acute tubular failure ensues, which causes oliguria and electrolyte imbalances.
- Lungs undergo diffuse alveolar damage ("shock lung").
- Intestines show superficial mucosal ischemic necrosis and hemorrhages, and with prolonged injury, bacteremia may ensue.

KP00710.indb 37 13/10/22 1:51 PM

Genetic Disorders and Disorders of Sexual Development

6

LEARNING OBJECTIVES

- ❑ Answer questions about disorders involving an extra autosome and chromosomal deletions
- ❑ Demonstrate understanding of Mendelian disorders, autosomal recessive/dominant, and X-linked recessive/dominant conditions
- ❑ Solve problems concerning triplet repeat mutations
- ❑ Explain information related to mitochondrial DNA disorders and multifactorial inheritance

CYTOGENETIC DISORDERS

Disorders Involving an Extra Autosome

Down syndrome (trisomy 21) is the **most common** of the chromosomal disorders.

The most common **karyotype** is 47, XX, +21. Down syndrome risk increases with maternal age to an incidence of 1 in 25 live births in women age ≥45. The pathogenesis involves meiotic nondisjunction (95%), Robertsonian translocation (4%), or mosaicism due to mitotic nondisjunction during embryogenesis (1%).

Clinical findings can include intellectual disability, mongoloid facial features (flat face, low-bridged nose, and epicanthal folds), Brushfield spots (speckled appearance of the iris), muscular hypotonia, broad short neck, palmar (simian) crease, and congenital heart defects. Endocardial cushion defect, if present, leads to the formation of an atrioventricular canal (a common connection between all 4 chambers of the heart). Additional clinical problems that can develop include duodenal atresia ("double-bubble" sign), Hirschsprung disease, increased risk (15–20 fold) of acute lymphoblastic leukemia (ALL), and Alzheimer disease (by age 40 virtually all will develop Alzheimer disease).

Prenatal tests include maternal serum tests, ultrasonography, amniocentesis, and chorionic villus sampling.

Median life expectancy is 47 years.

NOTE

Robertsonian Translocation

Defined as a translocation involving 2 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 ≥2 populations of cells within an individual.

KP00710.indb 39 13/10/22 1:51 PM

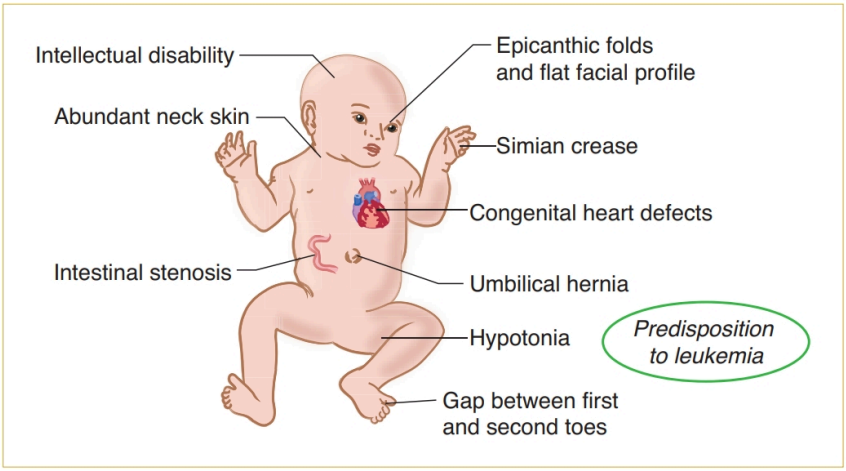


Figure 6-1. Down Syndrome

Edwards syndrome (trisomy 18) is caused by nondisjunction. The risk increases with maternal age.

Clinical findings can include intellectual disability, low-set ears and micrognathia, congenital heart defects, overlapping flexed fingers, and rocker-bottom feet. There is a very poor prognosis due to severe congenital malformations.

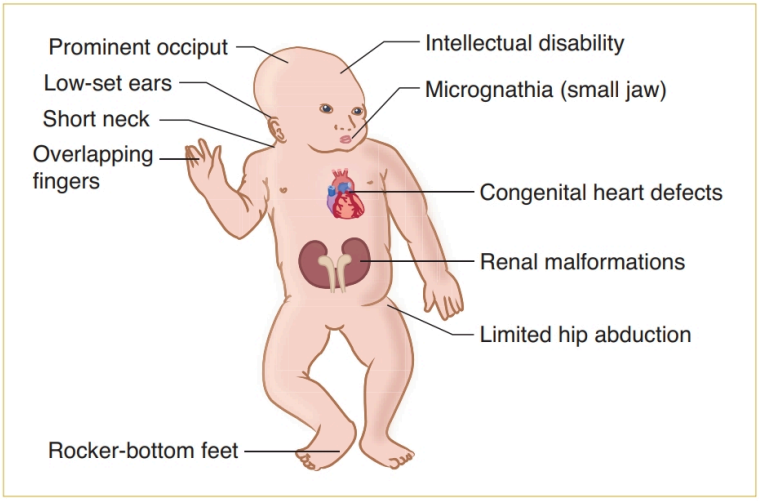


Figure 6-2. Edwards Syndrome

Patau syndrome (trisomy 13) is caused by nondisjunction. The risk increases with maternal age.

Clinical findings can include intellectual disability, cleft lip and/or palate, cardiac defects, renal abnormalities, microcephaly, holoprosencephaly, and polydactyly. The very poor prognosis is due to severe congenital malformations.

KP00710.indb 40 13/10/22 1:51 PM

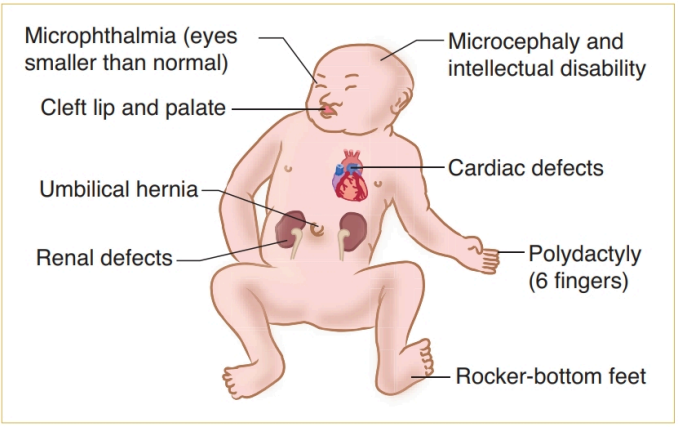


Figure 6-3. Patau Syndrome

Disorders Involving Chromosomal Deletions

Cri du chat syndrome is due to deletion of the short arm of chromosome 5. Clinical findings include a characteristic high-pitched catlike cry, intellectual disability, congenital heart disease, and microcephaly. **Microdeletions** include 13q14 (retinoblastoma gene) and 11p13 (WAGR complex, consisting of Wilms tumor, aniridia, genitourinary anomalies, and intellectual disability [formerly known as mental retardation]). Microdeletions are too small to be detected by karyotyping and require molecular techniques for detection.

Disorders Involving Sex Chromosomes

Klinefelter syndrome is caused by meiotic nondisjunction and is a common cause of male hypogonadism. The most common karyotype is 47,XXY. Lab studies show elevated FSH and LH with low levels of testosterone. Clinical findings include testicular atrophy, infertility due to azoospermia, eunuchoid body habitus, high-pitched voice, female distribution of hair, and gynecomastia.

Turner syndrome is a common cause of female hypogonadism. The most common karyotype is 45,X. The second X chromosome is necessary for oogenesis and normal development of the ovary. Clinically, patients fail to develop secondary sex characteristics and have short stature with widely spaced nipples. Other features include gonadal dysgenesis with atrophic streak ovaries, primary amenorrhea, and infertility.

Clinical features involving other organ systems include cystic hygroma and webbing of the neck, hypothyroidism, congenital heart disease (preductal coarctation of the aorta and bicuspid aortic valve), and hydrops fetalis. Females with 45,X/46,XY mosaicism are at risk for gonadoblastoma and microdeletions.

NOTE

The presence of a Y chromosome determines male phenotype due to the presence of the testes-determining factor gene (also called the sex-determining region Y [SRY]) on the Y chromosome.

KP00710.indb 41 13/10/22 1:51 PM

NOTE

In **Lyon's hypothesis of X-inactivation**, only one X is genetically active. Most (though not all) of the genes on the other X chromosome are inactivated.

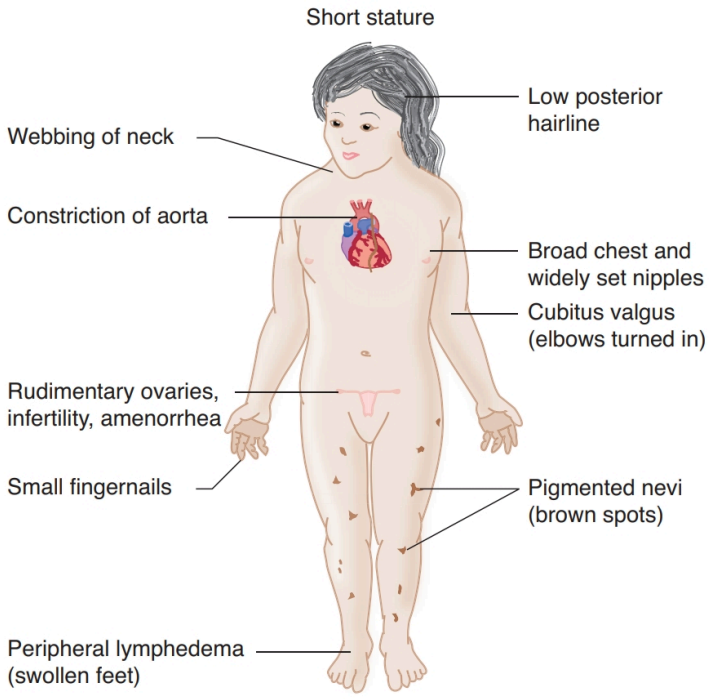


Figure 6-4. Turner Syndrome

DISORDERS WITH MENDELIAN INHERITANCE

General Principles

Mendelian disorders are characterized by single gene mutations. Common types of mutations include point mutations and frameshift mutations.

- **Point mutations** occur with a single nucleotide base substitution, which may produce a variety of effects. The form of point mutation called synonymous mutation (silent mutation) occurs when a base substitution results in a codon that codes for the same amino acid. The form of point mutation called missense mutation occurs when a base substitution results in a new codon and a change in amino acids. The form of point mutation called a nonsense mutation occurs when a base substitution produces a stop codon, and therefore produces a truncated protein.
- **Frameshift mutations** occur when insertion or deletion of bases leads to a shift in the reading frame of the gene.

The location of a mutation will alter its potential effects. Mutations involving coding regions of DNA may result in abnormal amino acid sequences, decreased production of the protein, truncated or abnormally folded protein, or altered or lost function of the protein. Mutations of promoter or enhancer regions may interfere with transcription factors, resulting in decreased transcription of the gene.

NOTE

Patterns of inheritance for genetic diseases show wide variation, and the genetic pattern of a disease may be classified as autosomal dominant, autosomal recessive, X-linked recessive, X-linked dominant, triplet repeat mutations, genomic imprinting, mitochondrial, or multifactorial.

KP00710.indb 42 13/10/22 1:51 PM

Table 6-1. 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

Autosomal Recessive Disorders

(This material is included here for reinforcement. It is also covered in the Physiology Lecture Notes.)

Cystic fibrosis (CF) is the most common lethal genetic disorder in Caucasians. It is due to mutation of the chloride channel protein, cystic fibrosis transmembrane conductance regulator (CFTR), whose *CFTR* gene is located on chromosome 7 and most commonly has been damaged by a deletion of the amino acid phenylalanine at position 508 (ΔF508). The defective chloride channel protein leads to abnormally thick viscous mucus, which obstructs the ducts of exocrine organs.

The **distribution of disease** reflects the distribution of eccrine sweat glands and exocrine glands.

- In the lungs, CF may cause recurrent pulmonary infections, chronic bronchitis, and bronchiectasis.
- In the pancreas, CF may cause plugging of pancreatic ducts (resulting in atrophy and fibrosis) and pancreatic insufficiency (leading to fat malabsorption, malodorous steatorrhea, and deficiency of fat-soluble vitamins).
- In the male reproductive system, CF may be associated with absence or obstruction of the vas deferens and epididymis, which often leads to male infertility.
- In the liver, plugging of the biliary canaliculi may result in biliary cirrhosis.
- In the GI tract, the thick secretions may cause small intestinal obstruction (meconium ileus).

Diagnosis can be established with a sweat test (elevated NaCl) or DNA probes. Due to improved therapies, some patients live into their forties, but with this increase in longevity there has been an increase in liver disease. Patients succumb to pulmonary disease. The 3 most common pulmonary infections are *S. aureus*, *H. influenzae*, and *P. aeruginosa*. Lung transplantation is a treatment option. Patients infected with *Burkholderia cepacia* complex and who undergo transplant have a worse prognosis.

NOTE

CF seems to break 2 rules of genetics:

- Inheritance is autosomal recessive, even though the affected protein is a receptor protein.
- The clinical manifestations vary widely, which is more characteristic of autosomal dominant disorders.

BRIDGE TO BIOCHEMISTRY

Most CF cases result from deletion of phenylalanine at position 508 (ΔF508), which interferes with proper protein folding and the post-translational processing of oligosaccharide side chains. The abnormal chloride channel protein is degraded by the cytosolic proteasome complex rather than translocated to the cell membrane.

KP00710.indb 43 13/10/22 1:51 PM

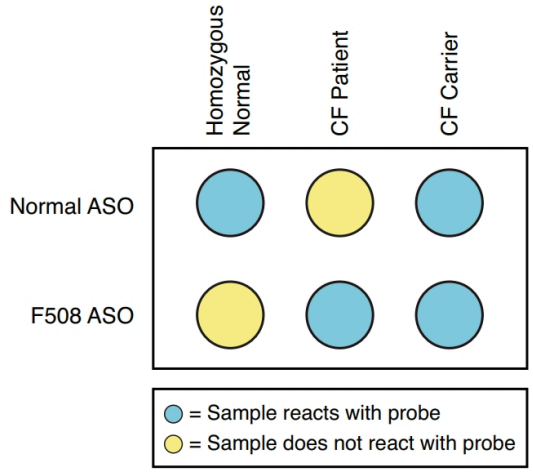


Figure 6-5. The Use of Allele-Specific Oligonucleotide (ASO) Probes for Cystic Fibrosis

BRIDGE TO BIOCHEMISTRY

Phenylalanine hydroxylase converts phenylalanine into tyrosine.

Phenylketonuria (PKU) is due to deficiency of phenylalanine hydroxylase, resulting in toxic levels of phenylalanine and a lack of tyrosine.

Clinically, affected children are normal at birth but, if undiagnosed and untreated, develop intellectual development disorder by age 6 months. The lack of tyrosine causes light-colored skin and hair, since melanin is a tyrosine derivative. Affected children may have a mousy or musty odor to the sweat and urine (secondary to metabolite [phenylacetate] accumulation).

Screening for PKU is done at birth. Treatment is dietary restriction of phenylalanine, including avoidance of the artificial sweetener aspartame.

A genetic variant, **benign hyperphenylalaninemia**, has partial enzyme deficiency with mildly increased levels of phenylalanine that are insufficient to cause intellectual disability.

In a minority of cases, an abnormality of the cofactor tetrahydrobiopterin causes a variant that does not respond to dietary restriction.

Transplacental accumulation of phenylalanine can cause problems with fetal development in cases of maternal PKU. Prevention requires maternal dietary restriction.

Alkaptonuria (ochronosis) occurs when deficiency of homogentisic acid oxidase results in the accumulation of homogentisic acid. The homogentisic acid has an affinity for connective tissues (especially cartilage), resulting in a black discoloration (as a consequence of oxidation of homogentisic acid).

Clinical features include urine that is initially pale yellow but turns black upon standing, and black-stained cartilage, which causes discoloration of the nose and ears. Alkaptonuria also predisposes for early onset of degenerative arthritis.

Albinism is caused by a lack of the enzyme tyrosinase needed for melanin production. Affected individuals show deficiency of melanin pigmentation in the skin, hair follicles, and eyes (oculocutaneous albinism), with resulting increased risk of basal cell and squamous cell carcinomas.

KP00710.indb 44 13/10/22 1:51 PM

The **glycogen storage diseases** are a group of rare diseases that have in common a deficiency of one of the enzymes necessary for the metabolism of glycogen, which results in the accumulation of glycogen in the liver, heart, and skeletal muscle.

- **Type I (von Gierke disease)** is due to a deficiency of *glucose-6-phosphatase* and is characterized clinically by hepatomegaly and hypoglycemia.
- **Type II (Pompe disease)** is due to a deficiency of *lysosomal α-1,4-glucosidase (acid maltase)* and is characterized clinically by hepatomegaly, skeletal muscle hypotonia, cardiomegaly, and death from cardiac failure by age 2 years.
- **Type V (McArdle syndrome)** is due to a deficiency of *muscle glycogen phosphorylase* and is characterized clinically by exercise-induced muscle cramps.

Tay-Sachs disease is due to a deficiency of hexosaminidase A (due to mutation of *HEXA* gene on chromosome 15), which leads to the accumulation of GM2 ganglioside in the lysosomes of the CNS and retina. Tay-Sachs is common in Ashkenazi Jews (1 in 30 carrier rate).

The distribution of disease involves the retina (cherry-red spot due to accentuation of the macula) and central nervous system (CNS) (dilated neurons with cytoplasmic vacuoles). Affected children are normal at birth, but by 6 months show onset of symptoms (progressive mental deterioration and motor incoordination) that progress to death by age 2–3 years. **Electron microscopy** shows distended lysosomes with whorled membranes; the diagnosis can also be established with enzyme assays and DNA probes.

NOTE

Lysosomal Storage Diseases

Defined as a deficiency of a lysosomal enzyme (acid hydrolase), which leads to the accumulation of a complex substrate within the lysosome leading to enlarged cells that become dysfunctional

- Tay-Sachs
- Niemann-Pick
- Gaucher
- Mucopolysaccharidosis
- Fabry
- Metachromatic leukodystrophy

Table 6-2. Lysosomal Storage Diseases

Disease	Enzyme Deficiency	Accumulating Substance
Tay-Sachs disease	Hexosaminidase A	GM2 ganglioside
Niemann-Pick disease types A and B	Sphingomyelinase	Sphingomyelin
Gaucher disease	Glucocerebrosidase	Glucocerebroside
Fabry disease	α-galactosidase A	Ceramide trihexoside
Metachromatic leukodystrophy	Arylsulfatase A	Sulfatide
Hurler syndrome	α-L-iduronidase	Dermatan sulfate Heparan sulfate
Hunter syndrome	L-iduronate sulfatase	Dermatan sulfate Heparan sulfate

KP00710.indb 45 13/10/22 1:51 PM

NOTE

"Zebra bodies" are concentric lamellated inclusions seen in the cytoplasm on electron microscopy. Although they are present in Niemann-Pick disease, they are also present in other diseases including Fabry disease and Hurler syndrome.

Niemann-Pick disease is caused by a deficiency of sphingomyelinase, which leads to the accumulation of sphingomyelin within the lysosomes of the CNS and reticuloendothelial system (monocytes and macrophages located in reticular connective tissue). Niemann-Pick is common in Ashkenazi Jews (note similarity to Tay-Sachs disease).

The distribution of disease depends on the form of disease but can involve the retina (cherry-red spot; note similarity to Tay-Sachs disease), CNS (distended neurons with a foamy cytoplasmic vacuolization; note similarity to Tay-Sachs disease), and reticuloendothelial system (hepatosplenomegaly, lymphadenopathy, and bone marrow involvement; note difference from Tay-Sachs disease).

In Niemann-Pick **types A and B**, there is a mutation affecting an enzyme that metabolizes lipids; organomegaly occurs, and with type A, there is severe neurologic damage. In **type C**—the most common form—a defect in cholesterol transport causes ataxia, dysarthria, and learning difficulties. All forms are lethal, usually before adulthood.

Gaucher disease is the most common lysosomal storage disorder. Deficiency of glucocerebrosidase leads to the accumulation of glucocerebroside, predominately in the lysosomes of the reticuloendothelial system (monocytes and macrophages located in reticular connective tissue).

Type I represents 99% of cases and presents in adulthood with hepatosplenomegaly; thrombocytopenia/pancytopenia secondary to hypersplenism; lymphadenopathy; and bone marrow involvement that may lead to bone pain, deformities, and fractures. CNS manifestations occur in **types II and III**.

The characteristic **Gaucher cells** are enlarged macrophages with a fibrillary (tissue paper–like) cytoplasm. Diagnosis can be established with biochemical enzyme assay of glucocerebrosidase activity.

Mucopolysaccharidosis (MPS) is a group of lysosomal storage disorders characterized by deficiencies in the lysosomal enzymes required for the degradation of mucopolysaccharides (glycosaminoglycans).

Clinical features include intellectual disability, cloudy cornea, hepatosplenomegaly, skeletal deformities and coarse facial features, joint abnormalities, and cardiac lesions. MPS I (Hurler syndrome) is the severe form and is due to deficiency of α-L-iduronidase. MPS II (Hunter syndrome) is a milder form, it shows X-linked recessive inheritance and is due to a deficiency of L-iduronate sulfatase.

Autosomal Dominant Disorders

Familial hypercholesterolemia is the most common inherited disorder (incidence 1 in 500) and is due to a mutation in the low density lipoprotein (LDL) receptor gene (LDLR) on chromosome 19. The mutations in the LDL receptor cause increased levels of circulating cholesterol, loss of feedback inhibition of HMG-coenzyme A (HMG-CoA) reductase, and increased phagocytosis of LDL by macrophages.

BRIDGE TO BIOCHEMISTRY

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

There are 5 major **classes of mutation**.

- **Class I:** no LDL receptor synthesis
- **Class II:** defect in transport out of the endoplasmic reticulum

KP00710.indb 46 13/10/22 1:51 PM

- **Class III:** defect in LDL receptor binding
- **Class IV:** defect in ability to internalize bound LDL
- **Class V:** defect in the recycling of the LDL receptor

Clinical features include elevated serum cholesterol (heterozygotes have elevations of 2–3 times the normal level and homozygotes have elevations of 5–6 times the normal level), skin xanthomas (collections of lipid-laden macrophages), xanthelasma around the eyes, and premature atherosclerosis (homozygotes often develop myocardial infarctions in late teens and twenties).

Marfan syndrome is due to a mutation of the **fibrillin** gene (*FBN1*) on chromosome 15q21. Fibrillin is a glycoprotein that functions as a scaffold for the alignment of elastic fibers.

Clinical features include skeletal changes (tall, thin build with long extremities, hyperextensible joints, pectus excavatum [inwardly depressed sternum], and pectus carinatum [pigeon breast]) and abnormal eyes (ectopia lentis, characterized by bilateral subluxation of the lens). The cardiovascular system is also particularly vulnerable; it may show cystic medial degeneration of the media of elastic arteries with a loss of elastic fibers and smooth muscle cells with increased risk of dissecting aortic aneurysm (a major cause of death), dilatation of the aortic ring potentially leading to aortic valve insufficiency, and/or mitral valve prolapse.

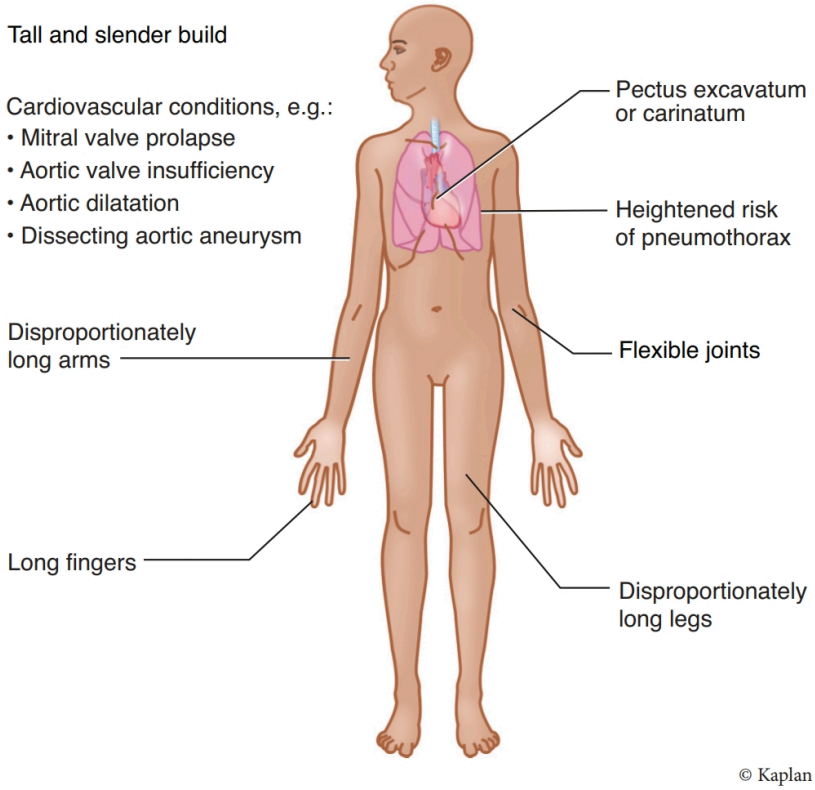


Figure 6-6. Clinical Features of Marfan Syndrome

KP00710.indb 47 13/10/22 1:51 PM

NOTE

Disorders of collagen biosynthesis include scurvy, osteogenesis imperfecta, Ehlers-Danlos syndrome, Alport syndrome, and Menkes disease.

Ehlers-Danlos syndrome (EDS) is a group of inherited connective tissue diseases that share a common a defect in collagen structure or synthesis. Clinically, the disease causes hyperextensible skin that is easily traumatized and hyperextensible joints secondary to effects on the joints and adjacent ligaments.

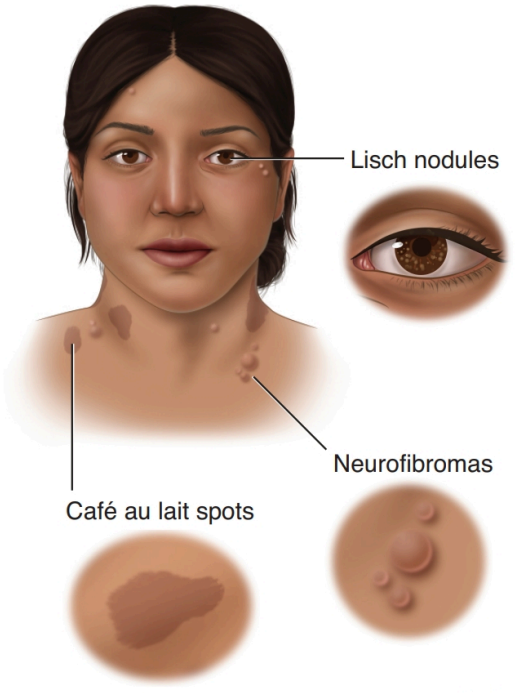
There are a number of variants with different modes of inheritance.

- **Kyphoscoliotic EDS:** autosomal recessive form
- **Vascular variant EDS:** autosomal dominant form that causes rupture of vessels and bowel wall
- **Classical EDS:** autosomal dominant form that causes a type V collagen defect; patients have a normal lifespan

Neurofibromatosis results from defects in tumor suppressor genes.

Type 1 (**von Recklinghausen disease**) neurofibromatosis (90% of cases) has an incidence of 1 in 3,000. The condition is due to a mutation of the tumor suppressor gene *NF1* located on chromosome 17 (17q11.2). The normal gene product (neurofibromin) inhibits p21 ras oncoprotein.

- Affected individuals characteristically have multiple neurofibromas and benign tumors of peripheral nerves that are often numerous and may be disfiguring. The plexiform variant of the neurofibromas is diagnostic.
- Rarely (3%), malignant transformation of a neurofibroma may occur.
- Other clinical features include pigmented skin lesions (6 or more "café-au-lait spots" that are light brown macules usually located over nerves); pigmented iris hamartomas (Lisch nodules); and increased risk of meningiomas and pheochromocytoma, an adrenal tumor that also occurs with von Hippel-Lindau disease and MEN 2.



© Kaplan

Figure 6-7. Clinical Features of Neurofibromatosis Type 1

KP00710.indb 48 13/10/22 1:51 PM

Type 2 (**bilateral acoustic**) neurofibromatosis (10% of cases) has an incidence of 1 in 45,000.

- There is a mutated tumor suppressor gene *NF-2* (22q12.2) on chromosome 22.
- The normal gene product (merlin) is a critical regulator of contact-dependent inhibition of proliferation.
- Clinical features include vestibular schwannomas (acoustic neuromas), and increased risk of meningioma and ependymomas.



© Richard P. Usatine, MD. Used with permission.

Figure 6-8. Multiple Subcutaneous Neural Tumors of Neurofibromatosis

von Hippel-Lindau disease is due to a mutation of the tumor suppressor gene *VHL* on chromosome 3p (3p26-p25). The normal gene product's main action is to tag proteins (e.g., hypoxia inducible factor 1a [a transcription factor that induces the expression of angiogenesis factors]) with ubiquitin for degradation.

Clinical manifestations can include retinal hemangioblastoma (von Hippel tumor); hemangioblastomas of the cerebellum, brain stem, and spinal cord (Lindau tumor); cysts of the liver, pancreas, and kidneys; and multiple bilateral renal cell carcinomas.

KP00710.indb 49 13/10/22 1:51 PM

X-Linked Recessive Conditions

In **X-linked recessive conditions**, males with a mutant recessive gene on the X chromosome have the condition, while daughters of affected males are obligate carriers, who in many situations are asymptomatic.

- Sons of affected males do not carry the mutation.
- Daughters of carrier females may be either normal or carriers.
- Sons of carrier females may be affected or normal (because males are hemizygous for the X chromosome).

Lesch-Nyhan syndrome results from deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGPRT), which impairs salvaging of the purines hypoxanthine and guanine. Clinical features include intellectual disability, hyperuricemia, and self-mutilation.

Testicular feminization is an androgen insensitivity that causes failure of normal masculinization of external genitalia of XY males.

In **Bruton agammaglobulinemia**, defective Bruton tyrosine kinase (*Btk*) at band Xq21.3 causes complete failure of immunoglobulin production characterized clinically by complete absence of antibodies in serum and recurrent bacterial infections. (*See* the Immunopathology chapter 7.)

In **Menkes disease**, a mutation of the *ATP7A* gene impairs copper distribution. Infants show failure to thrive, and death occurs in the first decade.

X-Linked Dominant Conditions

X-linked dominant conditions are similar to X-linked recessive, but both males and females show disease. An example is Alport syndrome, which is a hereditary glomerulonephritis with nerve deafness. Alport syndrome can also be inherited in other patterns.

NOTE

Most common genetic causes of intellectual developmental disorder:

- Down syndrome
- Fragile X syndrome

DISORDERS WITH PATTERNS OF INHERITANCE OTHER THAN MENDELIAN

Triplet Repeat Mutations

NOTE

Triplet repeat expansion can occur in a coding region (Huntington and spinobulbar muscular atrophy) or in an untranslated region of the gene (fragile X and myotonic dystrophy).

Fragile X syndrome is due to triplet nucleotide repeat mutations, so that the nucleotide sequence CGG repeats typically hundreds to thousands of times. The mutation occurs in the *FMR-1* gene (fragile X mental retardation-1) on the X chromosome (Xq27.3), and the disease behaves as an X-linked dominant disease that causes intellectual disability in all affected males and 50% of female carriers. The characteristic phenotype includes elongated face with a large jaw, large everted ears, and macroorchidism. The condition can be diagnosed with DNA probe analysis.

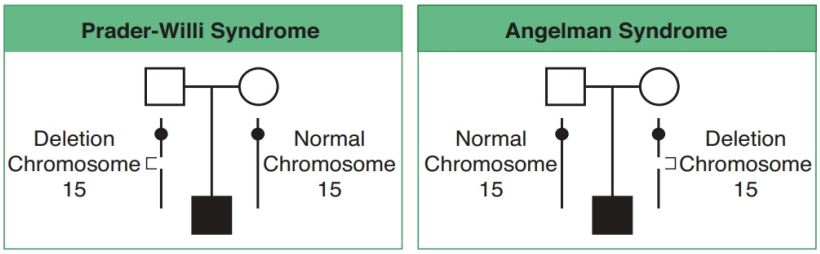
Huntington disease is due to a triplet repeat mutation (CAG) of the *HTT* gene that produces an abnormal protein (huntingtin), which is neurotoxic and causes atrophy of the caudate nucleus. Huntington disease has an early onset (age range: 20–50 years) of progressive dementia with choreiform movements.

KP00710.indb 50 13/10/22 1:51 PM

Genomic Imprinting

Genomic imprinting refers to differential expression of genes based on chromosomal inheritance from maternal versus paternal origin.

- In **Prader-Willi syndrome**, microdeletion on paternal chromosome 15 {del(15)(q11;q13)} causes intellectual disability, obesity, hypogonadism, and hypotonia.
- In **Angelman syndrome**, microdeletion on maternal chromosome 15 {del(15)(q11;q13)} causes intellectual disability, seizures, ataxia, and inappropriate laughter.



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

Figure 6-9. Genomic Imprinting

Mitochondrial DNA Disorders

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

- **Leber hereditary optic neuropathy** causes loss of retinal cells, which leads to central vision loss.
- **Myoclonic epilepsy with ragged red fibers (MERRF)** is a mitochondrial disorder characterized by epilepsy, ataxia, peripheral neuropathy, and deterioration in cognitive ability. Sensorineural hearing loss and ocular dysfunction can also develop. Patients have short stature and cardiomyopathy. On muscle biopsy, ragged red fibers are seen on Gomori trichrome staining due to the accumulation of mitochondria.

MULTIFACTORIAL INHERITANCE

Multifactorial inheritance refers to disease caused by a combination of multiple minor gene mutations and environmental factors. Examples include open neural tube defects and type 2 diabetes mellitus.

Polymorphisms are variants of genes; some diseases with polygenic inheritance are the result of multiple polymorphisms.

KP00710.indb 51 13/10/22 1:51 PM

DISORDERS OF SEXUAL DEVELOPMENT (DSD)

Disorders of sexual development are rare congenital conditions that affect sex chromosomes, gonads, and the ability to make sex hormones. The genitalia may be ambiguous or may not correspond to the anticipated sex. Some cases are diagnosed prenatally and others are not detected until after adolescence.

Determination of sex can be established by a variety of methods that do not necessarily completely agree.

- **Karyotypic** (genetic) sex refers to which sex chromosomes an individual has; the presence of a Y chromosome results in testicular development.
- **Gonadal** sex refers to the presence of ovarian or testicular tissue.
- **Ductal sex** refers to the presence of Müllerian (female: Fallopian tube, uterus, cervix, and upper portion of vagina) or Wolffian (male: epididymis, vas deferens, seminal vesicles, and ejaculatory ducts) duct adult derivatives.
- **Phenotypic** (genital) sex refers to the external appearance of the genitalia.

Individuals with **ovotesticular disorder** have both ovarian and testicular tissue, which is an extremely rare condition. The most common karyotype of ovotesticular disorder is 46,XX. The gonadal sex can be either an ovary on one side and testis on the other, or ovotestes, in which there is a gonad with both testicular and ovarian tissue. The ductal sex is often mixed, and the phenotypic sex shows ambiguous genitalia.

NOTE

Cloacal exstrophy is a birth defect involving the bladder, intestines, and genitalia.

The **46, XX DSD category** includes individuals (formerly characterized as *female pseudohermaphrodites*) with disorders of ovarian development, androgen excess, vaginal atresia, and cloacal exstrophy. The **46, XY category** includes individuals (formerly characterized as *male pseudohermaphrodites*) with disorders of testicular development, disorders of androgen synthesis, severe hypospadias, and cloacal exstrophy.

KP00710.indb 52 13/10/22 1:51 PM

Immunopathology 7

LEARNING OBJECTIVES

- ❑ Explain information related to hypersensitivity reactions and autoimmune diseases
- ❑ Answer questions about primary/secondary immune deficiency syndromes
- ❑ Demonstrate understanding of AIDS
- ❑ Answer questions about immunology of transplant rejection

HYPERSENSITIVITY REACTIONS

(This material is included here for reinforcement. It is also covered in the Immunology Lecture Notes.)

Immediate Hypersensitivity

Type I (immediate) hypersensitivity reactions **(anaphylactic type)** are characterized by IgE-dependent release of chemical mediators from mast cells and basophils. Cross-linking of IgE bound to antigen to IgE Fc receptors on the surface of mast cells and basophils causes degranulation. This binding triggers release of chemical mediators that include histamine and heparin; eosinophil chemotactic factor; leukotriene B4 and neutrophil chemotactic factor; and prostaglandin D4, platelet-activating factor (PAF), and leukotrienes C4 and D4. Influx of eosinophils amplifies and perpetuates the reaction. Effects may be systemic (anaphylaxis, as for example due to bee stings or drugs) or localized (food allergies, atopy, and asthma).

Antibody-Mediated Hypersensitivity

Type II hypersensitivity reactions (antibody-mediated) are mediated by IgG or IgM antibodies directed against a specific target cell or tissue. Reactions can take several forms.

- In complement-dependent cytotoxicity, fixation of complement results in osmotic lysis or opsonization of antibody-coated cells; examples include autoimmune hemolytic anemia, transfusion reactions, and erythroblastosis fetalis.
- In antibody-dependent cell-mediated cytotoxicity (ADCC), cytotoxic killing of an antibody-coated cell occurs; an example is pernicious anemia. Antireceptor antibodies can activate or interfere with receptors; examples include Graves disease and myasthenia gravis.

KP00710.indb 53 13/10/22 1:51 PM

Immune Complex–Mediated Hypersensitivity

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

Cell-Mediated Hypersensitivity

Type IV hypersensitivity reactions **(cell-mediated type)** are mediated by sensitized T lymphocytes. In delayed type hypersensitivity, CD4+ TH1 lymphocytes mediate granuloma formation; examples include the PPD skin test and tuberculosis.

In cytotoxic T-cell–mediated hypersensitivity, CD8+ T-cell lymphocytes destroy antigen-containing cells; examples include type 1 diabetes, virus-infected cells, immune reaction to tumor-associated antigens, and graft rejection.

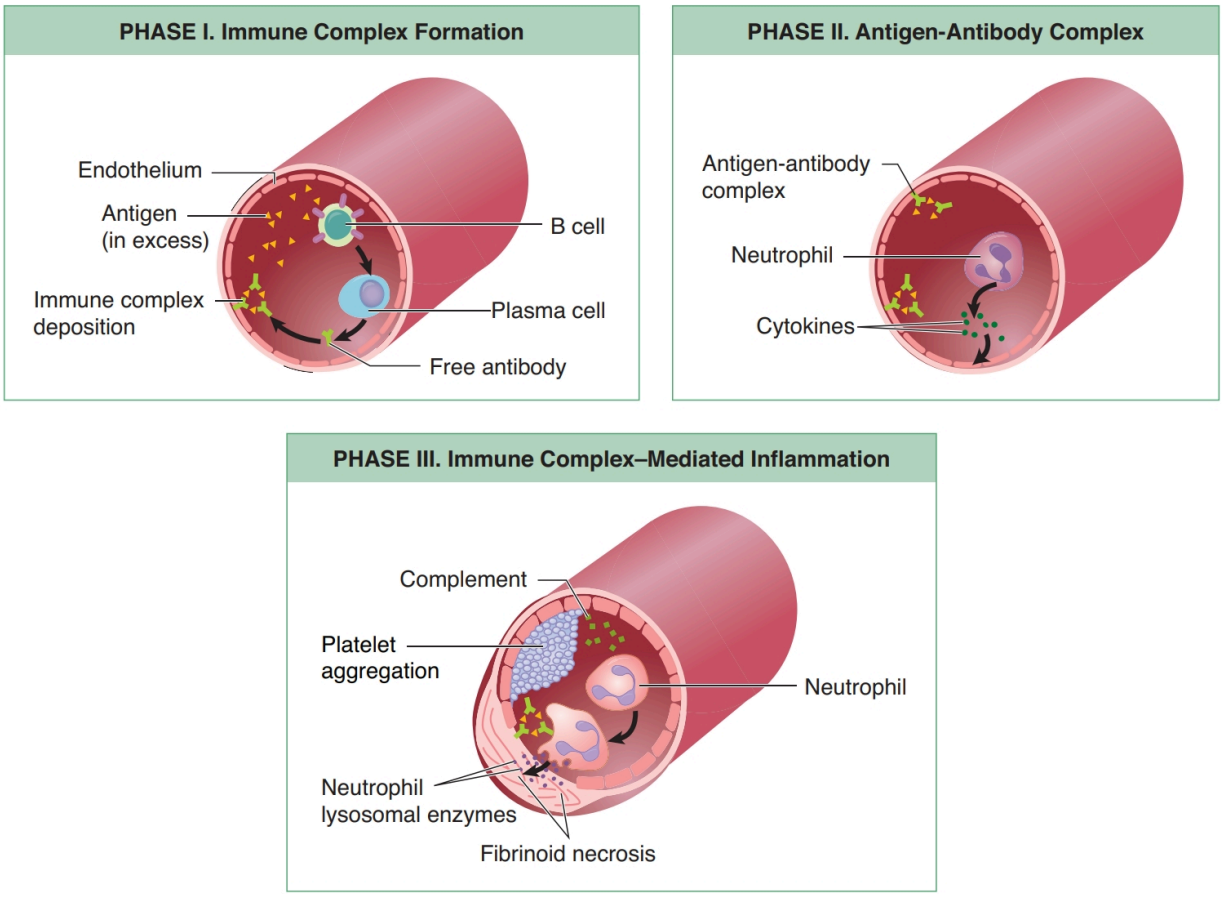


Figure 7-1. Type III Hypersensitivity

KP00710.indb 54 13/10/22 1:51 PM

AUTOIMMUNE DISEASES

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by loss of self-tolerance and production of autoantibodies. Females are affected much more often than males (M:F = 1:9); peak incidence is age 20–45; and African Americans are affected more often than Caucasians. The mechanism of injury in lupus is a mix of type II and III hypersensitivity reactions.

- Important **autoantibodies** that may be detected in the sera from lupus patients include antinuclear antibody (ANA) (>95%); anti-dsDNA (40–60%); anti-Sm (20–30%); antihistone antibodies; nonhistone nuclear RNA proteins; and blood cells.
- SLE affects **many organ systems**.
  - Hematologic (type II hypersensitivity reaction) manifestations can include hemolytic anemia, thrombocytopenia, neutropenia, and lymphopenia.
  - Skeletal manifestations include arthritis characterized by polyarthralgia and synovitis without joint deformity (type III hypersensitivity reaction).
  - Skin (type III hypersensitivity reaction) manifestations can include a malar "butterfly" rash; maculopapular rash; and ulcerations and bullae formation.
  - Serosal surfaces may also be affected, with resulting pericarditis, pleuritis, or pleural effusions (type III hypersensitivity reaction).
  - CNS manifestations include focal neurologic symptoms, seizures, and psychosis (type III hypersensitivity reaction).
  - Cardiac manifestations include Libman-Sacks endocarditis (nonbacterial verrucous endocarditis) (type III hypersensitivity reaction).
- Of particular importance are the renal manifestations (type III hypersensitivity) classified by the Society of Nephrology/Renal Pathology Society as follows.
  - **Class I**: minimal mesangial lupus nephritis
  - **Class II**: mesangial proliferative lupus nephritis
  - **Class III**: focal (< 50%) lupus nephritis
  - **Class IV**: diffuse (> 50%) lupus nephritis
  - **Class V**: membranous lupus nephritis
  - **Class VI**: advanced sclerosing lupus nephritis
- Lupus is treated with **steroids** and **immunosuppressive agents**. It tends to have a chronic, unpredictable course with remissions and relapses. The 10-year survival is 85%, with death frequently being due to renal failure or infections.

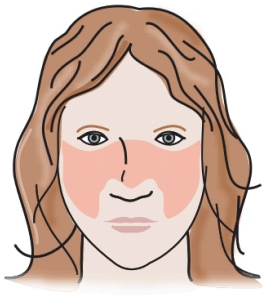
Sjögren syndrome (sicca syndrome) is an autoimmune disease characterized by destruction of the lacrimal and salivary glands, resulting in the inability to produce saliva and tears. Females are affected more often than males, with typical age 30–50.

NOTE

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

CLINICAL CORRELATE

Antihistone antibodies: Hydralazine, isoniazid, and procainamide can cause a lupus-like syndrome with antihistone antibodies.



Butterfly Rash

CLINICAL CORRELATE

Maternal **anti-Ro (SS-A) antibodies** have been implicated in the pathogenesis of congenital complete heart block.

KP00710.indb 55 13/10/22 1:51 PM

Clinical manifestations include keratoconjunctivitis sicca (dry eyes) and corneal ulcers; xerostomia (dry mouth); and Mikulicz syndrome (enlargement of the salivary and lacrimal glands). Sjögren syndrome is often associated with rheumatoid arthritis and other autoimmune diseases. The characteristic autoantibodies are the anti-ribonucleoprotein antibodies SS-A (Ro) and SS-B (La). There is an increased risk of developing non-Hodgkin lymphoma.

NOTE

CREST Syndrome

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

Scleroderma (progressive systemic sclerosis) is an autoimmune disease characterized by fibroblast stimulation and deposition of collagen in the skin and internal organs. It affects females more than males, with typical age range of 20 to 55 years. The pathogenesis involves activation of fibroblasts by cytokines interleukin 1 (IL-1), platelet-derived growth factor (PDGF), and/or fibroblast growth factor (FGF) with the resulting activated fibroblasts causing fibrosis.

- **Diffuse scleroderma** has anti-DNA topoisomerase I antibodies (Scl-70) (70%), widespread skin involvement, and early involvement of the visceral organs. Organs that can be affected include the esophagus (dysphagia), GI tract (malabsorption), lungs (pulmonary fibrosis which causes dyspnea on exertion), heart (cardiac fibrosis which may manifest as arrhythmias), and kidney (fibrosis that may manifest as renal insufficiency).
- **Localized scleroderma** (CREST syndrome) has anti-centromere antibodies, skin involvement of the face and hands, late involvement of visceral organs, and a relatively benign clinical course.

Dermatomyositis and polymyositis. See Skeletal Muscle chapter.

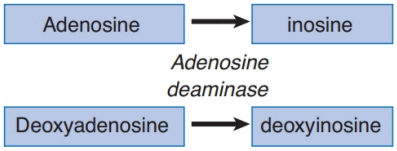
Mixed connective tissue disease is an overlap condition with features of systemic lupus erythematosus, systemic sclerosis, and polymyositis. Antiribonucleoprotein antibodies are nearly always positive.

IMMUNE DEFICIENCY DISEASES

Primary Immune Deficiency Syndromes

X-linked agammaglobulinemia of Bruton is an immunodeficiency characterized by a developmental failure to produce mature B cells and plasma cells, resulting in agammaglobulinemia. The condition occurs because of loss of function mutations of B-cell Bruton tyrosine kinase (BTK). Clinically, the disease affects male infants who have recurrent infections beginning at 6 months of life due to the loss of passive maternal immunity. Common infections include pharyngitis, otitis media, bronchitis, and pneumonia; common infecting organisms include *H. influenza, S. pneumococcus*, and *S. aureus*.

NOTE



Adenosine deaminase is an important enzyme in purine metabolism; a deficiency of it results in accumulation of deoxyadenosine within lymphoid progenitor cells.

Common variable immunodeficiency is a group of disorders characterized by defects in B-cell maturation that can lead to defective IgA or IgG production. Clinically, both sexes are affected with onset in childhood of recurrent bacterial infections and with increased susceptibility to *Giardia lamblia*. Complications include increased frequency of developing autoimmune disease, non-Hodgkin lymphoma, and gastric cancer.

DiGeorge syndrome is an embryologic failure to develop the 3rd and 4th pharyngeal pouches, resulting in the absence of the parathyroid glands and thymus. Clinical findings can include neonatal hypocalcemia and tetany, T-cell deficiency, and recurrent infections with viral and fungal organisms.

KP00710.indb 56 13/10/22 1:51 PM

Severe combined immunodeficiency (SCID) is a combined deficiency of cell-mediated and humoral immunity that is often caused by a progenitor-cell defect. The modes of inheritance are variable and can include X-linked (mutation of the common [gamma] chain of the interleukin receptors IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21) and autosomal recessive (deficiency of adenosine deaminase). Clinical features include recurrent infections with bacteria, fungi, viruses, and protozoa; susceptibility to *Candida*, cytomegalovirus (CMV) and *Pneumocystis jiroveci* infections, and adverse reactions to live virus immunizations. SCID is treated with hematopoietic stem cell transplantation since the prognosis without treatment is death of most infants within a year.

Wiskott-Aldrich syndrome is an X-linked recessive disease with mutation in the gene for Wiskott-Aldrich syndrome protein (WASP). The disease has a clinical triad of recurrent infections, severe thrombocytopenia, and eczema (chronic spongiform dermatitis). Treatment is hematopoietic stem cell transplantation. Complications include increased risk of non-Hodgkin lymphoma and death due to infection or hemorrhage.

Complement system disorders can involve a variety of factors, with deficiencies of different factors producing different clinical patterns.

In both the classical and alternate pathways, C3 deficiency causes both recurrent bacterial infections and immune complex disease, while C5, C6, C7, and C8 deficiencies cause recurrent meningococcal and gonococcal infections.

- In the classical pathway only, C1q, C1r, C1s, C2, and C4 deficiencies cause marked increases in immune complex diseases, including infections with pyogenic bacteria.
- In the alternate pathway, Factor B and properdin deficiencies cause increased neisserial infections. Deficiencies in complement regulatory proteins can cause C1-INH deficiency (hereditary angioedema), which is characterized clinically by edema at mucosal surfaces with low C2 and C4 levels.

MHC class II deficiency can be caused by defects in positive selection of thymocytes. Few CD4+ lymphocytes develop and as a result, patients suffer from severe immunodeficiency. Mutations in genes (i.e., *CIITA*) that encode proteins that regulate MHC class II gene expression are the cause. CD8+ T cells are unaffected.

Hyper IgM syndrome is characterized by normal B and T lymphocyte numbers and normal to elevated IgM levels but significantly decreased IgA, IgG, and IgE levels. Mutations in the gene for CD40 ligand result in the most common form of X-linked hyper IgM syndrome.

Selective IgA deficiency has unknown genetic etiology. Many affected individuals appear healthy while others have significant illness. Sinopulmonary infections, diarrhea and adverse reactions to transfusions can occur. Levels of IgA are undetectable whereas levels of other isotypes are normal. There is an association with autoimmune disease.

Phagocyte deficiencies (*See* chronic granulomatous disease in Inflammation chapter.)

KP00710.indb 57 13/10/22 1:51 PM

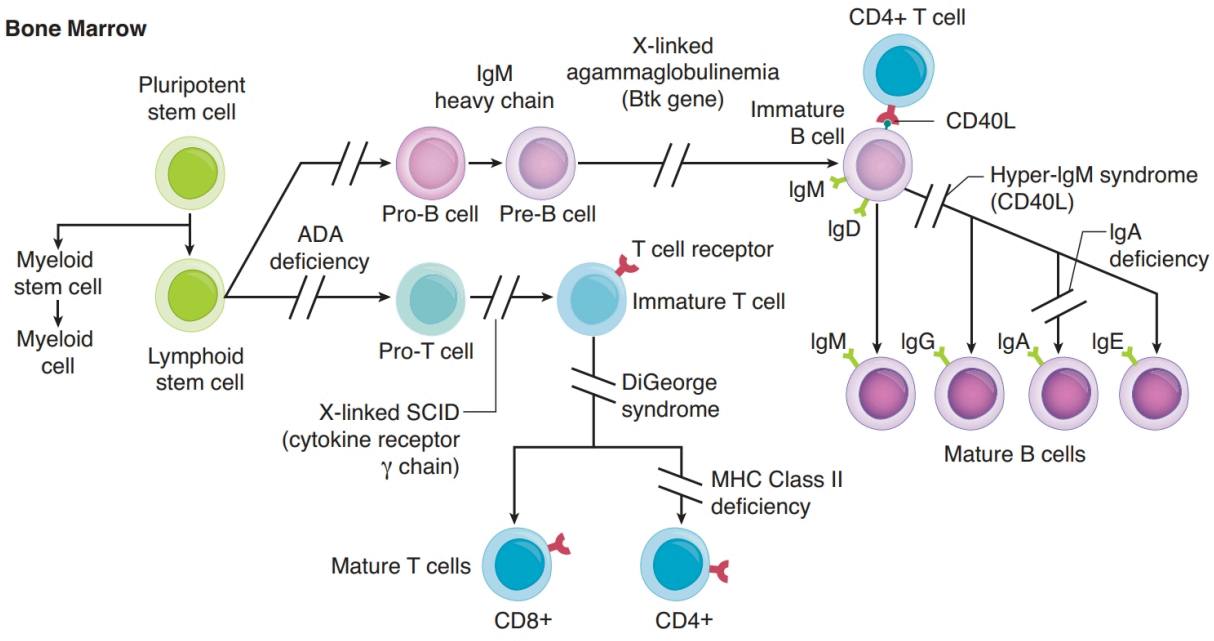


Figure 7-2. Primary Immune Deficiency Syndromes

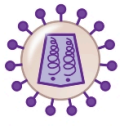
Secondary Immune Deficiency Syndromes

Systemic diseases that can cause secondary immunodeficiency include diabetes mellitus, collagen vascular disease (e.g., systemic lupus erythematosus), and chronic alcoholism. Secondary immunodeficiency is more common.

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

AIDS can be diagnosed when a person is HIV-positive and has CD4 count <200 cells/mL, **or** when a person is HIV-positive and has an AIDS-defining disease. Males are affected more frequently than females.

HIV Biology



Retrovirus

The ***human immunodeficiency virus*** (HIV) is an enveloped RNA retrovirus that contains reverse transcriptase. HIV infects CD4-positive cells, including CD4+ T lymphocytes, all macrophages, lymph node follicular dendritic cells, and Langerhans cells. The mechanism of infection is by binding of CD4 by the viral gp120, followed by entry into cell by fusion, which requires gp41 and coreceptors CCR5 (β-chemokine receptor 5) and CXCR4 (α-chemokine receptor).

Clinical Principles

Transmission of HIV can occur by many mechanisms, including sexual contact (most common mode, including both homosexual transmission and an increasing rate of heterosexual transmission, with important cofactors including herpes and syphilis infection); parenteral transmission; IV drug use; blood transfusions (including those done in hemophiliacs); accidental needle sticks in hospital workers; and vertical transmission.

KP00710.indb 58 13/10/22 1:51 PM

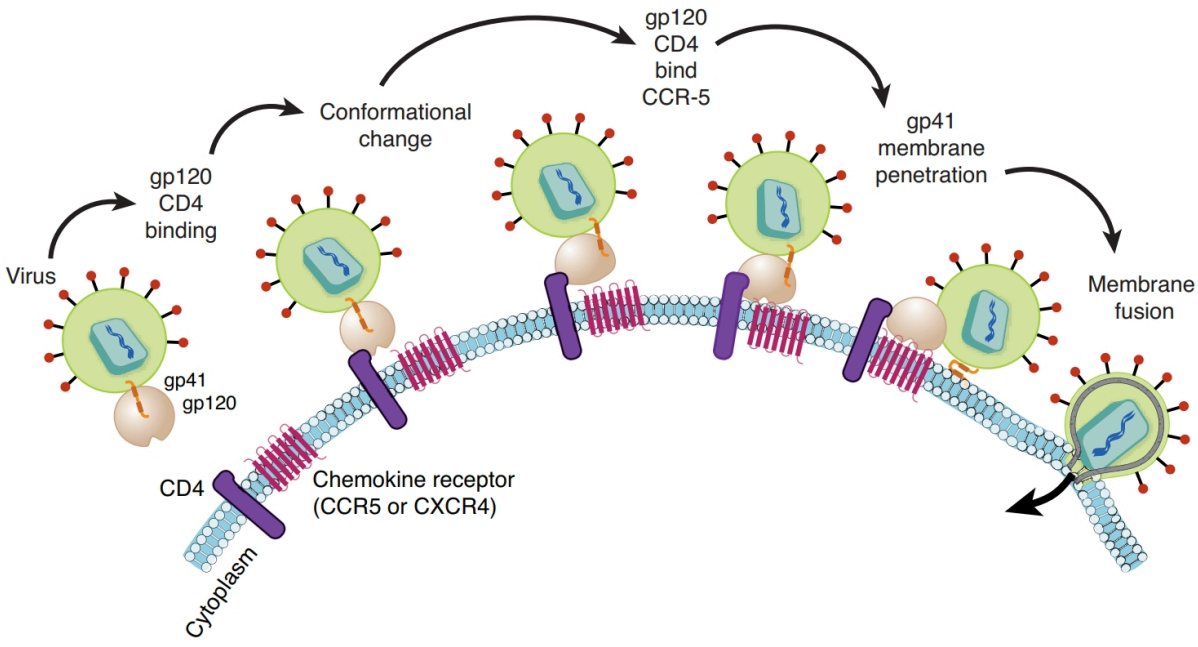


Figure 7-3. Mechanisms of HIV Infection

Diagnosis. The CDC recommends initial testing with an antigen/antibody combination immunoassay, followed by a confirmatory HIV-1/HIV-2 antibody differentiation immunoassay. If the confirmatory test is negative, testing with an HIV-1 nucleic acid test is done. Treatment varies, and can include combination antiretroviral treatment, reverse transcriptase inhibitors, protease inhibitors, and prophylaxis for opportunistic infections based on CD4 count.

The **clinical manifestations** of HIV infection vary over time.

- The **acute phase** is characterized by viremia with a reduction in CD4 count, mononucleosis-like viral symptoms and lymphadenopathy, and seroconversion.
- The **latent phase** is characterized by asymptomatic or persistent generalized lymphadenopathy with continued viral replication in the lymph nodes and spleen, low level of virus in the blood, and minor opportunistic infections including oral thrush (candidiasis) and herpes zoster. The average duration of latent phase is 10 years.
- **Progression to AIDS** (third phase) occurs with reduction of CD4 count to <200 cells/mL, which is accompanied by reemergence of viremia and development of AIDS-defining diseases, possibly to eventual death.

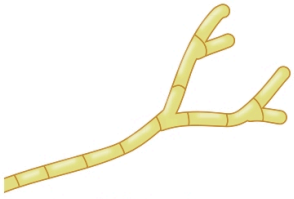
NOTE

Macrophages and follicular dendritic cells are reservoirs for the virus.

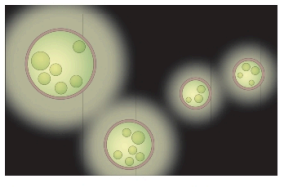
NOTE

The CD4+ cell count is used to determine the health of the immune system and for recommendations on instituting prophylaxis for opportunistic diseases. Viral load is followed to assess treatment efficacy.

KP00710.indb 59 13/10/22 1:51 PM



Septate Hyphae
(*Aspergillus*)



Cryptococcus neoformans

Table 7-1. Opportunistic Infection and Common Sites of Infection in AIDS Patients

Opportunistic Infection	Common Sites of Infection
Pneumocystis jiroveci	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)
Bartonella spp.	Skin, mucosa, bone (bacillary angiomatosis)

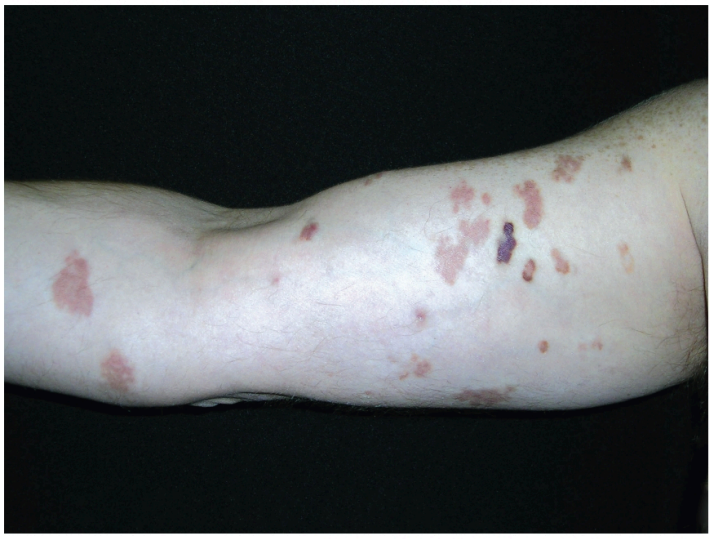
AIDS-Defining Diseases

These neoplastic and nonneoplastic conditions can establish a diagnosis of AIDS in HIV+ individuals, regardless of CD4 counts.

Hairy leukoplakia is an Epstein-Barr virus (EBV)–associated condition due to infection of squamous cells. White plaques are present on the tongue.

Kaposi sarcoma is the most common neoplasm in AIDS patients. (*See* Vascular Pathology chapter.)

KP00710.indb 60 13/10/22 1:51 PM



© Richard P. Usatine, MD. Used with permission.

Figure 7-4. Kaposi Sarcoma in an AIDS Patient

Non-Hodgkin lymphomas tend to be high-grade B-cell lymphomas; extranodal CNS lymphomas are common.

Other AIDS-defining diseases include cervical cancer, HIV-wasting syndrome, AIDS nephropathy, and AIDS dementia complex.

TRANSPLANT IMMUNOLOGY

Transplant Rejection

Rejection is caused largely by differences in HLA alleles between donor and recipient. Immunosuppressive agents are used to prevent and mitigate rejection.

- **Hyperacute rejection** occurs within minutes to hours due to preformed antibodies in the recipient. Lymphocyte cross-matching has almost eliminated this problem.
- **Acute rejection** occurs in the first 6 months and may be cellular (CD8+ T lymphocytes kill graft cells) or antibody-mediated.
- **Chronic rejection** occurs after months or years and may be cell-mediated or antibody-mediated. The vasculature components are targeted, and the histopathologic changes depend on the organ involved.

KP00710.indb 61 13/10/22 1:51 PM

8 Amyloidosis

LEARNING OBJECTIVES

- ❑ Answer questions about structure of amyloid
- ❑ Demonstrate understanding of types of amyloidosis
- ❑ Explain information related to the diagnosis of amyloidosis

AMYLOID STRUCTURE

- Individual molecular subunits form β-pleated sheets. Amorphous eosinophilic extracellular deposits of amyloid are seen on the H&E stain. These deposits stain red with the Congo red stain, and apple green birefringence of the amyloid is seen on the Congo red stain under polarized light.
- The fibrillary protein of amyloid varies with each disease. Also present in amyloid are serum amyloid P (SAP) and glycosaminoglycans (heparan sulfate).

AMYLOIDOSIS

Amyloidosis is a group of diseases characterized by the deposition of an extracellular protein that has specific properties.

Primary amyloidosis has amyloid light chain (AL) amyloid, whose fibrillary protein is made of kappa or lambda light chains. Primary amyloidosis may be seen in plasma cell disorders (multiple myeloma, B-cell lymphomas, etc.) but most cases occur independent of other diseases.

Reactive systemic amyloidosis (secondary amyloidosis) has amyloid-associated (AA) protein, whose precursor is serum amyloid A (SAA), an acute phase reactant produced by the liver which is elevated with ongoing chronic inflammation and neoplasia. Reactive systemic amyloidosis can be seen with a wide variety of chronic diseases, including rheumatoid arthritis, systemic lupus erythematosus, tuberculosis, bronchiectasis, osteomyelitis, inflammatory bowel disease, and cancer.

Familial Mediterranean fever has AA type amyloid with fibrillary protein composed of serum amyloid A (SAA). This autosomal recessive disease is characterized by recurrent inflammation, fever, and neutrophil dysfunction. Gain of function mutations of *pyrin* are present.

Hemodialysis-associated amyloidosis has Aβ2M type amyloid with precursor protein β2-microglobulin. This form of amyloidosis may cause carpal tunnel syndrome and joint disease.

CLINICAL CORRELATE

Carpal tunnel syndrome is caused when fibrosis, edema, or another pathologic process compresses and damages the median nerve within the tunnel formed by the carpal bones and flexor retinaculum.

KP00710.indb 63 13/10/22 1:51 PM

Senile cerebral amyloidosis (Alzheimer disease) has Aβ type amyloid with fibrillary protein composed of β-amyloid precursor protein (βAPP). It is found in Alzheimer plaques and in cerebral vessels. The gene for βAPP is located on chromosome 21.

TTR = transporter of thyroxine and retinol

Senile cardiac/systemic amyloidosis has ATTR type amyloid with fibrillary protein composed of transthyretin. This type of amyloidosis is seen in men older than 70 years and may cause heart failure as a result of restrictive/infiltrative cardiomyopathy. Four percent of African Americans have a transthyretin (TTR) V1221 mutation with 1% being homozygous, serving as a risk for cardiac disease.

Endocrine type amyloidosis is seen in medullary carcinoma of the thyroid (procalcitonin), adult-onset diabetes (amylin), and pancreatic islet cell tumors (amylin).

CLINICAL DIAGNOSIS

In **systemic forms** of amyloidosis, the kidney is the most commonly involved organ, and patients may experience nephrotic syndrome and/or progressive renal failure. Cardiac involvement may cause restrictive cardiomyopathy and conduction disturbances. Other clinical features include hepatosplenomegaly and involvement of the gastrointestinal tract, which may produce tongue enlargement (macroglossia, primarily in AL type) and malabsorption.

Diagnosis in systemic forms of amyloidosis can be established with biopsy of the rectal mucosa, gingiva, or the abdominal fat pad; Congo red stain shows apple green birefringence under polarized light of amyloid deposits. The prognosis of systemic amyloidosis is poor. AL amyloidosis is diagnosed by serum and urinary protein electrophoresis and immunoelectrophoresis. Proteomic analysis is another diagnostic tool.

KP00710.indb 64 13/10/22 1:51 PM

9 Principles of Neoplasia

LEARNING OBJECTIVES

- ❑ Use knowledge of epidemiology of neoplasias
- ❑ Answer questions about causes of neoplasia
- ❑ Solve problems concerning carcinogenesis
- ❑ Answer questions about diagnosis of cancer
- ❑ Discuss paraneoplastic syndromes

GENERAL PRINCIPLES

Carcinogenesis is a multistep process involving a sequence of initiation (mutation) followed by promotion (proliferation).

- Initiators can be direct-acting chemical carcinogens (mutagens which cause cancer directly by modifying DNA) or indirect-acting chemical carcinogens (procarcinogens that require metabolic conversion to form active carcinogens).
- Promotors cause cellular proliferation of mutated (initiated) cells, which may lead to accumulation of additional mutations.

Definitions

The term **neoplasm** is used interchangeably with the term **tumor**. **Tumors may be benign or malignant**. Some tumors fall in between the spectrum of benign and malignant.

Cancer is a disorder characterized by an abnormal growth of malignant cells.

- **Sarcoma** is a malignant tumor arising from mesenchymal cells.
- **Carcinoma** is a malignant tumor arising from epithelial cells.
- **Lymphoma** and **leukemia** arise from blood cells and their progenitors.

EPIDEMIOLOGY

Cancer is the **second leading cause of death** in the United States. In 2018, approximately 1,700,000 new cases of cancer were diagnosed in the United States and 600,000 people died from the disease. The most common cancers are (1) breast, (2) lung, and (3) prostate.

KP00710.indb 65 13/10/22 1:51 PM

Tumor Progression

Tumor progression refers to the tendency of a tumor to become more malignant over time. This progression can be related to both **natural selection** (evolution of a more malignant clone over time due to a selective growth advantage) and **genetic instability** (malignant cells are more prone to mutate and accumulate additional genetic defects).

Cancer in Men

In men, the sites with the highest new cancer rates are (in order of decreasing frequency):

- Prostate
- Lung and bronchus
- Colon and rectum

These same sites also have a high mortality rate, although lung and bronchus cancers more commonly cause death than prostate cancer.

Cancer in Women

In women, the sites with the highest new cancer rates are (in order of decreasing frequency):

- Breast
- Lung and bronchus
- Colon and rectum

These same sites have a high mortality rate, although lung and bronchus cancers more commonly cause death than breast cancer.

Cancer in Children

In children, the most common cancers are acute lymphocytic leukemia, CNS malignancy, neuroblastoma, and non-Hodgkin lymphoma.

Geographic and Racial Factors

- Stomach cancer is **much more prevalent** in Japan than in the United States.
- Breast cancer is **much more prevalent** in the United States than in Japan.
- Liver hepatoma is **much more prevalent** in Asia than in the United States.
- Prostate cancer is **more prevalent** in African Americans than in Caucasians.

CAUSES OF NEOPLASIA

Carcinogens

- **Chemical carcinogens** are numerous, and include nitrosamines (gastric cancer), cigarette smoke (multiple malignancies), polycyclic aromatic hydrocarbons (bronchogenic carcinoma), asbestos (bronchogenic

KP00710.indb 66 13/10/22 1:51 PM

carcinoma, mesothelioma), chromium and nickel (bronchogenic carcinoma), arsenic (squamous cell carcinomas of skin and lung, angiosarcoma of liver), vinyl chloride (angiosarcoma of liver), aromatic amines and azo dyes (hepatocellular carcinoma), alkylating agents (leukemia, lymphoma, other cancers), benzene (leukemia), and naphthylamine (bladder cancer). Potential carcinogens are screened by the **Ames test,** which detects any mutagenic effects of potential carcinogens on bacterial cells in culture; mutagenicity *in vitro* correlates well with carcinogenicity in vivo.

- **Radiation.** Ultraviolet B sunlight is the most carcinogenic because it produces pyrimidine dimers in DNA, leading to transcriptional errors and mutations of oncogenes and tumor suppressor genes, thereby increasing the risk of skin cancer. Xeroderma pigmentosum is an autosomal recessive inherited defect in DNA repair, in which the pyrimidine dimers formed with ultraviolet B sunlight cannot be repaired; this defect predisposes to skin cancer. Ionizing radiation includes x-rays and gamma rays, alpha and beta particles, protons, and neutrons. Cells in mitosis or the G2 phase of the cell cycle are most sensitive to radiation. Radiation causes cross-linking and chain breaks in nucleic acids. Atomic bomb survivors experienced an increased incidence of leukemias, thyroid cancer, and other cancers. Uranium miners historically had increased lung cancer, related to inhalation of radioactive radon, which is a decay product of uranium.

Chronic Inflammation

Persistent chronic inflammation promotes cancer. The link between colitis and colorectal carcinoma is an example.

Oncogenic Viruses

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

DNA oncogenic viruses include the following:

- Hepatitis B virus (hepatocellular carcinoma)
- Epstein-Barr virus (EBV), which has been implicated in Burkitt lymphoma, B-cell lymphomas in immunosuppressed patients, nasopharyngeal carcinoma
- Human papilloma virus (HPV), which causes benign squamous papillomas (warts-condyloma acuminatum) and a variety of carcinomas (cervical, vulvar, vaginal, penile, and anal)
- Kaposi-sarcoma-associated herpesvirus (HHV8), which causes Kaposi sarcoma

Loss of Immune Regulation

Immunosurveillance normally destroys neoplastic cells via recognition of "non-self" antigens, and both humoral and cell-mediated immune responses play a role. Patients with immune system dysfunction have an increased number of neoplasms, especially malignant lymphomas.

KP00710.indb 67 13/10/22 1:51 PM

CANCER BIOLOGY

Carcinogenesis

Carcinogenesis is a multistep process, and development of all human cancers appears to require the accumulation of multiple genetic changes. These changes can involve inherited germline mutations or acquired mutations. Once a single severely mutated cell forms, monoclonal expansion of the cell's line can cause a tumor. The most important mutations in tumorigenesis involve growth promoting genes (proto-oncogenes), growth inhibiting tumor suppressor genes, the genes regulating apoptosis and senescence, and DNA repair genes.

Proto-oncogenes are normal cellular genes involved with growth and cellular differentiation. Oncogenes are derived from proto-oncogenes via a change in the gene sequence (resulting in a new gene product, e.g., oncoprotein) or a loss of gene regulation (resulting in overexpression of the normal gene product).

Mechanisms of oncogene activation include point mutations, chromosomal translocations, gene amplification, and insertional mutagenesis. Activated oncogenes lack regulatory control and are overexpressed, resulting in unregulated cellular proliferation.

Table 9-1. Clinically Important Oncogenes

Oncogene	Tumor	Gene Product	Mechanism of Activation
FGF3 & *FGF4*	Cancer of the stomach, breast, bladder, and Kaposi sarcoma	**Growth factors** Fibroblast growth factor	Overexpression
PDGFRA	Astrocytoma	Platelet-derived growth factor	Overexpression
ERBB1	Squamous cell carcinoma of lung	**Growth factor receptors** Epidermal growth factor receptor	Overexpression
ERBB2	Breast, ovary, lung	Epidermal growth factor receptor	Amplification
ERBB3	Breast	Epidermal growth factor receptor	Overexpression
RET	MEN 2A & 2B, familial thyroid (medullary) cancer	Glial neurotrophic factor receptor	Point mutation
ABL	CML, ALL	**Signal transduction proteins** bcr-abl fusion protein with tyrosine kinase activity	Translocation t(9;22)
KRAS	Lung, pancreas, and colon	GTP binding protein	Point mutation
MYC	Burkitt lymphoma	Nuclear regulatory protein	Translocation t(8;14)
MYCL	Small cell lung carcinoma	Nuclear regulatory protein	Amplification
MYCN	Neuroblastoma	Nuclear regulatory protein	Amplification
CCND1	Mantle cell lymphoma	**Cell cycle regulatory proteins** Cyclin D protein	Translocation t(11;14)
CDK4	Melanoma, GBM	Cyclin dependent kinase	Amplification

KP00710.indb 68 13/10/22 1:51 PM

Inactivation of tumor suppressor genes. Tumor suppressor genes encode proteins that regulate and suppress cell proliferation by inhibiting progression of the cell through the cell cycle. The mechanism of action of tumor suppressor genes may vary. As examples, p53 prevents a cell with damaged DNA from entering S-phase, while Rb prevents the cell from entering S-phase until the appropriate growth signals are present.

Table 9-2. Clinically Important Tumor Suppressor Genes

Chromosome	Gene	Tumors
3p25.3	*VHL*	von Hippel-Lindau disease, renal cell carcinoma
11p13	*WT1*	Wilms tumor
11p15.5	*WT2*	Wilms tumor
13q14.2	*RB1*	Retinoblastoma, osteosarcoma
17p13.1	*TP53*	Lung, breast, colon, and others
17q21.31	*BRCA1*	Hereditary breast and ovary cancer
13q13.1	*BRCA2*	Hereditary breast cancer
5q22.2	*APC*	Adenomatous polyps and colon cancer
18q21.2	*DCC*	Colon cancer
17q11.2	*NF1*	Neurofibromas
22q12.2	*NF2*	Acoustic neuromas, meningiomas

Regulation of apoptosis. Tumor genesis related to changes in regulation of apoptosis occurs in the follicular lymphomas that have the translocation t(14;18). Normally, Bcl-2 prevents apoptosis (programmed cell death). In the follicular lymphomas with this translocation, the Bcl-2 regulator of apoptosis is overexpressed, because the translocation connects the immunoglobulin heavy chain gene on chromosome 14 (which turns on easily in B lymphocytes) to the *BCL2* gene on chromosome 18, thereby leading to a situation in which lymphocytes fail to die as expected and instead produce a tumor.

Other examples of apoptosis regulators include Bax, Bad, bcl-xS, and Bid; p53 promotes apoptosis in mutated cells by stimulating bax synthesis. The protein c-myc promotes cellular proliferation and when associated with p53 leads to apoptosis and when associated with Bcl-2 inhibits apoptosis.

DNA repair. Mutations of DNA repair genes cause genetic instability. The cell's ability to repair damaged DNA depends on *p53.* For example, BRCA1 and BRCA2 proteins are important for double-strand break repair. Mutations of genes coding for these proteins are linked to breast and ovarian cancer susceptibility. DNA repair mutations are usually inherited. Diseases associated with DNA repair include xeroderma pigmentosum and hereditary nonpolyposis colorectal cancer.

Other Hallmarks of Cancer

Limitless replication is possible due in part to upregulation of telomerase.

Sustained angiogenesis is possible due in part to activation of the Notch signaling pathway.

NOTE

Knudson's "two-hit hypothesis" states that at least 2 tumor suppressor genes must be inactivated for oncogenesis to occur. In cancers arising in individuals with inherited germline mutations, the "first hit" is the inherited germline mutation and the "second hit" is an acquired somatic mutation. Examples of inherited germline mutations include:

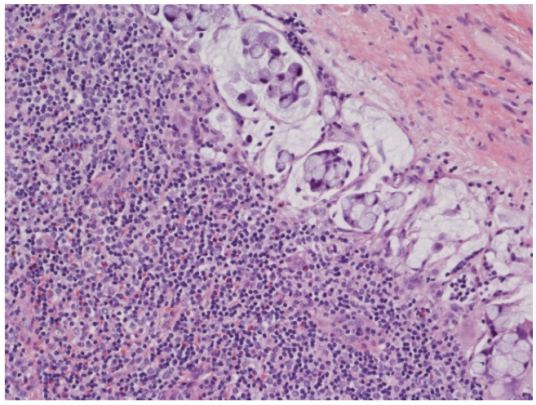
- Familial retinoblastoma (germline mutation of *RB1* on chromosome 13 is associated with a high rate of retinoblastoma and osteosarcoma)
- Li-Fraumeni syndrome (germline mutation of *TP53* on chromosome 17 is associated with a high rate of many types of tumor)

BRIDGE TO BIOCHEMISTRY

Diseases associated with DNA repair include xeroderma pigmentosum and hereditary nonpolyposis colorectal cancer.

KP00710.indb 69 13/10/22 1:51 PM

Invasiveness. Malignant cells must dissociate from tumors (loss of E-cadherin function) and degrade the extracellular matrix before spreading to distant sites. Cancer-associated glycans are being investigated for their role in cancer spread and as targets for therapy.



© Gregg Barré, MD. Used with permission.

Figure 9-1. Involvement of Lymph Node by Signet Ring Cell Carcinoma

Metastasis is the spread of a malignant tumor beyond its tissue of origin. Lymphatic spread is the most common initial route of spread for epithelial carcinomas. Early hematogenous spread is typically seen with most sarcomas (e.g., osteogenic sarcoma), renal cell carcinoma (because of the proximity of the large renal vein), hepatocellular carcinoma (because of the presence of the hepatic sinusoids), follicular carcinoma of the thyroid, and choriocarcinoma (because of its propensity to seek vessels). Seeding of body cavities and surfaces occurs in ovarian carcinoma.

DIAGNOSIS OF CANCER

Table 9-3. General Features of Benign Versus Malignant Neoplasms

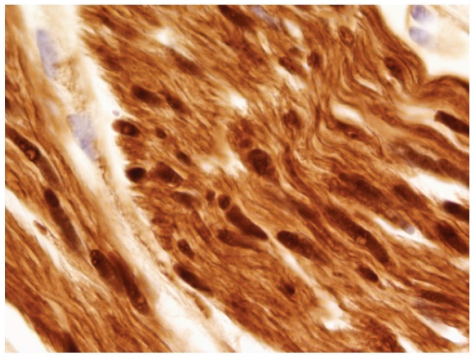
	Benign	Malignant
Gross	• Small size • Slow growing • Encapsulated or well-demarcated borders	• Larger in size • Rapid growth • Necrosis and hemorrhage are commonly seen • Poorly demarcated
Micro	• Expansile growth with well-circumscribed borders • Tend to be well differentiated • Resemble the normal 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

KP00710.indb 70 13/10/22 1:51 PM

Histological Diagnosis of Cancer

Microscopic examination of tissue (**histology**) or cells (**cytology**) is required to make the diagnosis of cancer. Material suitable for diagnosis of a tumor may be obtained by complete excision, biopsy, fine needle aspiration, or cytologic smears (Pap test).

- **Immunohistochemistry** may be helpful in confirming the tissue of origin of metastatic or poorly differentiated tumors. The technique uses monoclonal antibodies that are specific for a cellular component. Among the many antibodies that are clinically useful are:
  - All of the serum tumor markers
  - Thyroglobulin (thyroid cancers)
  - S100 (melanoma and neural tumors)
  - Actin (smooth and skeletal muscle)
  - CD markers (lymphomas/leukemias)
  - Estrogen receptors (breast cancer)
  - Intermediate filaments



© Gregg Barré, MD. Used with permission.

Figure 9-2. S100 Staining of a Neurofibroma

Table 9-4. 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

NOTE

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

KP00710.indb 71 13/10/22 1:52 PM

- **Ancillary tests** for the diagnosis of cancer include electron microscopy, flow cytometry, cytogenetics, and PCR/DNA probes.

Serum Tumor Markers

Tumor markers are usually normal cellular components that are increased in neoplasms but may also be elevated in nonneoplastic conditions. Serum tumor markers are used for screening (e.g., prostate specific antigen [PSA]) for cancer, monitoring treatment efficacy, and detecting recurrence of cancers.

- **Clinically useful tumor markers** include alpha-fetoprotein (AFP, used for hepatoma, nonseminomatous testicular germ cell tumors); beta human chorionic gonadotropin (hCG, used for trophoblastic tumors, choriocarcinoma); calcitonin (used for medullary carcinoma of the thyroid); carcinoembryonic antigen (CEA, used for carcinomas of the lung, pancreas, stomach, breast, and colon); CA-125 (used for malignant ovarian epithelial tumors); CA19-9 (used for malignant pancreatic adenocarcinoma); placental alkaline phosphatase (used for seminoma); and prostate specific antigen (PSA, used for prostate cancer).

Grading and Staging of Cancer

Tumor grade is a histologic estimate of the malignancy of a tumor, and typically uses criteria such as the degree of differentiation from low grade (well-differentiated) to high grade (poorly differentiated/anaplastic) and the number of mitoses.

Tumor stage is a clinical estimate of the extent of tumor spread. TNM staging system criteria are used for most tumor types:

- **T** indicates the size of the primary tumor.
- **N** indicates extent of regional lymph node spread.
- **M** indicates the presence or absence of metastatic disease.

In general, staging is a better predictor of prognosis than tumor grade.

PARANEOPLASTIC SYNDROMES

Paraneoplastic syndromes are symptoms in cancer patients, often endocrine or neurologic, that do not originate directly from tumor bulk or metastatic spread. Sometimes symptoms of the paraneoplastic syndrome precede diagnosis of cancer.

- **Small cell lung cancer** is the cancer that most frequently causes paraneoplastic syndromes, such as **Lambert-Eaton myasthenic syndrome**. (See the chapter on skeletal muscle and peripheral nerve pathology.)
- **Paraneoplastic acanthosis nigricans** is most often associated with gastrointestinal cancer. (See the skin pathology chapter.)
- **Hypertrophic osteoarthropathy** is characterized by clubbing of the digits, ossifying periostitis of the long bones, and arthritis. This condition was previously known as hypertrophic *pulmonary* osteoarthropathy due to its first descriptions in association with chronic inflammatory pulmonary disease. However, it is now known to be associated with many other nonneoplastic diseases (including inflammatory bowel disease) and

KP00710.indb 72 13/10/22 1:52 PM

conditions (pregnancy). As a paraneoplastic syndrome, hypertrophic osteoarthropathy is most frequently seen with **squamous cell carcinoma of the lung**.

- Certain **endocrine and metabolic syndromes** are commonly associated with specific primary cancers:
  - **Cushing syndrome** and **neuroendocrine lung tumors** (carcinoid and small cell carcinoma)
  - **Syndrome of inappropriate ADH secretion (SIADH)** and **small cell lung cancer**
  - **Hypercalcemia due to secretion of a PTH-related protein** and squamous cell carcinomas of the head and neck, esophagus, cervix, and lung

Paraneoplastic Syndromes

- Endocrine/metabolic syndromes include Cushing syndrome secondary to ACTH production, SIADH secondary to ADH production, and hypercalcemia secondary to PTH production (squamous cell carcinoma).
- Lambert-Eaton syndrome (*See* Skeletal Muscle and Peripheral Nerve Pathology chapter.)
- Acanthosis nigricans (*See* Skin Pathology chapter.)
- Hypertrophic pulmonary osteoarthropathy is characterized by periosteal new bone formation with clubbing and arthritis.

KP00710.indb 73 13/10/22 1:52 PM

10 Skin Pathology

LEARNING OBJECTIVES

- ❑ Solve problems concerning disorders of pigmentation
- ❑ Answer questions about melanocytic tumors
- ❑ Explain information related to epidermal and dermal lesions
- ❑ Explain information related to malignant tumors

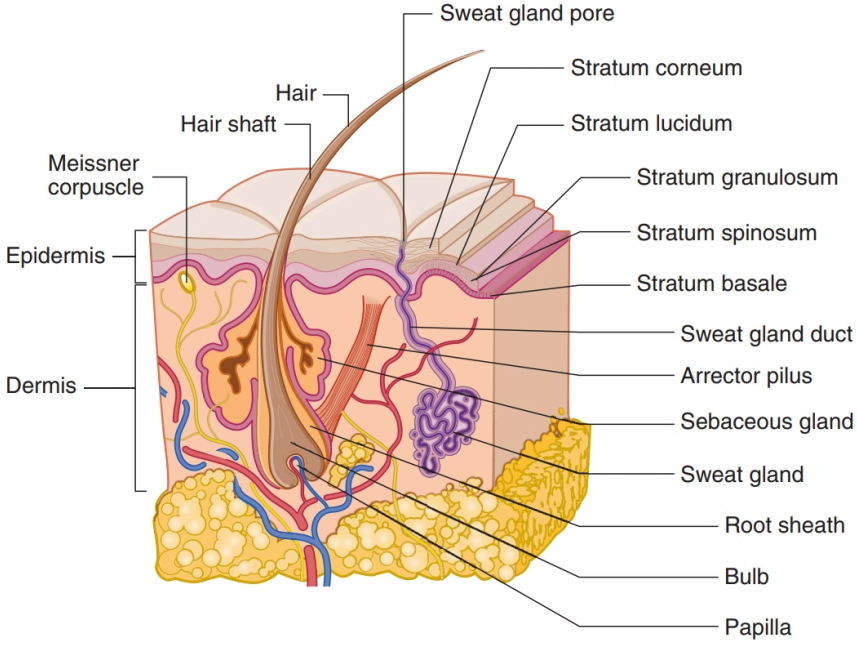


Figure 10-1. Skin

PIGMENTATION DISORDERS

Hypopigmentation

Vitiligo causes irregular, completely depigmented skin patches. It is common and can affect any race; there may also be a familial predisposition. The disease has an unknown etiology that is possibly autoimmune. Microscopically, affected areas are devoid of epidermal melanocytes.

KP00710.indb 75 13/10/22 1:52 PM

Albinism refers to heterogeneous group of inherited disorders that cause congenital hypopigmentation. Their precise diagnosis is dependent on their molecular signature.

- **Oculocutaneous albinism** is a group of four autosomal recessive disorders with hypopigmentation of hair, skin, and eyes and a predisposition to skin cancer.
- **Syndromic albinism** is the term for those types of albinism with systemic pathology, for example, **Chediak-Higashi syndrome**, an oculocutaneous albinism with increased susceptibility to bacterial infections and shortened life expectancy. Syndromic albinism mutations cause defects in the packaging of melanin.
- **X-linked ocular albinism** presents with nystagmus, decreased visual acuity, and hypopigmentation of the iris.



© Richard P. Usatine, MD Used with permission.

Figure 10-2. Vitiligo

Hyperpigmentation

Melasma causes irregular blotchy patches of hyperpigmentation on the face; it is associated with sun exposure, oral contraceptive use, and pregnancy ("mask of pregnancy") and may regress after pregnancy.

Addison disease causes generalized hyperpigmentation due to increased melanin in the basal layer. (See the endocrine pathology chapter.)

BENIGN MELANOCYTIC LESIONS AND MALIGNANT MELANOMA

Benign Melanocytic Lesions

Ephelides (freckles) are light brown macules distributed in areas of sun exposure. Microscopically, there is increased melanin in the basal cell layer, but the number of melanocytes is not increased.

KP00710.indb 76 13/10/22 1:52 PM

Solar lentigines (actinic lentigines) are hyperpigmented macules that occur in adults in sun-exposed areas. Microscopically, the rete ridges are elongated and there is a discontinuous increase in the number of epidermal melanocytes.

Congenital nevi (birthmarks) are present at birth; giant congenital nevi have increased risk of developing melanoma.

Melanocytic nevus (mole) is a benign tumor of melanocytes that is related to sun exposure. Types of nevi include junctional, compound, and intradermal. Nevi have uniform tan to brown color with sharp, well-circumscribed borders and tend to be stable in shape and size. Malignant transformation is uncommon.

Dysplastic nevus is a controversial term in clinical medicine, but pathologists use the term for those nevi that microscopically show **architectural disorder** and melanocytic atypia.

Malignant Melanoma

Malignant melanoma is a malignancy of melanocytes. The incidence is increasing at a rapid rate, with peak in ages 40–70. Risk factors include chronic sun exposure, sunburn, fair skin, and familial melanoma (associated with loss of function mutation of the p16 tumor suppressor gene, *CDKN2A*, on chromosome 9; somatic mutations of *NRAS* and *BRAF* also occur). Melanomas characteristically form skin lesions of large diameter with asymmetric and irregular borders and variegated color; the lesions may be macules, papules, or nodules. Melanomas on males have increased frequency on the upper back; females have increased frequency on the back and legs.

Several **types of melanomas** occur:

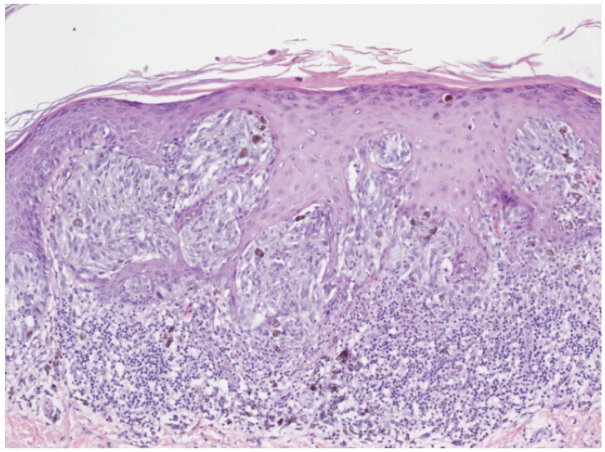
- **Lentigo maligna melanoma** is usually located on the face or neck of older individuals and has the best prognosis.
- **Superficial spreading melanoma** is the most common type of melanoma and has a primarily horizontal growth pattern.
- **Acral lentiginous melanoma** is the most common melanoma in dark-skinned individuals; it affects palms, soles, and subungual area.
- **Nodular melanoma** is a nodular tumor with a vertical growth pattern that has the worst prognosis of the melanomas.

KP00710.indb 77 13/10/22 1:52 PM



© Richard P. Usatine, MD Used with Permission.

Figure 10-3. Melanoma (Note size, irregular borders, and variegated color)



© Gregg Barré MD Used with permission.

Figure 10-4. Malignant Melanoma (Note nests of melanocytes)

The **prognosis** of melanomas is determined by TNM staging; T status is based on the depth of invasion (Breslow thickness measured histologically in millimeters).

Local disease is treated with wide surgical excision and sometimes sentinel node biopsy. Systemic disease is treated with chemotherapy or immunotherapy. Metastases may occur after years of dormancy.

BENIGN SKIN GROWTHS

Seborrheic keratoses are benign squamoproliferative neoplasms that are very common in middle-aged and elderly individuals; they may occur on the trunk, head, neck, and the extremities. The lesions are tan to brown coin-shaped plaques that have a granular surface with a "stuck on" appearance, characterized microscopically by basaloid epidermal hyperplasia and "horn cysts" (keratin-filled epidermal pseudocysts). They are usually left untreated, but may be removed if they become irritated or for cosmetic purposes. The sign of Leser-Trélat (paraneoplastic syndrome) is the sudden development of multiple lesions which may accompany an internal malignancy.

Verrucae (warts) are caused by human papillomavirus. Verruca vulgaris is the most common type.

Epidermoid cyst is a common benign skin cyst lined with stratified squamous epithelium and filled with keratin debris.

Acrochordons are small (usually under 5 mm) pedunculated, fleshy growths that commonly arise on the neck and skin folds. They are sometimes removed for cosmetic reasons. Microscopically, they have a connective tissue stalk and stratified squamous epithelium.

KP00710.indb 78 13/10/22 1:52 PM

DERMATOLOGIC DISORDERS PRESENTING WITH A RASH OR DRY SKIN

Good clinicopathologic correlation is key to the diagnosis of skin conditions presenting as a rash. Many skin conditions display more than one type of dermatologic appearance. These disorders have been placed into clinically descriptive categories that represent a predominating clinical lesion.

Lesion Lexicon

- A flat lesion is called a **macule** if it is 5 mm in diameter or smaller; if it is larger, it is called a **patch**.
- A raised lesion is called a **papule** if it is 5 mm in diameter or smaller; if it is larger, it is called a **nodule**.
- A blister is called a **vesicle** if it is 5 mm in diameter or smaller; if it is larger, it is called a **bulla** (plural **bullae**).

Vesicular and Bullous Disease

Pemphigus is a rare, potentially fatal autoimmune disorder that is characterized by intraepidermal blister formation. **Pemphigus vulgaris** is the most common form. The pathogenesis involves the production of autoantibodies directed against a part of the keratinocyte desmosome called desmoglein 3, with resulting loss of intercellular adhesion (acantholysis) and blister formation. Pemphigus causes mucosal lesions and easily ruptured, flaccid blisters. Oral involvement is common.

- Microscopic examination shows intraepidermal acantholysis; the acantholysis leaves behind a basal layer of keratinocytes, which has a tombstone-like arrangement. Immunofluorescence shows a net-like pattern of IgG staining between the epidermal keratinocytes that create bullae.
- Treatment is with immunosuppression.

Bullous pemphigoid is a relatively common autoimmune disorder of older individuals characterized by subepidermal blister formation with tense bullae that do not rupture easily. The condition results from production of autoantibodies directed against a part of the keratinocyte hemidesmosome called bullous pemphigoid-antigens 1 and 2. Immunofluorescence shows linear deposits of IgG at the dermal-epidermal junction.

Dermatitis herpetiformis is a rare immune disorder that is often associated with celiac sprue; it is characterized by subepidermal blister formation with itchy, grouped vesicles and occasional bullae on the extensor surfaces. Production of IgA antibodies directed against gliadin and other antigens deposit in the tips of the dermal papillae and result in subepidermal blister formation. Routine microscopy shows microabscesses at the tips of the dermal papillae that can lead to eventual subepidermal separation results in blister formation; immunofluorescence shows granular IgA deposits at the tips of the dermal papillae. Dermatitis herpetiformis often responds to a gluten-free diet.

Porphyria cutanea tarda is an acquired and familial disorder of heme synthesis. Patients experience upper extremity blistering secondary to sun exposure and minor trauma. Microscopically, there are subepidermal blisters with minimal inflammation. Dermal vessels are thickened. Direct immunofluorescence shows

KP00710.indb 79 13/10/22 1:52 PM

deposition of immunoglobulins and complement at the epidermal basement membrane and around dermal vessels.

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

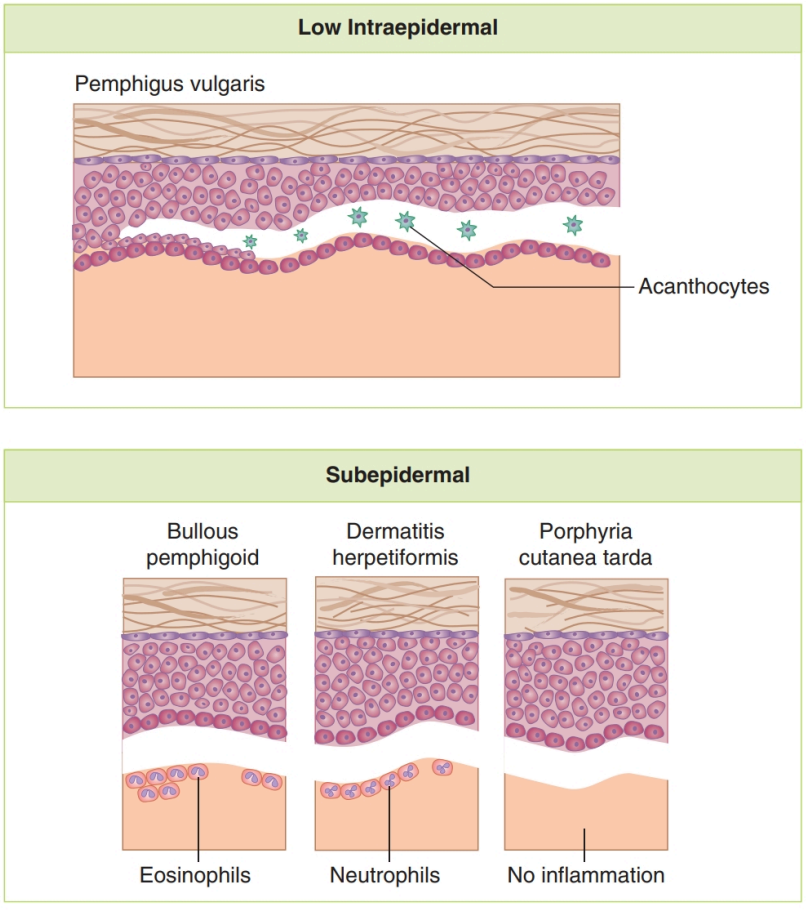


Figure 10-5. Intraepidermal and Subepidermal Blisters

Erythematous Diseases

Polymorphous light eruption is the most common idiopathic form of photodermatoses. It causes pruritic erythematous macules, papules, plaques, or vesicles on exposure to sunlight. There is dermal edema and inflammation.

Pityriasis rosea is a self-limiting dermatitis that often begins as a single patch followed weeks later by the development of other patches and a papular eruption on the trunk. Pruritus is common. The rash tends to occur in children and young adults and may be a viral exanthem; it is not contagious.

KP00710.indb 80 13/10/22 1:52 PM

Erythema nodosum causes raised, erythematous, painful nodules of subcutaneous adipose tissue, typically on the anterior shins, which can be associated with granulomatous diseases and streptococcal infection.

Psoriasis is an autoimmune disorder with a clear genetic component that causes increased proliferation and turnover of epidermal keratinocytes; it affects 1% of the U.S. population. The most common form is psoriasis vulgaris. Common sites of involvement include the knees, elbows, and scalp; the classic skin lesion is a well-demarcated erythematous plaque with a silvery scale. Removal of scale results in pinpoint bleeding (Auspitz sign). Nail beds show pitting and discoloration. Psoriasis may be associated with arthritis, enteropathy, and myopathy.



© Richard P. Usatine, MD Used with permission.

Figure 10-6. The Silvery Plaques of Psoriasis

- **Microscopically**, the lesions show epidermal hyperplasia (acanthosis), patchy hyperkeratinization with parakeratosis, uniform elongation and thickening of the rete ridges, thinning of the epidermis over the dermal papillae, and Munro microabscesses.
- Treatment is topical steroids and ultraviolet irradiation; severe systemic disease may be treated with methotrexate.

Papular Diseases

Granuloma annulare is a chronic inflammatory disorder that causes papules and plaques. Palisaded granulomas are present microscopically. The pathogenesis is immunologic, but most cases occur in healthy patients.

KP00710.indb 81 13/10/22 1:52 PM

Eczema

Eczema is a group of related inflammatory skin diseases characterized by pruritus and epidermal spongiosis (edema).

- **Acute eczema** causes a vesicular, erythematous rash.
- **Chronic eczema** develops following repetitive scratching, and is characterized by dry, thickened, hyperkeratotic skin.
- **Atopic dermatitis** is often inherited. Defects in the keratinocyte barrier are due to mutations in the filaggrin gene (*FLG*).
- **Contact dermatitis** can be either allergic type (poison ivy, nickel in jewelry) or photodermatitis type (such as photosensitivity reaction after tetracycline).

Photodermatoses

Polymorphous light eruption is the most common idiopathic form of photodermatosis and causes pruritic erythematous macules, papules, plaques, or vesicles on exposure to sunlight. There is dermal edema and inflammation.

Phototoxic dermatitis manifests as sunburn in sun-exposed areas. Drugs known to cause this reaction include phenothiazine, furosemide, and ciprofloxacin.

Cutaneous lupus erythematosus may be acute (facial butterfly rash), subacute (photosensitive rash on anterior chest, upper back and upper extremities), or chronic (discoid plaques, usually above the neck). Direct immunofluorescence shows deposition of immunoglobulin and complement at the dermal-epidermal junction. Serologies for autoantibodies and clinical correlation help establish the diagnosis.

Dry Skin

Ichthyosis vulgaris is a common inherited (autosomal dominant) skin disorder characterized by a thickened stratum corneum with absent stratum granulosum. Onset is in childhood. Patients have hyperkeratotic, dry skin on the trunk and extensor surfaces of limb areas.

Xerosis is a common cause of pruritus and dry skin in the elderly that is due to decreased skin lipids. Cancer patients receiving epidermal growth factor receptor inhibitor are susceptible. Treatment is with emollients.

SYSTEMIC DISEASE PRESENTING WITH SKIN CHANGES

Clinical Principles

Sometimes skin lesions herald the onset of a systemic disease. The cutaneous signs of disease may resolve with treatment of the underlying illness.

Examples

Acanthosis nigricans causes raised, thickened, hyperpigmented skin on the axillae, groin, and posterior neck due to elevation of dermal papillae, hyperkeratosis, and an increase in melanin in the basal layer. It is often associated with obesity and hyperinsulinism. **Paraneoplastic acanthosis nigricans** can occur with many types of cancers, but most commonly it occurs with gastrointestinal cancer.

KP00710.indb 82 13/10/22 1:52 PM

Systemic lupus erythematosus often presents as a triad of rash, joint pain, and fever. A **malar rash** is a bilateral, erythematous facial rash covering the cheeks and crossing the bridge of the nose.

NONMELANOMA SKIN CANCER

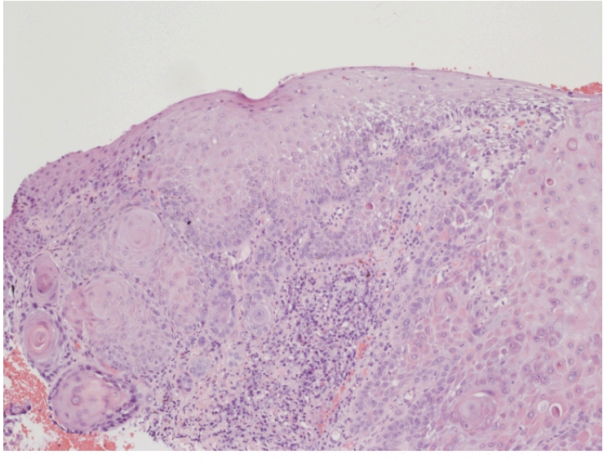
General Concepts

Skin cancer is the most common cancer, and nonmelanoma skin cancer is the most common type.

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) has peak incidence at age 60. Risk factors include chronic sun exposure (ultraviolet UVB); fair complexion; chronic skin ulcers or sinus tracts; long-term exposure to hydrocarbons, arsenic, burns, and radiation; immunosuppression; and xeroderma pigmentosum. *TP53* and *HRAS* mutations are common.

- Precursors include **actinic keratosis** (a sun-induced dysplasia of the keratinocytes that causes rough, red papules on the face, arms, and hands) and Bowen disease (squamous cell carcinoma *in situ*).
- **Squamous cell carcinoma** occurs on sun-exposed areas (face and hands) and causes a tan nodular mass which commonly ulcerates. Microscopic examination shows nests of atypical keratinocytes that invade the dermis, (oftentimes) formation of keratin pearls, and intercellular bridges (desmosomes) between tumor cells. Squamous cell carcinoma of the skin rarely metastasizes and complete excision is usually curative.
- A variant is **keratoacanthoma** (well differentiated SCC), which causes rapidly growing, dome-shaped nodules with a central keratin-filled crater; these are often self-limited and may regress spontaneously.



© Gregg Barré MD Used with permission.

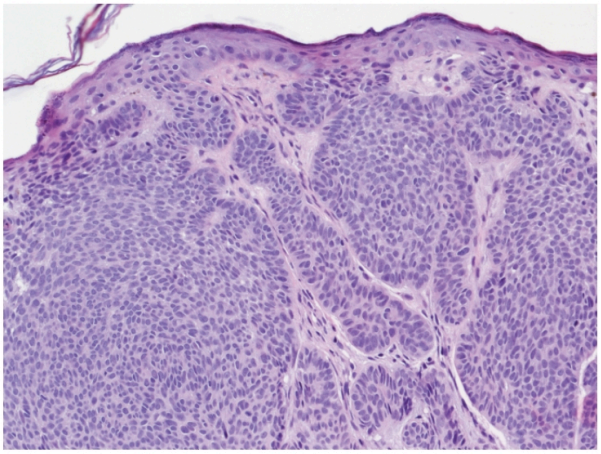
Figure 10-7. Squamous Cell Carcinoma (Note Keratin Pearls)

KP00710.indb 83 13/10/22 1:52 PM

Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the **most common tumor in adults in the Western world**; it is most common in middle-aged or elderly individuals and arises from the basal cells of hair follicles. Risk factors include chronic sun exposure, fair complexion, immunosuppression, and xeroderma pigmentosum.

BCC occurs on sun-exposed, hair-bearing areas (face), and may form pearly papules; nodules with heaped-up, translucent borders, telangiectasia, or ulcers (rodent ulcer). Microscopically, it shows invasive nests of basaloid cells with a palisading growth pattern.



© Gregg Barré, MD Used with permission.

Figure 10-8. Basal Cell Carcinoma

BCC grows slowly and rarely metastasizes, but it may be locally aggressive. Shave biopsies have a 50% recurrence rate, but complete excision is usually curative. Mutations affecting the Hedgehog pathway are seen in sporadic and familial cases.



© Richard P. Usatine, MD Used with permission.

Figure 10-9. Pearly Papule Characteristic of a Basal Cell Carcinoma

KP00710.indb 84 13/10/22 1:52 PM

VASCULAR TUMORS OF SKIN

Benign Vascular Tumors

Hemangiomas have a variety of clinical appearances (macular, plaque-like, lobular). (See the vascular pathology chapter.)

Pyogenic granulomas are not granulomas but capillary hemangiomas that often occur after trauma on the skin and in the mouth. They appear as well-demarcated, red or pink fleshy growths that can ulcerate.

Malignant Vascular Tumors

Kaposi sarcoma skin lesions vary over time; phases include a patch, plaque, and nodule stages of disease. (See the vascular pathology chapter.)

Cutaneous angiosarcoma is a highly malignant tumor with a poor prognosis. It occurs in several clinical settings:

- As a highly malignant tumor on the face in the elderly
- As a complication of lymphedema on the arm of a patient years after breast surgery (Stewart-Treves syndrome)
- As a complication of radiotherapy

KP00710.indb 85 13/10/22 1:52 PM

Red Blood Cell Pathology: Anemias

11

LEARNING OBJECTIVES

- ❑ Explain information related to red blood cell (RBC) morphology
- ❑ Solve problems using knowledge of microcytic, normocytic, and macrocytic anemias
- ❑ Demonstrate understanding of polycythemia vera

RED BLOOD CELL MORPHOLOGY

Red Cell Shapes

Abnormal size is called anisocytosis (*aniso* means unequal). Abnormal shape is called poikilocytosis (*poikilo* means various). **Elliptocytes** may be seen in hereditary elliptocytosis. **Spherocytes** result from decreased erythrocyte membrane, and they may be seen in hereditary spherocytosis and in autoimmune hemolytic anemia. **Target cells** result from increased erythrocyte membrane, and they may be seen in hemoglobinopathies, thalassemia, and liver disease. **Acanthocytes** have irregular spicules on their surfaces; numerous acanthocytes can be seen in abetalipoproteinemia. **Echinocytes** (burr cells) have smooth undulations on their surface; they may be seen in uremia or more commonly as an artifact.

Schistocytes are erythrocyte fragments (helmet cells are a type of schistocyte); they can be seen in microangiopathic hemolytic anemias or traumatic hemolysis. **Bite cells** are erythrocytes with "bites" of cytoplasm being removed by splenic macrophages; they may be seen in G6PD deficiency. **Teardrop cells** (dacrocytes) may be seen in thalassemia and myelofibrosis. **Sickle cells** (drepanocytes) are seen in sickle cell anemia. **Rouleaux** ("stack of coins") refers to erythrocytes lining up in a row. Rouleaux are characteristic of multiple myeloma.

Red Cell Inclusions

Basophilic stippling results from cytoplasmic remnants of RNA; it may indicate reticulocytosis or lead poisoning. **Howell-Jolly bodies** are remnants of nuclear chromatin that may occur in severe anemias or patients without spleens. **Pappenheimer bodies** are composed of iron, and they may be found in the peripheral blood following splenectomy. **Ring sideroblasts** have iron trapped abnormally in mitochondria, forming a ring around nucleus; they can be seen in sideroblastic anemia. **Heinz bodies** result from denatured hemoglobin; they can be seen with glucose-6-phosphate dehydrogenase deficiency.

KP00710.indb 87 13/10/22 1:52 PM

ANEMIAS

General Concepts

Anemia is a reduction below normal limits of the total circulating red cell mass. Signs of anemia include palpitations, dizziness, angina, pallor of skin and nails, weakness, claudication, fatigue, and lethargy.

- **Reticulocytes** are immature, larger red cells (macrocytic cells) that are spherical and have a bluish color (polychromasia) due to free ribosomal RNA. Reticulocytes do not have a nucleus; note that any erythrocyte with a nucleus (nRBC) in peripheral blood is abnormal. Reticulocyte maturation to a mature erythrocyte takes about 1 day. The reticulocyte count is the percentage of red immature cells present in peripheral blood (normal 0.5–1.5%). The corrected reticulocyte count takes into consideration the degree of anemia and is calculated as (patient's hct/45) × (reticulocyte count); the idea behind the calculation is to scale the reticulocyte count by multiplying by the ratio of the patient's hematocrit to "normal" hematocrit of 45%. When interpreting the corrected reticulocyte count, <2% indicates poor bone marrow response and >3% indicates good bone marrow response.
- The reticulocyte production index is the corrected reticulocyte count/2; use this measure if bone marrow reticulocytes (shift cells) are present (polychromasia). The division by 2 is because shift cells take twice as long as reticulocytes to mature (2 days versus 1 day).

Classification of anemia can be based on color: normochromic anemias have normal red cell color (central pallor of about a third the diameter of the erythrocyte); hypochromic anemias have decreased color (seen as an increased central pallor of erythrocyte); and hyperchromic anemias, while theoretically possible, are usually instead called spherocytosis and have increased color (loss of central pallor of erythrocyte). Classification of anemia can also be based on size (MCV).

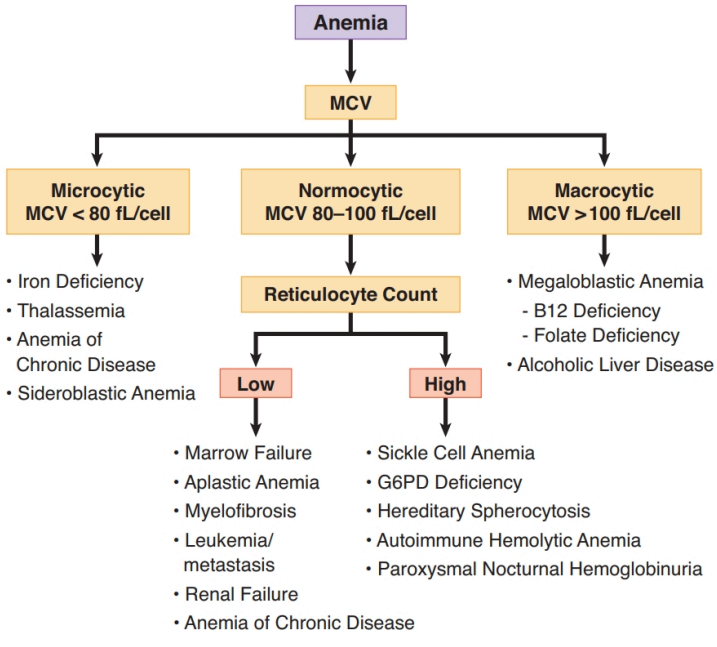


Figure 11-1. Classification of Anemias Based on MCV

BRIDGE TO PHYSIOLOGY

Patients with anemia have normal SaO_2 and PaO_2, but they have reduced oxygen content due to the low level of hemoglobin.

NOTE

RBC indices:

- **Mean corpuscular volume** (MCV): average volume of a RBC
- **Mean corpuscular hemoglobin** (MCH): average content (mass) of hemoglobin per cell
- **Mean corpuscular hemoglobin concentration** (MCHC): average concentration of hemoglobin in a given volume of packed erythrocytes
- **Red cell distribution width** (RDW): coefficient of variation of RBC volume and a measure of anisocytosis

KP00710.indb 88 13/10/22 1:52 PM

The pathogenesis of anemia varies with the underlying disease. Blood loss can cause anemia. **Hemolytic anemias** are also important, and include hereditary spherocytosis, glucose-6-phosphate dehydrogenase deficiency, sickle cell disease, hemoglobin C disease, thalassemia, and paroxysmal nocturnal hemoglobinuria. **Immunohemolytic anemias**, which are hemolytic anemias with an immune component to the pathology, include autoimmune hemolytic anemia (AIHA), cold AIHA, incompatible blood transfusions, and hemolytic disease of the newborn. **Anemias of diminished erythropoiesis** include megaloblastic anemia (B12 and folate deficiencies), iron deficiency anemia, anemia of chronic disease, aplastic anemia, myelophthisic anemia, and sideroblastic anemia.

Microcytic Anemias

Iron deficiency anemia.

- **Iron physiology.** Functionally available iron is normally found in hemoglobin, myoglobin, and enzymes (catalase and cytochromes). Additionally, **ferritin** is the physiological storage form (plasma ferritin is normally close to the total body Fe), and hemosiderin (Prussian blue positive) is iron precipitated in tissues in the form of degraded ferritin mixed with lysosomal debris.
- Iron is transported in the bloodstream by **transferrin.** Transferrin saturation is reported as a percentage; it represents the ratio of the serum iron to the total iron-binding capacity, multiplied by 100.

Causes of iron deficiency.

- **Dietary deficiency** of iron is seen in elderly populations, children, and the poor. Increased demand for iron is seen in children and pregnant women.
  - Additionally, iron deficiency can develop because of **decreased absorption,** either due to generalized malabsorption or more specifically after gastrectomy (due to decreased acid, which is needed for ferrous absorption) or when there is decreased small intestinal transit time (causing "dumping syndrome").
  - Iron deficiency can also be due to **chronic blood loss** due to gynecologic (menstrual bleeding) or gastrointestinal causes (in the United States, think carcinoma; in the rest of the world, think hookworm).
- The sequence of events during iron deficiency is as follows:
  - **Initially**, decreased storage iron results in decreased serum ferritin and decreased bone marrow iron on Prussian blue stains.
  - The **next stage** is decreased circulating iron, which causes decreased serum iron, increased total iron binding capacity, and decreased % saturation.
  - The **last stage** is formation of microcytic/hypochromic anemia, with decreased MCV, decreased MCHC, and high RDW.
- **Other clinical features of iron deficiency** include increased free erythrocyte protoporphyrin (FEP), oral epithelial atrophy if Plummer-Vinson syndrome is present, koilonychia (concave or spoon nails with abnormal ridging and splitting), and pica (eating nonfood substances, e.g., dirt).

KP00710.indb 89 13/10/22 1:52 PM

Table 11-1. Iron Panel for Microcytic Anemias

	Iron Deficiency	AOCD	Thalassemia Minor
Serum iron	↓	↓	Normal
TIBC	↑	↓	Normal
% saturation	↓	↓	Normal
Serum ferritin	↓	↑	Normal

Anemia of chronic disease (AOCD) (or anemia of inflammation) is characterized by iron being trapped in bone marrow macrophages, leading to decreased utilization of endogenous iron stores. Laboratory studies show increased serum ferritin with decreased total iron binding capacity. Increased IL-6 increases plasma hepcidin, which is a negative regulator of iron uptake in the small intestine and of iron release from macrophages.

Thalassemia syndromes are quantitative, not qualitative, abnormalities of hemoglobin. α-thalassemia has decreased α-globin chains with relative excess β chains, while β-thalassemia has decreased β-globin chains with relative excess α chains. It is hypothesized that the thalassemia genes have been selectively preserved in the human genome because the thalassemias provide a protective advantage to carriers exposed to diseases such as malaria.

NOTE

Composition of hemoglobins:

- HbA (2 alpha, 2 beta)
- HbA2 (2 alpha, 2 delta)
- HbF (2 alpha, 2 gamma)
- Hb Barts (4 gamma)
- Hb H (4 beta)

α-thalassemia. There are a total of 4 α-globin chain genes, 2 from each parent. α-thalassemia is due to gene deletions in the α-globin chain genes, and the clinical manifestations depend upon the number of genes that are affected. α chains are normally expressed prenatally and postnatally; therefore, there is prenatal and postnatal disease. In normal individuals, 4 α genes (αα/αα) are present and 100% of the α chains are normal.

- In the **silent carrier state**, one deletion is present, and the total number of α genes available is 3 (−α/αα), which produce 75% of the needed α chains. Individuals with the silent carrier state are completely asymptomatic and all lab tests are normal.
- In **α-thalassemia trait**, 2 deletions are present, and the total number of available α genes is 2, which produce 50% of the needed α chains. The genotype cis (– –/αα) is seen in Asians, while the genotype trans (−α/−α) is seen in African Americans (offspring don't develop hemoglobin H disease or hydrops fetalis).
- **Hemoglobin H disease** is characterized by 3 deletions, with the number of α genes being 1 (– –/−α), which produces 25% of the normal α chains. There is increased Hb H (β4), which forms Heinz bodies that can be seen with crystal blue stain.
- **Hydrops fetalis** has 4 deletions and is lethal in utero, because the number of α genes is 0 (– –/– –), producing 0% α chains.

β-thalassemia. There are a total of 2 β-globin chain genes. In contrast to the α-globin chain genes, the 2 β-globin chain genes are expressed postnatally only, and therefore there is only postnatal disease and not prenatal disease. The damage to the genes is mainly by point mutations, which form either some β chains (β+) or none (β0).

KP00710.indb 90 13/10/22 1:52 PM

- **β-thalassemia minor** is seen when one of the β-globin chain genes has been damaged. The condition is asymptomatic, and characterized on laboratory studies by increased hemoglobin A2 (8%) and increased hemoglobin F (5%).
- **β-thalassemia intermedia** causes varying degrees of anemia, but no transfusions are needed.
- **β-thalassemia major** (Cooley anemia). Patients are normal at birth, and symptoms develop at about 6 months as hemoglobin F levels decline. Severe hemolytic anemia results from decreased erythrocyte life span. This severe anemia causes multiple problems:
  - 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.

Erythroid hyperplasia in the bone marrow causes "crewcut" skull x-ray and increased size of maxilla ("chipmunk face"). The peripheral blood shows microcytic/hypochromic anemia with numerous target cells and increased reticulocytes. Hemoglobin electrophoresis shows increased hemoglobin F (90%), normal or increased hemoglobin A2, and decreased hemoglobin A. Treatment is hematopoietic stem cell transplantation.

Sideroblastic anemia is a disorder in which the body has adequate iron stores, but is unable to incorporate the iron into hemoglobin. It is associated with ring sideroblasts (accumulated iron in mitochondria of erythroblasts) in bone marrow. Sideroblastic anemia may be either pyridoxine (vitamin B6) responsive or pyridoxine unresponsive; the latter is a form of myelodysplastic syndrome (refractory anemia with ring sideroblasts). The peripheral blood may show a dimorphic erythrocyte population. Laboratory studies show increased serum iron, ferritin, FEP, and % saturation of TIBC, with decreased TIBC.

Normocytic Anemias

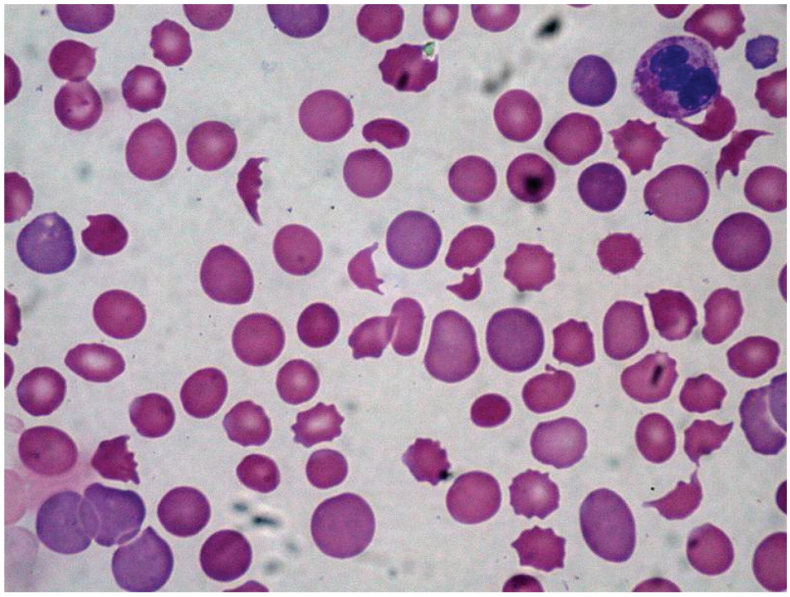
Anemias of blood loss. Acute blood loss may cause shock or death. If the patient survives, the resulting hemodilution caused by shift of water from the interstitium will lower the hematocrit. There will be a marked reticulocytosis in 5—7 days. Chronic blood loss, such as from the gastrointestinal tract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

Hemolytic anemias.

- In **intravascular (IV) hemolysis**, release of hemoglobin into the blood causes hemoglobinemia and hemoglobinuria; increased bilirubin from erythrocytes causes jaundice and an increased risk of pigment (bilirubin) gallstones. The hemoglobin may be oxidized to methemoglobin, which causes methemoglobinemia and methemoglobinuria. Markedly decreased (because they have been used up) hemoglobin-binding proteins in the blood, such as haptoglobin and hemopexin, are characteristic. No splenomegaly is seen.

KP00710.indb 91 13/10/22 1:52 PM

- In **extravascular (EV) hemolysis**, splenomegaly results if the EV hemolysis occurs in the spleen and hepatomegaly results if the EV hemolysis occurs in the liver. EV hemolysis causes increased bilirubin and decreased haptoglobin, but not to the degree seen with intravascular hemolysis. In EV hemolysis, there is an absence of hemoglobinemia, hemoglobinuria, and methemoglobin formation.



© commons.wikimedia.org.

Figure 11-2. DIC with Microangiopathic Hemolytic Anemia as Evidenced by Helmet Cells/Schistocytes

Sickle cell disease is an inherited blood disorder leading to the formation of hemoglobin S and increased propensity for the affected RBCs to become sickle-shaped and occlude small vessels. The genetic abnormality is a single nucleotide change that causes valine (neutral) to replace normal glutamic acid (acidic) at the sixth position of the β-globin chain. This biochemical change then makes a critical point on the surface of the hemoglobin molecule become hydrophobic, making it feel "sticky" to an adjacent hemoglobin molecule, thereby favoring hemoglobin precipitation in crystalline form.

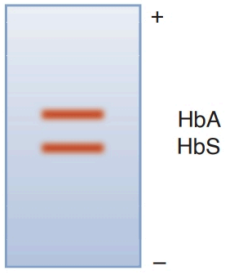
Heterozygous (AS) genome causes sickle cell trait. About 8% of African Americans are heterozygous for hemoglobin S. Patients with sickle trait have fewer symptoms than those with sickle disease, and also have resistance to *Plasmodium falciparum* infection (malaria), which may be why the disease has remained in the human genetic pool. Homozygous (SS) genome causes clinical disease (sickle cell anemia).

There are several factors affecting formation of irreversibly sickled RBCs.

- **Increased concentration** (dehydration) makes symptoms worse; decreased concentration of sickled hemoglobin (as is seen if a sickle cell patient also has a thalassemia) makes symptoms better.

NOTE

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



Hemoglobin electrophoresis at pH 8.4

11_Preclinical_Pathology_Ch11.indd 92 10/6/22 8:51 PM

- **Decreased pH** decreases oxygen affinity and makes symptoms worse.
- **Increased hemoglobin F** makes symptoms better (rationale for therapy with hydroxyurea, which increases blood hemoglobin F levels).
- The **presence of hemoglobin C** (SC: double-heterozygote individual) makes symptoms better.

Clinical features include increased erythrocyte destruction which causes a severe hemolytic anemia, accompanied by erythroid hyperplasia in the bone marrow and increased bilirubin leading to jaundice and gallstone (pigment) formation. Capillary thrombi result from sickle cells blocking small vessels and may cause vaso-occlusive (painful) crises; hand-foot syndrome (swelling) in children; and autosplenectomy, which is seen in older children and adults. Howell-Jolly bodies will appear in peripheral blood after autosplenectomy, and the lack of a functional spleen predisposes to increased incidence of infections (encapsulated organisms), increased incidence of *Salmonella* osteomyelitis (leg pain), leg ulcers, and risk of aplastic crisis (especially with *parvovirus B19* infection). Emergencies that may occur include priapism and acute chest syndrome.

For testing, hemoglobin electrophoresis is used to diagnose the disease, though genetic testing can be performed on amniotic fluid for prenatal diagnosis. Newborn screening is now mandatory in the United States and is commonly performed via high performance liquid chromatography. Treatment is hydroxyurea (to increase hemoglobin F) and hematopoietic stem cell transplantation.

Hemoglobin C disease occurs when a single nucleotide change in a codon causes lysine (basic) to replace normal glutamic acid (acidic) at the beta 6 position. Hemoglobin C disease is characterized by mild normochromic-normocytic anemia, splenomegaly, target cells, and rod-shaped crystals in erythrocytes (the latter being characteristic).

Glucose-6-phosphate dehydrogenase deficiency (G6PD) is a genetic disorder affecting the hexose monophosphate shunt pathway. It results in decreased levels of the antioxidant glutathione (GSH), leaving erythrocytes sensitive to injury by oxidant stresses leading to hemolysis. In some variants, G6PD is not due to decreased synthesis but rather to defective protein folding, resulting in a protein having a decreased half-life. The condition has X-linked inheritance.

- In **African Americans (A^- type)** with G6PD, the hemolysis is secondary to acute oxidative stress, such as oxidative drugs (primaquine, sulfonamides, anti-tuberculosis drugs), and more typically by viral or bacterial infections. The hemolysis is intermittent (even if the offending drug is continued) because only older erythrocytes have decreased levels of glucose-6-phosphate dehydrogenase.
- In individuals with G6PD of **Mediterranean type**, the disease is associated with favism due to ingestion of fava beans; more severe hemolysis occurs because all erythrocytes have decreased glucose-6-phosphate dehydrogenase activity in that there is both decreased synthesis and decreased stability.
- In **both forms**, the oxidation of hemoglobin forms **Heinz bodies**; these cannot be seen with normal peripheral blood stains (Wright-Giemsa) but can be visualized with supravital stains (methylene blue and crystal violet). The Heinz bodies are "eaten" by splenic macrophages (extravascular hemolysis), which may form "bite cell" erythrocytes that are visible on routine peripheral blood smears.

BRIDGE TO BIOCHEMISTRY

G6PD is the rate-limiting enzyme in the hexose-monophosphate shunt (HMP).

It normally produces NADPH, which keeps glutathione reduced.

Glutathione protects RBCs by breaking down hydrogen peroxide.

KP00710.indb 93 13/10/22 1:52 PM

Hereditary spherocytosis (HS) is an autosomal dominant disorder caused by a defect involving ankyrin and spectrin in the erythrocyte membrane; this causes a decrease in the erythrocyte surface membrane (spherocytosis). Spherocytes are not flexible and are removed in the spleen by macrophages (i.e., extravascular hemolysis). This causes multiple problems, including splenomegaly with a mild to moderate hemolytic anemia, increased bilirubin and increased risk for jaundice and pigment gallstones secondary to chronic hemolysis, and increased risk for acute red-cell aplasia due to parvovirus B19 infection. Laboratory testing shows increased osmotic fragility and normal MCH with increased MCHC. Treatment is splenectomy and folic acid.

CLINICAL CORRELATE

The differential diagnosis of spherocytes in the peripheral blood includes warm AIHA and hereditary spherocytosis. Use the osmotic fragility test (HS) and direct Coombs test (AIHA) to tell them apart. The Coombs test is negative in hereditary spherocytosis.

Autoimmune hemolytic anemia (AIHA) is most commonly warm AIHA, in which the antibodies are IgG that are usually against Rh antigens and are active at 37°C. Erythrocytes to which the antibodies attach are removed by splenic macrophages, which tends to induce splenomegaly as the spleen responds to the perceived need for increased phagocytosis.

The etiology varies; most cases are idiopathic, but some cases are related to autoimmune diseases such as systemic lupus erythematosus, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (WDLL), or medications (penicillin). The peripheral blood smear typically shows microspherocytes, and laboratory confirmation can be obtained by demonstrating a positive direct Coombs test (direct antiglobulin test [DAT]).

Paroxysmal nocturnal hemoglobinuria (PNH) is a hemolytic anemia caused by an acquired somatic mutation of a gene (*PIGA*) that encodes an anchor for proteins (CD55 and CD59) in the cell membrane, causing complement-mediated lysis in red cells, white cells, and platelets. The condition causes episodes (paroxysms) of hemolysis at night.

CLINICAL CORRELATE

Increased levels of 2,3-bisphosphoglycerate (2,3 BPG) in cells can be seen in pyruvate kinase deficiency, which may affect tissue oxygenation. This will cause a "right shift" in the oxygen-hemoglobin dissociation curve, implying hemoglobin has a decreased affinity for oxygen.

Acidosis *in vivo* occurs during sleep (breathing slowly retains CO_2) and exercise (lactic acidosis), and the acidosis in turn causes activation of complement. PNH is a clonal stem cell disorder that affects all blood cell lines, leading to pancytopenia (anemia, leukopenia, and thrombocytopenia) that is apparent in the peripheral blood. Venous thrombosis may ensue.

Most PNH patients have mild disease and don't require treatment, but a monoclonal antibody against complement protein C5 can be therapeutic.

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

Hereditary elliptocytosis is a mild, hereditary, hemolytic anemia caused by a defect in spectrin. It is characterized by osmotically fragile ovoid erythrocytes ("elliptocytes").

Aplastic anemia is the term used when marrow failure causes a pancytopenia of the blood. Idiopathic causes for aplastic anemia are most commonly seen; when the etiology is known, the aplastic anemia may be due to medications (alkylating agents, chloramphenicol), chemical agents (benzene, insecticides), infection (EBV, CMV, parvovirus, hepatitis), or whole body radiation (therapeutic or nuclear exposure).

KP00710.indb 94 13/10/22 1:52 PM

Macrocytic Anemias

The basic cause of **megaloblastic anemias** is impaired DNA synthesis (delayed mitoses) without impairment of RNA synthesis; this produces a nuclear-cytoplasmic asynchrony that affects all rapidly proliferating cell lines, including cells of the bone marrow, gastrointestinal tract, and gynecologic system. The erythrocytes are the most obvious rapidly proliferating cells that exhibit these changes, and specifically show megaloblastic maturation, with megaloblasts in bone marrow forming macro-ovalocytes in peripheral blood. Autohemolysis of the affected megaloblasts in bone marrow (ineffective erythropoiesis) will cause increased bilirubin and increased lactate dehydrogenase (LDH). White blood cell (WBC) changes include giant metamyelocytes in bone marrow and hypersegmented neutrophils (>5 lobes) in peripheral blood. Note that platelets are not increased in size.

Megaloblastic anemia due to vitamin B12 (cobalamin) deficiency

- Dietary deficiency is rare because B12 is stored in the liver and it takes years to develop dietary deficiency; it is usually seen only in strict vegetarians (diet with no animal protein, milk, or eggs).
- Decreased absorption of vitamin B12 is more common and may be caused by decreased intrinsic factor associated with gastrectomy or pernicious anemia (an autoimmune gastritis); pancreatic insufficiency (pancreatic proteases normally break down B12-R complexes in duodenum); or intestinal malabsorption due to parasites (fish tapeworm [*Diphyllobothrium latum*]), bacteria (blind-loop syndrome), or Crohn disease of the ileum.
- Clinically, B12 deficiency causes weakness due to anemia (megaloblastic anemia) and sore ("beefy") tongue due to generalized epithelial atrophy. Unlike folate deficiency, B12 deficiency can also cause the CNS effects of subacute combined degeneration of the spinal cord, characterized by demyelination of the posterior and lateral columns of the spinal cord; the posterior (sensory) tract damage causes loss of vibratory and position sense, while the lateral cord damage involves dorsal spinocerebellar tracts (arm and leg dystaxia) and corticospinal tracts (spastic paralysis).
- Lab tests show low serum B12, increased serum homocysteine, and increased methylmalonic acid in urine. Treatment is intramuscular vitamin B12, which will cause increased reticulocytes in about 5 days.

Megaloblastic anemia due to folate deficiency can be caused by multiple processes:

- **Decreased intake** in chronic alcoholics and the elderly
- **Decreased absorption** in the upper small intestine
- **Increased requirement for folate** during pregnancy and infancy
- Folate antagonists, e.g., methotrexate

Clinically, folate deficiency produces megaloblastic anemia without neurologic disease symptoms. Lab tests show low serum folate levels and increased serum homocysteine. Treatment is folate replacement.

NOTE

Normal Sequence of B12 Absorption

1. Dietary B12 binds to salivary haptocorrin.
2. Haptocorrin B12 complex is broken down by pancreatic proteases.
3. Free B12 binds to IF, which is secreted by gastric parietal cells.
4. B12-IF complex is absorbed by ileal mucosal epithelial cells.
5. B12 is transported in blood bound to transcobalamin.



Subacute combined degeneration

11_Preclinical_Pathology_Ch11.indd 95 10/6/22 8:51 PM

POLYCYTHEMIA

Polycythemia Vera

Polycythemia vera is caused by a clonal expansion of a multipotent myeloid stem cell that primarily produces extra erythrocytes. (*See* Hematopoietic Pathology chapter)

Secondary Polycythemia

Secondary polycythemia refers to increased red cell mass due to compromised ability of blood to supply oxygen to tissues. Causes include chronic obstructive pulmonary disease and cyanotic congenital heart disease. Erythropoietin levels can be appropriately high. Secondary polycythemia may also be caused by inappropriately high erythropoietin levels, with renal cell carcinoma excreting erythropoietin being the typical cause.

Relative Polycythemia

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

KP00710.indb 96 13/10/22 1:52 PM

12 Vascular Pathology

LEARNING OBJECTIVES

- ❑ Demonstrate understanding of the vasculitides
- ❑ Differentiate primary and secondary Raynaud phenomena
- ❑ Answer questions about arteriosclerosis, hypertension, aneurysms, and arteriovenous fistulas
- ❑ Explain information related to venous disease
- ❑ Demonstrate understanding of vascular neoplasms

THE VASCULITIDES

The vasculitides are a group of systemic disorders with vessel inflammation and myriad clinical presentations. There are many systems used to categorize them. The system below is based largely on the size of the vessels involved.

Large Vessel Vasculitides

Takayasu arteritis occurs in younger patients (age <50). Initial symptoms may be nonspecific (fatigue) with a variable course to more severe symptoms (blindness) and involvement of the aortic arch. Microscopically, there is vessel wall thickening and variable inflammation (from a mononuclear adventitial infiltrate to medial necrosis with granulomas).

Giant cell arteritis was formerly called temporal arteritis, but the temporal arteries are not always involved. The vertebral and ophthalmic arteries and aorta are often involved. The typical presentation evolves from nonspecific symptoms (headache) to more severe symptoms (blindness). Microscopically, there are inner media granulomas in classic cases. Treatment is steroids and anti-TNF therapy.

Medium Vessel Vasculitides

Kawasaki disease presents with mucocutaneous symptoms and cervical lymph node enlargement in children. Involvement of the coronary arteries leads to cardiovascular sequelae, which can be circumvented with immunoglobulin therapy. Microscopically, there is transmural vascular inflammation.

Polyarteritis nodosa is a systemic necrotizing vasculitis occurring most often in young adults (M > F). It has an association with hepatitis B virus. The clinical course is one of episodic nonspecific symptoms (low-grade fever). Pulmonary involvement is rare; renal artery involvement can be fatal. Immunosuppressive therapy can achieve remission in most cases.

NOTE

Thromboangiitis obliterans (Buerger's disease) is often categorized with the vasculitides, but the main lesion is thrombosis; inflammation may extend from vessels into adjacent soft tissue and nerves. The disease, which presents with severe distal extremity pain and ulceration, is seen most often in young male cigarette smokers. Pharmacologic therapies have not been successful.

KP00710.indb 97 13/10/22 1:52 PM

Small Vessel Vasculitides

Small vessel vasculitides include those that are ANCA (antineutrophil cytoplasmic antibody)-associated (**granulomatosis with polyangiitis**, formerly known as Wegener's granulomatosis; and **eosinophilic granulomatosis with polyangiitis**, formerly known as Churg-Strauss syndrome) and those that are mediated by immune complexes (e.g., anti-glomerular basement membrane disease and IgA vasculitis, also known as Henoch-Schönlein purpura).

Granulomatosis with polyangiitis typically occurs in middle-aged men; it is characterized by granulomas of the lung and upper respiratory tract, glomerulonephritis, and a necrotizing granulomatous vasculitis. PR3-ANCAs are present in most cases.

Eosinophilic granulomatosis with polyangiitis is associated with asthma, extravascular granulomas (respiratory tract), and a systemic vasculitis that features eosinophils; eosinophil counts may be extremely high in peripheral blood. T lymphocytes and antibodies to MPO (P-ANCA) play a role in the etiology. There may be increased IgG4 levels. ANCA is present in cases with glomerulonephritis. The sequential phases are allergic, followed by eosinophilic and vasculitic. Cardiac involvement may be fatal. Steroids are therapeutic. Microscopic findings depend upon the organ biopsied: Purpuric leg lesions show a leukocytoclastic vasculitis; the glomerulonephritis tends not to show eosinophilic infiltrates; the extravascular pulmonary granulomas contain eosinophils.

Other small vessel vasculitides include **variable vessel vasculitides**, e.g., Behcet's disease; **single organ vasculitides**, e.g., CNS vasculitides; and **vasculitis associated with systemic disease**, e.g., rheumatoid vasculitis.

RAYNAUD PHENOMENA

Primary Raynaud Phenomenon

Primary Raynaud phenomenon typically occurs in young women as episodic small artery vasospasm in the extremities, nose, or ears; it results in blanching and cyanosis of the fingers or toes upon stress or (more commonly) exposure to cold. The pathogenesis may involve CNS and intravascular factors.

Secondary Raynaud Phenomenon

Secondary Raynaud phenomenon is caused by arterial insufficiency secondary to an underlying disease such as scleroderma (CREST).

NOTE

Arteriosclerosis is a group of diseases that cause arterial wall thickening ("hardening of the arteries")

- Mönckeberg medial calcific sclerosis
- Arteriolosclerosis
- Atherosclerosis

ARTERIOSCLEROSIS

Mönckeberg Medical Calcific Sclerosis

Mönckeberg medial calcific sclerosis is a medial calcification of medium-sized (muscular) arteries, such as femoral, tibial, radial, and ulnar arteries. It is asymptomatic but may be detected by x-ray.

KP00710.indb 98 13/10/22 1:52 PM

Arteriosclerosis

Arteriolosclerosis refers to sclerosis of arterioles; it affects small arteries and arterioles. Microscopically, either hyaline arteriolosclerosis (pink, glassy arterial wall thickening with luminal narrowing seen in benign hypertension, diabetes, and aging) or hyperplastic arteriolosclerosis (smooth-muscle proliferation resulting in concentric ["onion skin"] wall thickening and luminal narrowing seen in malignant hypertension) may occur.

Atherosclerosis

Atherosclerosis is a common vascular disorder characterized by lipid deposition and intimal thickening of large and medium-sized (elastic and muscular) arteries, resulting in fatty streaks and atheromatous plaques over a period of decades (a type of chronic inflammatory condition). Particularly likely to be affected are the aorta and a number of important muscular arteries (coronary, carotid, cerebral, renal, iliac, and popliteal arteries).

Risk factors for atherosclerosis are as follows:

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

Morphologic features:

- The earliest (clinically reversible) stage in atherosclerosis is the **fatty streak**, which is seen grossly as a flat, yellow intimal streak and is characterized microscopically by lipid-laden macrophages (foam cells).
- **Stable atheromatous plaques** have a dense fibrous cap, a small lipid core and less inflammation than their vulnerable counterparts. They cause chronic ischemia.
- **Vulnerable atheromatous plaques** are at risk for rupture, thrombosis or embolization due to their composition (thin fibrous cap, large lipid core, dense inflammation).

Clinical complications of atherosclerosis are protean; these complications include ischemic heart disease (myocardial infarctions); cerebrovascular accidents (CVA); atheroemboli (transient ischemic attacks [TIAs] and renal infarcts); aneurysm formation; peripheral vascular disease; and mesenteric artery occlusion.

HYPERTENSION (HTN)

Definitions

Hypertension is an elevated blood pressure leading to end-organ damage, or a sustained diastolic pressure >80 mm Hg and/or systolic pressure >130 mm Hg.

Malignant (accelerated) hypertension accounts for 5% of the cases and is characterized by markedly elevated pressures (e.g., systolic pressure >180 mm Hg and/or diastolic >120 mm Hg), which can rapidly cause end-organ damage.

KP00710.indb 99 13/10/22 1:52 PM

Funduscopic examination may demonstrate retinal hemorrhages, exudates, and papilledema. See chapter 15 for a discussion of renal pathology. Malignant hypertension is a medical emergency; if untreated, most patients will die within 2 years from renal failure, intracerebral hemorrhage, or chronic heart failure.

Epidemiology

Hypertension is very common, affecting 25% of the U.S. population. African Americans tend to be more seriously affected than Caucasians, and the risk increases with age. Approximately 95% of cases of hypertension are **idiopathic hypertension** (essential hypertension); the remainder are due to **secondary hypertension** related to renal disease, pheochromocytoma, or other disease processes.

Complications

Mild to moderate elevations in blood pressure cause end-organ damage by damaging arterioles with hyaline arteriolosclerosis. Late manifestations of hypertension include concentric left ventricular hypertrophy; congestive heart failure; accelerated atherosclerosis; myocardial infarction; aneurysm formation, rupture, and dissection; intracerebral hemorrhage; and chronic renal failure.

ANEURYSMS AND ARTERIOVENOUS FISTULAS

Aneurysms

Aneurysms are congenital or acquired weakness of the vessel wall media, resulting in a localized dilatation or outpouching. Complications include thrombus formation, thromboembolism, and compression of nearby structures. Rupture or dissection may cause sudden death.

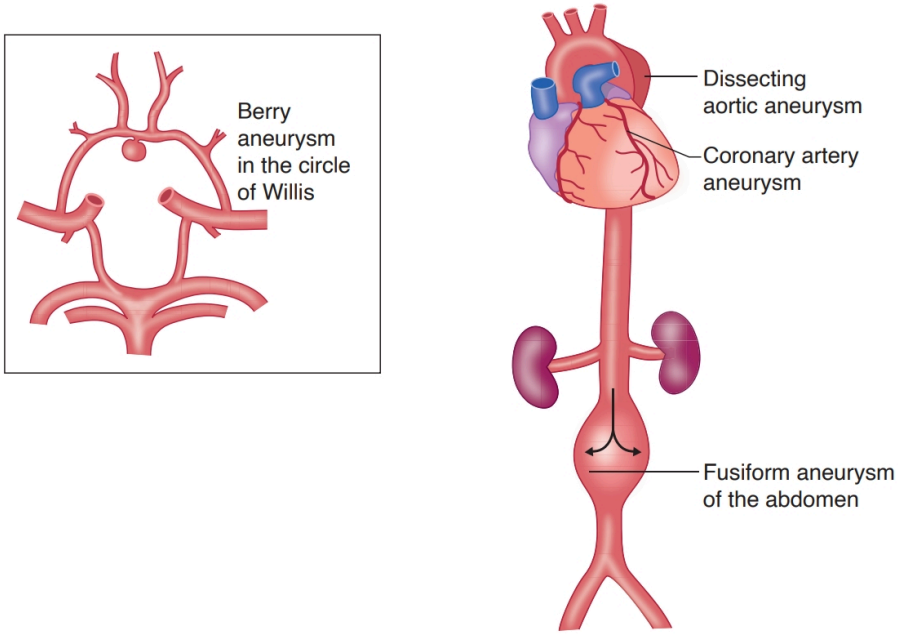


Figure 12-1. Location of Aneurysms

12_Preclinical_Pathology_Ch12.indd 100 26/09/22 5:14 PM

Atherosclerotic aneurysms are due to weakening of the media secondary to atheroma formation, and typically occur in the abdominal aorta below the renal arteries. They are associated with hypertension. Half of aortic aneurysms >6 cm in diameter will rupture within 10 years. Those >5 cm are treated surgically.

Syphilitic aneurysms involve the ascending aorta in tertiary syphilis (late stage). Syphilitic (luetic) aortitis causes an obliterative endarteritis of the vasa vasorum, leading to ischemia and smooth-muscle atrophy of the aortic media. Syphilitic aneurysms may dilate the aortic valve ring, causing aortic insufficiency.

Aortic dissecting aneurysm occurs when blood from the vessel lumen enters an intimal tear and dissects through the layers of the media. The etiology usually involves degeneration (cystic medial degeneration) of the tunica media. Aortic dissecting aneurysm presents with severe tearing pain. The dissecting aneurysm may compress and obstruct the aortic branches (e.g., renal or coronary arteries). Hypertension and Marfan syndrome are predisposing factors.

Berry aneurysm is a congenital aneurysm of the circle of Willis.

Microaneurysms are small aneurysms commonly seen in hypertension and diabetes.

Mycotic aneurysms are aneurysms usually due to bacterial or fungal infections.

Arteriovenous (AV) Fistulas

Arteriovenous (AV) fistulas are a direct communication between a vein and an artery without an intervening capillary bed. They may be congenital or acquired (e.g., trauma). Potential complications include shunting of blood, which may lead to high-output heart failure and risk of rupture and hemorrhage.

VENOUS DISEASE

Deep Vein Thrombosis

Deep vein thrombosis (DVT) usually affects deep leg veins (90%), with iliac, femoral, and popliteal veins being particularly commonly affected. It is often asymptomatic and is consequently a commonly missed diagnosis. When symptomatic, it can produce unilateral leg swelling with warmth, erythema, and positive Homan sign (increased resistance to passive dorsiflexion of the ankle by the examiner). The diagnosis can be established with Doppler "duplex" ultrasound. The major complication is pulmonary embolus.

Varicose Veins

Varicose veins are dilated, tortuous veins caused by increased intraluminal pressure. A variety of veins can be affected.

- **Superficial veins of the lower extremities** are particularly vulnerable due to a lack of structural support from superficial fat and/or incompetent valve(s). Varicosities of these superficial veins are very common (15% of the U.S. population); occur more frequently in females than males; and are common in pregnancy.

KP00710.indb 101 13/10/22 1:52 PM

- **Esophageal varices** are due to portal hypertension (usually caused by cirrhosis) and may be a source of life-threatening hemorrhage.
- Varices of the anal region are commonly called **hemorrhoids**; are associated with constipation and pregnancy; and may be complicated by either bleeding (streaks of red blood on hard stools) or thrombosis (painful).

Venous Insufficiency

Venous insufficiency is more common in women than men, and the incidence increases with age. Lower extremities demonstrate edema, hyperpigmentation and ulceration due to venous hypertension and incompetent valves.

VASCULAR ECTASIAS

A **vascular ectasia** is a dilatation of a vessel; it is not a neoplasm. Examples include:

- **Nevus flammeus nuchae** is a neck "birthmark" or "stork bite" that regresses.
- **Port wine stain** is a vascular birthmark that does not regress.
- **Spider telangiectasias** occur on the face, blanch with pressure, and are associated with pregnancy.

VASCULAR NEOPLASMS

Benign Tumors

Hemangiomas are extremely common, benign vascular tumors. They are the most common tumor in infants appearing on the skin, mucous membranes, or internal organs. The major types are capillary and cavernous hemangiomas. Hemangiomas may spontaneously regress.

CLINICAL CORRELATE

Port wine stains are large, flat, vascular malformations that are closely related to hemangiomas and are often seen on the head in the trigeminal nerve distribution.



© Richard P. Usatine, MD
Used with permission.

Figure 12-2. Hemangioma

KP00710.indb 102 13/10/22 1:52 PM

Hemangioblastomas are associated with von Hippel-Lindau disease, which may cause multiple hemangioblastomas involving the cerebellum, brain stem, spinal cord, and retina, as well as renal cell carcinoma.

Glomus tumors (glomangioma) are benign, small, painful tumors of the glomus body that usually occur under fingernails.

Malignant Tumors

Kaposi sarcoma is a malignant tumor of endothelial cells associated with Kaposi-sarcoma–associated virus (HHV8). The condition causes multiple red-purple patches, plaques, or nodules that may remain confined to the skin or may disseminate. Microscopically, there is a proliferation of spindle-shaped endothelial cells with slit-like vascular spaces and extravasated erythrocytes.

- The **classic European form** occurs in older men of Eastern European or Mediterranean origin, who develop red-purple skin plaques on the lower extremities.
- The **transplant-associated form** occurs in patients on immunosuppression for organ transplants; involves skin and viscera; may regress with reduction of immunosuppression.
- The **African form** occurs in African children and young men in whom generalized lymphatic spread is common.
- The **AIDS-associated form** is most common in homosexual male AIDS patients; it is an aggressive form with frequent widespread visceral dissemination. Common sites of involvement include skin, GI tract, lymph nodes, and lungs. This form of Kaposi sarcoma is responsive to chemotherapy and interferon-alpha, and only rarely causes death.

Angiosarcoma (hemangiosarcoma) is a malignant vascular tumor with a high mortality that most commonly occurs in skin, breast, liver, and soft tissues. Liver angiosarcomas are associated with vinyl chloride, arsenic, and thorotrast.

KP00710.indb 103 13/10/22 1:52 PM

Cardiac Pathology 13

LEARNING OBJECTIVES

- ❑ Determine the pathophysiology and different presentations of ischemic heart disease
- ❑ Define congestive heart failure and recognize the differences between left vs right heart failure
- ❑ Identify the pathophysiologic characteristics and presentation of the various valvular heart diseases, including carcinoid heart disease
- ❑ Differentiate the pathophysiologic characteristics of the most common congenital heart diseases
- ❑ Classify the different cardiomyopathies according to clinical presentation
- ❑ Outline the clinical characteristics of cardiac tumors and pericardial diseases

ISCHEMIC HEART DISEASE

Epidemiology

Ischemic heart disease is usually secondary to coronary artery disease (CAD); it is the most common cause of death in the United States. It is most often seen in middle-age men and postmenopausal women.

Clinical Presentations of Heart Disease

Angina pectoris is due to transient cardiac ischemia without cell death resulting in substernal chest pain.

- **Stable angina** (most common type) is caused by coronary artery atherosclerosis with luminal narrowing >75%. Chest pain is brought on by increased cardiac demand (exertional or emotional), and is relieved by rest or nitroglycerin (vasodilation). Electrocardiogram shows ST segment depression (subendocardial ischemia).
- **Prinzmetal variant angina** is caused by coronary artery vasospasm and produces episodic chest pain often at rest; it is relieved by nitroglycerin (vasodilatation). Electrocardiogram shows transient ST segment elevation (transmural ischemia).

KP00710.indb 105 13/10/22 1:52 PM

- **Unstable or crescendo angina** is caused by formation of a nonocclusive thrombus in an area of coronary atherosclerosis, and is characterized by increasing frequency, intensity, and duration of episodes; episodes typically occur at rest. This form of angina has a high risk for myocardial infarction.

Myocardial infarction (MI) occurs when a localized area of cardiac muscle undergoes coagulative necrosis due to ischemia. It is the most common cause of death in the United States. The mechanism leading to infarction is coronary artery atherosclerosis (90% of cases). Other causes include decreased circulatory volume, decreased oxygenation, decreased oxygen-carrying capacity, or increased cardiac workload, due to systemic hypertension, for instance.

- **Distribution of coronary artery thrombosis.** The left anterior descending artery (LAD) is involved in 45% of cases; the right coronary artery (RCA) is involved in 35% of cases; and the left circumflex coronary artery (LCA) is involved in 15% of cases.

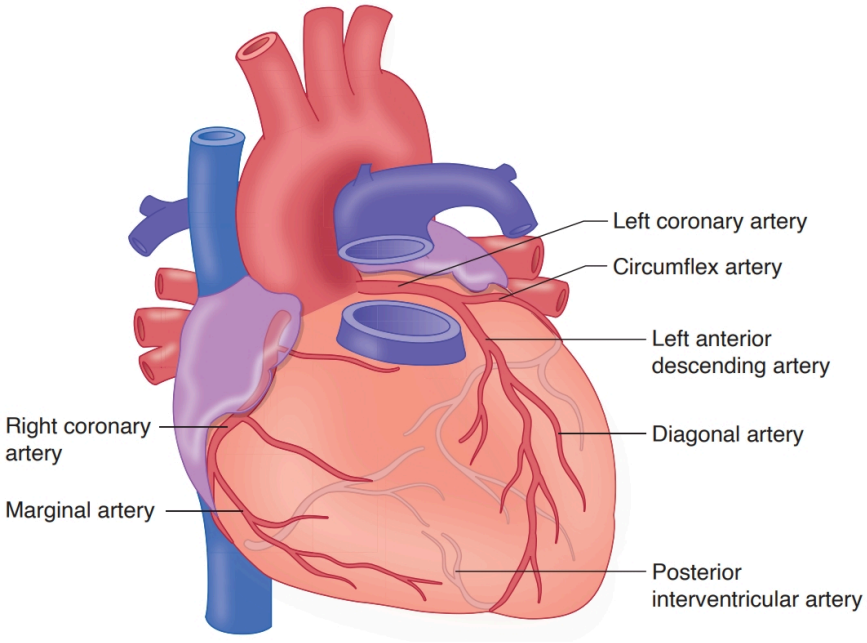


Figure 13-1. Arterial Supply to the Heart

Infarctions are classified as transmural, subendocardial, or microscopic.

- **Transmural** infarction (most common type) is considered to have occurred when ischemic necrosis involves >50% of myocardial wall. It is associated with regional vascular occlusion by thrombus. It causes ST elevated MIs (STEMIs) due to atherosclerosis and acute thrombosis.
- **Subendocardial** infarction is considered to have occurred when ischemic necrosis involves <50% of myocardial wall. It is associated with hypoperfusion due to shock. ECG changes are not noted. This type of infarction occurs in a setting of CAD with a decrease in oxygen delivery or an increase in demand.
- **Microscopic** infarction is caused by small vessel occlusion due to vasculitis, emboli, or spasm. ECG changes are not noted.

13_Preclinical_Pathology_Ch13.indd 106 26/09/22 5:18 PM

The **clinical presentation** of MI is classically a sudden onset of severe "crushing" substernal chest pain that radiates to the left arm, jaw, and neck. The pain may be accompanied by chest heaviness, tightness, and shortness of breath; diaphoresis, nausea, and vomiting; jugular venous distension (JVD); anxiety and often "feeling of impending doom." Electrocardiogram initially shows ST segment elevation. Q waves representing myocardial coagulative necrosis develop in 24–48 hours.

Table 13-1. Serum Markers Used to Diagnose Myocardial Infarctions

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

The **microscopic and gross changes** represent a spectrum that is preceded by biochemical changes, going from aerobic metabolism to anaerobic metabolism within minutes. The time intervals are variable and depend on the size of the infarct, as well as other factors.

Table 13-2. Gross Sequence of Changes

Time Post-Infarction	Gross Appearance
0–12 h	No visible gross change
12–24 h	Vague pallor and softening
1–7 days	Yellow pallor
7–10 days	Central pallor with a red border
6–8 wks	White, firm scar

Table 13-3. Microscopic Sequence of Changes

Time Post-Infarction	Microscopic Appearance
1–4 h	None or wavy myocyte fibers at border or contraction band necrosis
4 h–3 days	Coagulative necrosis
1–3 days	Neutrophilic infiltrate
3–7 days	Macrophages
7–10 days	Granulation tissue
3–8 wks	Remodeled type III collagen becoming dense, collagenous scar

Complications of MI include cardiac arrhythmias that may lead to sudden cardiac death; congestive heart failure; cardiogenic shock (>40–50% myocardium is necrotic); mural thrombus and thromboembolism; fibrinous pericarditis; ventricular

CLINICAL CORRELATE

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

KP00710.indb 107 13/10/22 1:52 PM

aneurysm; and cardiac rupture. Cardiac rupture most commonly occurs 3–7 days after MI. Effects vary with the site of rupture: ventricular free wall rupture causes cardiac tamponade; interventricular septum rupture causes left to right shunt; and papillary muscle rupture causes mitral insufficiency.

Sudden cardiac death is defined to be death within 1 hour of the onset of symptoms. The mechanism is typically a fatal cardiac arrhythmia (usually ventricular fibrillation). CAD is the most common underlying cause (80%); other causes include hypertrophic cardiomyopathy, mitral valve prolapse, aortic valve stenosis, congenital heart abnormalities, and myocarditis.

Chronic ischemic heart disease is the insidious onset of progressive congestive heart failure. It is characterized by left ventricular dilation due to accumulated ischemic myocardial damage (replacement fibrosis) and functional loss of hypertrophied noninfarcted cardiac myocytes.

CLINICAL CORRELATE

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

CONGESTIVE HEART FAILURE

Physiologic Basis

Congestive heart failure (CHF) refers to the presence of insufficient cardiac output to meet the metabolic demand of the body's tissues and organs. It is the final common pathway for many cardiac diseases and has an increasing incidence in the United States. Complications include both **forward failure** (decreased organ perfusion) and **backward failure** (passive congestion of organs). Right- and left-sided heart failure often occur together.

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").

Left Heart Failure

Left heart failure can be caused by ischemic heart disease, systemic hypertension, myocardial diseases, and aortic or mitral valve disease. The heart has increased heart weight and shows left ventricular hypertrophy and dilatation. The lungs are heavy and edematous. Left heart failure presents with dyspnea, orthopnea, paroxysmal nocturnal dyspnea, rales, and S3 gallop.

Microscopically, the heart shows cardiac myocyte hypertrophy with "enlarged pleiotropic nuclei," while the lung shows pulmonary capillary congestion and alveolar edema with intra-alveolar hemosiderin-laden macrophages ("heart failure cells"). Complications include passive pulmonary congestion and edema, activation of the renin-angiotensin-aldosterone system leading to secondary hyperaldosteronism, and cardiogenic shock.

NOTE

Cor pulmonale is right-sided heart failure caused by pulmonary hypertension from intrinsic lung disease.

Lung disease → pulmonary HTN → ↑ right ventricular pressure → right ventricular hypertrophy → right-sided heart failure

Right Heart Failure

Right heart failure is most commonly caused by left-sided heart failure, with other causes including pulmonary or tricuspid valve disease and *cor pulmonale*. Right heart failure presents with JVD, hepatosplenomegaly, dependent edema, ascites, weight gain, and pleural and pericardial effusions. Grossly, right ventricular hypertrophy and dilatation develop. Chronic passive congestion of the liver may develop and may progress to cardiac sclerosis/cirrhosis (only with long-standing congestion).

KP00710.indb 108 13/10/22 1:52 PM

VALVULAR HEART DISEASE

Left Heart

- **Bicuspid aortic valve** is the most common heart valve defect. It is heritable, and *NOTCH1* mutations are associated with some cases. Although it is a congenital cardiac malformation, it sometimes does not cause morbidity until adult life. In the majority of cases, it causes valve stenosis (whereby the valve does not completely open), but it can cause valvular insufficiency (whereby the valve does not completely close). Infectious endocarditis and aortic dilatation and dissection are possible complications.
- **Degenerative calcific aortic valve stenosis** is a common valvular abnormality characterized by age-related dystrophic calcification, degeneration, and stenosis of the aortic valve. Less commonly it occurs in the setting of bicuspid aortic valve. It can lead to concentric left ventricular hypertrophy (LVH) and congestive heart failure with increased risk of sudden death. The calcifications are on the outflow side of the cusps. Treatment is aortic valve replacement.
- **Mitral valve prolapse** has enlarged, floppy mitral valve leaflets that prolapse into the left atrium and microscopically show myxomatous degeneration. The condition affects individuals with Marfan syndrome. Patients are asymptomatic and a mid-systolic click can be heard on auscultation. Complications include infectious endocarditis and septic emboli, rupture of chordae tendineae with resulting mitral insufficiency, and rarely sudden death.

Right Heart

The topics **tricuspid atresia** and **pulmonary atresia** are discussed under congenital heart disease later in this chapter.

Carcinoid heart disease is right-sided endocardial and valvular fibrosis secondary to serotonin exposure in patients with carcinoid tumors that have metastasized to the liver. It is a plaque-like thickening (endocardial fibrosis) of the endocardium and valves of the right side of the heart. Many patients experience carcinoid syndrome (also related to secretion of serotonin and other metabolically active products of the tumors), characterized by skin flushing, diarrhea, cramping, bronchospasm, wheezing, and telangiectasias. The diagnosis can be established by demonstrating elevated urinary 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of the breakdown of serotonin via monoamine oxidase.

Inflammatory Valvular Disease

Infective bacterial endocarditis (or more aptly **infective endocarditis**) refers to bacterial infection of the cardiac valves, characterized by vegetations on the valve leaflets. Risk factors include rheumatic heart disease, mitral valve prolapse, bicuspid aortic valve, degenerative calcific aortic stenosis, congenital heart disease, artificial valves, indwelling catheters, dental procedures, immunosuppression, and intravenous drug use.

- **Acute endocarditis** is typically due to a *high virulence organism* that can colonize a normal valve, such as *Staphylococcus aureus*. Acute endocarditis produces large destructive vegetations (fibrin, platelets, bacteria, and neutrophils). The prognosis is poor, with mortality of 10–40%.

CLINICAL CORRELATE

Endocarditis involving the tricuspid valve is highly suggestive of IV drug use or central line bacteremia.

KP00710.indb 109 13/10/22 1:52 PM

- **Subacute endocarditis** is typically due to a low virulence organism, such as *Streptococcus group viridans*, which usually colonizes a previously damaged valve. The disease course is typically indolent with <10% mortality.

BRIDGE TO MICROBIOLOGY

Viridans streptococci

- Alpha-hemolytic
- Bile-resistant
- Optochin-resistant

Clinically, endocarditis presents with fever, chills, weight loss, and cardiac murmur. Embolic phenomena may occur, and may affect systemic organs; retina (Roth spots); and distal extremities (Osler nodes [painful, red subcutaneous nodules on the fingers and toes], Janeway lesions [painless, red lesions on the palms and soles], and splinter fingernail hemorrhages). Diagnosis is by serial blood cultures. Complications include septic emboli, valve damage resulting in insufficiency and congestive heart failure, myocardial abscess, and dehiscence of an artificial heart valve.

Rheumatic heart disease

Rheumatic fever is a systemic recurrent inflammatory disease, triggered by a pharyngeal infection with *Group A β-hemolytic streptococci.* In genetically susceptible individuals, the infection results in production of antibodies that cross-react with cardiac antigens (type II hypersensitivity reaction). Rheumatic fever affects children (ages 5–15 years), and there is a decreasing incidence in the United States. Symptoms occur 2–3 weeks after a pharyngeal infection; laboratory studies show elevated antistreptolysin O (ASO) titers.

The Jones criteria are illustrated below. Diagnosis of rheumatic fever requires **2 major** OR **1 major and 2 minor criteria,** plus a preceding group A strep infection.

Table 13-4. WHO Criteria for Rheumatic Fever Based on Revised Jones Criteria

Major Criteria	Minor Criteria
Carditis	Fever
Polyarthritis	Polyarthralgia
Chorea	Labs: elevated ESR or leukocyte count
Erythema marginatum	ECG: prolonged P-R interval
Subcutaneous nodules	

- **Acute rheumatic heart disease** affects myocardium, endocardium, and pericardium. The myocardium can develop myocarditis, whose most distinctive feature is the **Aschoff body,** in which fibrinoid necrosis is surrounded by macrophages **(Anitschkow cells)**, lymphocytes, and plasma cells. Fibrinous pericarditis may be present. Endocarditis may be a prominent feature that typically involves mitral and aortic valves (forming fibrin vegetations along the lines of closure) and may also cause left atrial endocardial thickening (MacCallum plaques).
- **Chronic rheumatic heart disease** is characterized by mitral and aortic valvular fibrosis, characterized by valve thickening and calcification; fusion of the valve commissures; and damaged chordae tendineae (short, thickened, and fused). Complications can include mitral stenosis and/or regurgitation, aortic stenosis and/or regurgitation, congestive heart failure, and infective endocarditis.

KP00710.indb 110 13/10/22 1:52 PM

Postoperative endocarditis occurs in pediatric patients after repair of congenital heart disease. The pathogen is often *Staph aureus*; other pathogens include *Candida* species.

Noninfective endocarditis, also known as marantic endocarditis, is characterized by small, sterile vegetations along the valve leaflet line of closure in patients with a debilitating disease. The major complications are embolism and secondary infection of the vegetations.

- **Libman-Sacks endocarditis** is a manifestation of systemic lupus erythematosus that most commonly affects the mitral and aortic valves with vegetations and thickening.
- **Antiphospholipid antibody syndrome** can also cause marantic endocarditis.

CLINICAL CORRELATE

S. bovis endocarditis or septicemia is associated with a higher incidence of occult colorectal tumors.

Colonoscopy should be performed in all patients with *S. bovis* bacteremia or endocarditis.

MYOCARDITIS

Myocarditis arises from infectious (Coxsackie A and B viruses, Chagas disease) and immune causes. Clinically, the patient may be asymptomatic or may suffer from acute heart failure or even dilated cardiomyopathy.

Clinicopathologic Features of Myocarditis

In myocarditis, inflammatory infiltrates damage myocytes. Clinically, the patient may be asymptomatic or may suffer acute heart failure with subsequent dilated cardiomyopathy or sudden death. Some patients recover without complications.

Causes of Myocarditis

Infectious causes include coxsackieviruses A and B, enteroviruses and *Trypanosoma cruzi* (Chagas disease), *Toxoplasma gondii*, and *Borrelia burgdorferi* (Lyme disease).

Noninfectious causes include systemic lupus erythematosus, rheumatoid arthritis, and drug hypersensitivity reactions.

CONGENITAL HEART DISEASE

Congenital heart disease is the most common cause of childhood heart disease in the United States; 90% of cases are idiopathic and 5% are associated with genetic disease (trisomies, cri du chat, Turner syndrome, etc.), viral infection (especially congenital rubella), or drugs and alcohol. Some of the congenital heart defects have already been discussed in the section on valvular heart disease.

KP00710.indb 111 13/10/22 1:52 PM

Table 13-5. 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	Secondary pulmonary HTN → reversal of shunt (Eisenmenger syndrome)
• Tetralogy of Fallot • Transposition of the great arteries • Truncus arteriosus • Tricuspid atresia • Pulmonary atresia	• Ventricular septal defect • Atrial septal defect • Patent ductus arteriosus

NOTE

"Overriding aorta" refers to the location of the aorta relative to the VSD.

Right-to-Left Shunts

Tetralogy of Fallot is the most common cause of congenital cyanotic heart disease. The classic tetrad includes **right ventricular outflow obstruction/stenosis; right ventricular hypertrophy; ventricular septal defect;** and **overriding aorta**. Clinical findings include cyanosis, shortness of breath, digital clubbing, and polycythemia. Progressive pulmonary outflow stenosis and cyanosis develop over time; treatment is surgical correction.

Transposition of the great arteries is an abnormal development of the truncoconal septum whereby the aorta arises from the right ventricle, and the pulmonary artery arises from the left ventricle. The risk is increased in infants of diabetic mothers. Affected babies develop early cyanosis and right ventricular hypertrophy. To survive, infants must have mixing of blood by a VSD, ASD, or PDA. The prognosis is poor without surgery.

Pulmonary atresia is a critical congenital heart defect. The pulmonary valve fails to form. The degree of development of the right ventricle is related to the presence or absence of a compensatory ventricular septal defect. Most cases are treated surgically.

Tricuspid atresia is another critical congenital heart defect. The tricuspid valve fails to form, resulting in right ventricular hypoplasia. Treatment includes medication (prostaglandin E1) or stenting to keep the ductus arteriosus patent, and corrective surgery.

BRIDGE TO PHARMACOLOGY

To keep PDA open: prostaglandin E2

To close PDA: indomethacin

Truncus arteriosus is a failure to develop a dividing septum between the aorta and pulmonary artery, resulting in a common trunk. Blood flows from the pulmonary trunk to the aorta. Truncus arteriosus causes early cyanosis and congestive heart failure, with a poor prognosis without surgery.

KP00710.indb 112 13/10/22 1:52 PM

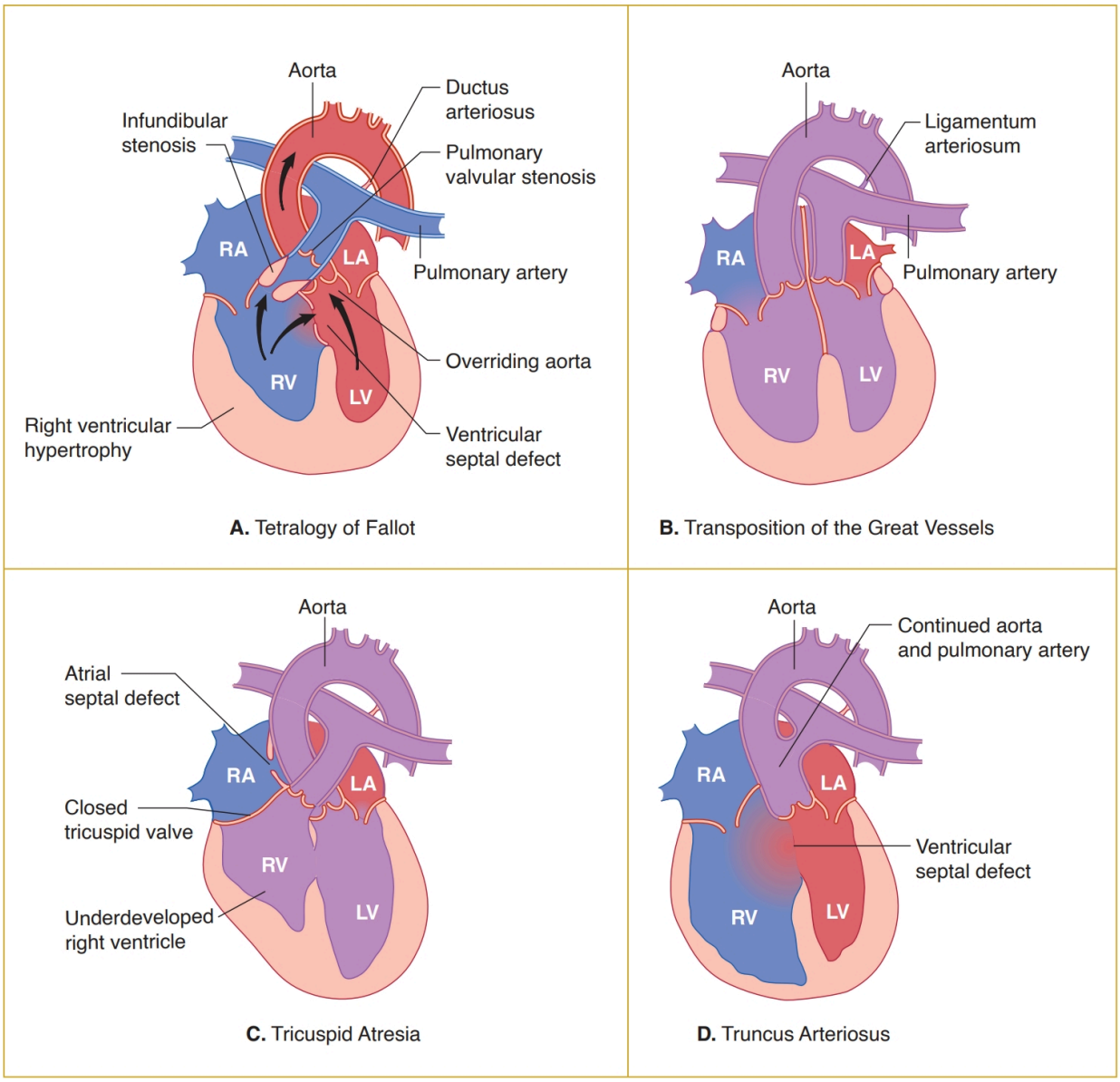


Figure 13-2. Common Forms of Cyanotic Congenital Heart Disease

Left-to-Right Shunts

Ventricular septal defect (VSD), which consists of a direct communication between the ventricular chambers, is the second most common congenital heart defect (the most common is a bicuspid aortic valve).

- A **small ventricular septal defect** may be asymptomatic and close spontaneously, or it may produce a jet stream that damages the endocardium and increases the risk of infective endocarditis.
- A **large ventricular septal defect** may cause **Eisenmenger complex**, which is characterized by secondary pulmonary hypertension, right ventricular hypertrophy, reversal of the shunt, and late cyanosis.

BRIDGE TO EMBRYOLOGY

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

13_Preclinical_Pathology_Ch13.indd 113 26/09/22 5:18 PM

- In **both types**, a systolic murmur can be heard on auscultation. Ventricular septal defects are commonly associated with other heart defects. Large ventricular septal defects can be surgically corrected.

Atrial septal defect (ASD) is a direct communication between the atrial chambers. The most common type is an ostium secundum defect. Complications include Eisenmenger syndrome and paradoxical emboli.

Patent ductus arteriosus (PDA) is a direct communication between the aorta and pulmonary artery due to the continued patency of the ductus arteriosus after birth. It is associated with prematurity and congenital rubella infections. Clinical findings include machinery murmur, late cyanosis, and congestive heart failure. Eisenmenger syndrome may develop as a complication.

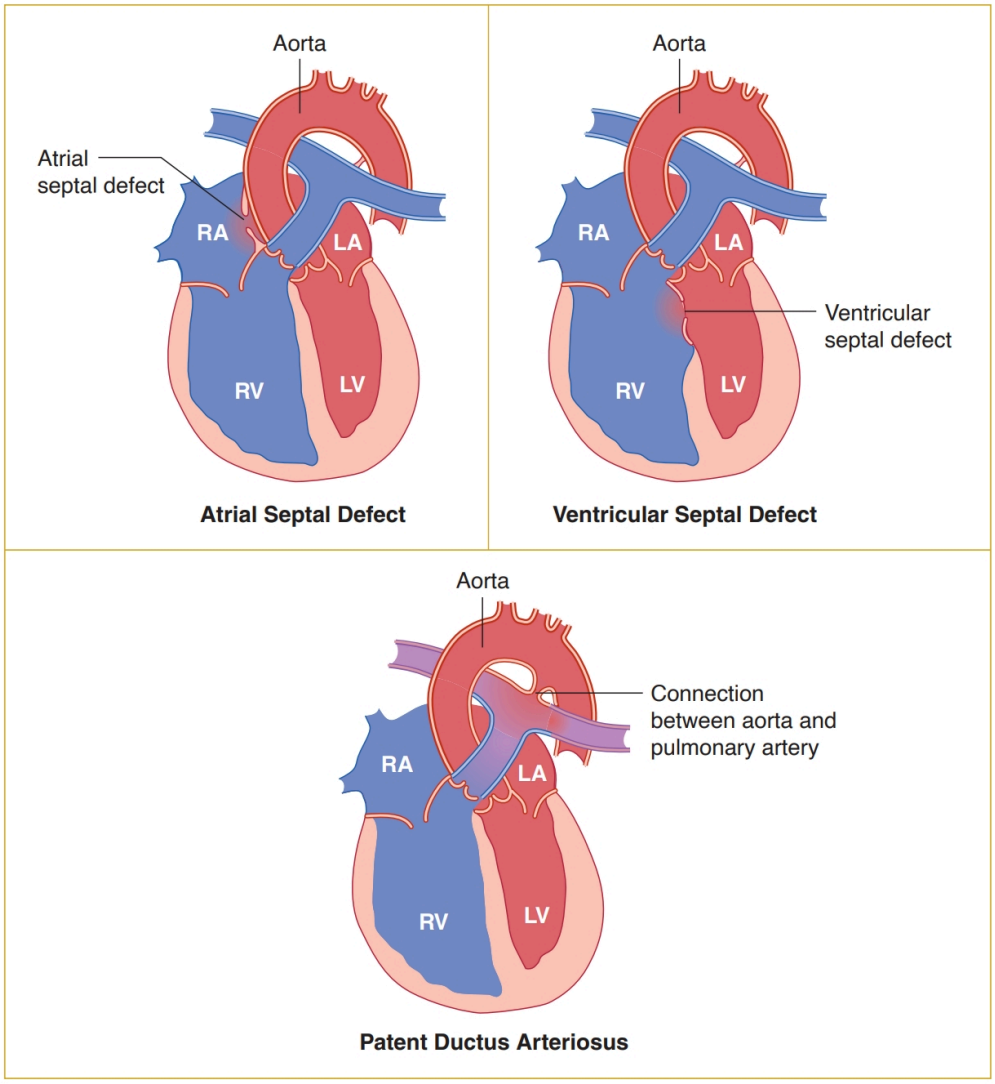


Figure 13-3. Common Forms of Acyanotic Congenital Heart Disease

13_Preclinical_Pathology_Ch13.indd 114 26/09/22 5:18 PM

Coarctation of the Aorta

Coarctation of the aorta is a segmental narrowing of the aorta.

- **Preductal coarctation** (infantile-type) is associated with Turner syndrome and causes severe narrowing of aorta proximal to the ductus arteriosus. It is usually associated with a patent ductus arteriosus (PDA), which supplies blood to aorta distal to the narrowing, and right ventricular hypertrophy (secondary to the need for the right ventricle to supply the aorta through the patent ductus arteriosus). It presents in infancy with congestive heart failure that is accompanied by weak pulses and cyanosis in the lower extremities; the prognosis is poor without surgical correction.
- **Postductal coarctation** (adult-type) causes stricture or narrowing of the aorta distal to the ductus arteriosus. It can present in a child or an adult with hypertension in the upper extremities, and hypotension and weak pulses in the lower extremities. Some collateral circulation may be supplied via the internal mammary and intercostal arteries; the effects of this collateral circulation may be visible on chest x-ray with notching of the ribs due to bone remodeling as a consequence of increased blood flow through the intercostal arteries.

Complications can include congestive heart failure (the heart is trying too hard), intracerebral hemorrhage (the blood pressure in the carotid arteries is too high), and dissecting aortic aneurysm (the blood pressure in the aortic route is too high).

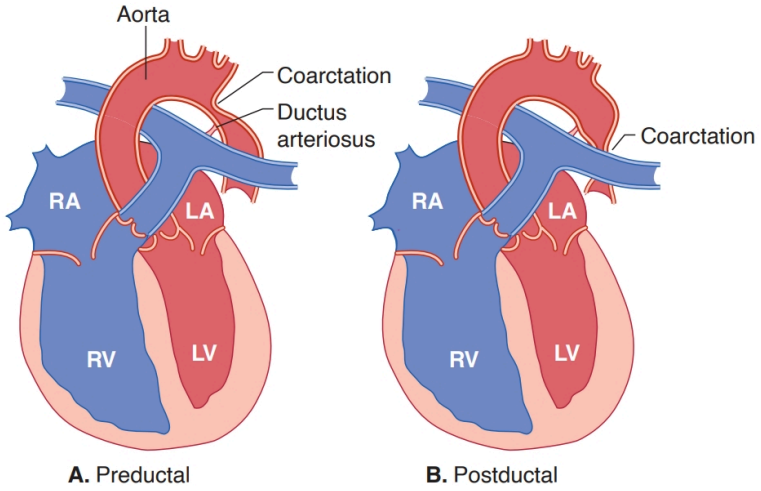


Figure 13-4. Coarctation of the Aorta

PRIMARY CARDIOMYOPATHIES (DIAGNOSIS OF EXCLUSION)

Dilated Cardiomyopathy

Dilated cardiomyopathy (most common form) is cardiac enlargement with dilatation of all 4 chambers, resulting in progressive congestive heart failure (typical mode of presentation). The cause is genetic in 20–50% of cases, but some

13_Preclinical_Pathology_Ch13.indd 115 26/09/22 5:18 PM

cases are related to alcohol, medications (Adriamycin [doxorubicin]), cocaine, viral myocarditis (Coxsackievirus B and enteroviruses), parasitic infections (Chagas disease), iron overload or pregnancy.

In cases of all types, the underlying etiology leads to destruction of myocardial contractility, which affects systolic function. Echocardiogram typically shows decreased ejection fraction. Complications include mural thrombi and cardiac arrhythmias; prognosis is poor with 5-year survival of 25%. Treatment is heart transplantation. There is myocyte hypertrophy with interstitial fibrosis on microscopy, and eccentric hypertrophy seen on gross examination.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (also called asymmetrical septal hypertrophy, and idiopathic hypertrophic subaortic stenosis [IHSS]) is a common cause of sudden cardiac death in young athletes. The condition is an asymmetrical hypertrophy of cardiac muscle that causes decreased compliance affecting diastolic function. Hypertrophic cardiomyopathy can be an autosomal dominant disorder (>50% of cases) or idiopathic. The muscle hypertrophy is due to the increased synthesis of actin and myosin, and on microscopic examination, the cardiac muscle fibers are hypertrophied and in disarray. Hypertrophic cardiomyopathy is most prominent in the ventricular septum, where it can obstruct the ventricular outflow tract. This can potentially lead to death during severe exercise when the cardiac outflow tract collapses, preventing blood from exiting the heart.

Restrictive Cardiomyopathy

Restrictive cardiomyopathy (uncommon form) is caused by diseases which produce restriction of cardiac filling during diastole; etiologies include amyloidosis, sarcoidosis, endomyocardial fibroelastosis, and Loeffler endomyocarditis. In all of these diseases, increased deposition of material leads to decreased compliance, affecting diastolic function. On gross examination, the ventricles are not enlarged and the cavities are not dilated. Microscopy will reflect the underlying cause.

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy causes thinning of the right ventricle due to autosomal dominant mutations that encode desmosomal junctional proteins. On microscopy, there is fatty infiltration of the myocardium.

NOTE

Tuberous Sclerosis Complex

- Autosomal dominant
- Mutation in genes *TSC1* and *TSC2*, which encode tumor suppressor proteins hamartin and tuberin, respectively
- Multiple hamartomas
- Cortical tubers
- Renal angiomyolipomas
- Cardiac rhabdomyomas
- Pulmonary hamartomas

CARDIAC TUMORS

General Concepts

Primary cardiac tumors are rare. The majority are benign; the malignant tumors are sarcomas and lymphomas. Treatment is excision.

Benign Common Tumors

The **myxoma** is the most common tumor in adults, and the **rhabdomyoma** is the most common tumor in children.

KP00710.indb 116 13/10/22 1:52 PM

- **Cardiac myxoma** is a benign tumor usually arising within the left atrium near the fossa ovalis in decades 3–6 of life; it can present like mitral valve disease. In 10% of cases there is an autosomal dominant condition known as Carney complex (myxomas with endocrine abnormalities and lentigines or pigmented nevi). Cardiac myxoma is characterized microscopically by stellate-shaped cells within a myxoid background. Complications include tumor emboli and "ball-valve" obstruction of the valves.
- **Cardiac rhabdomyoma** is a benign tumor usually arising within the myocardium that is associated with tuberous sclerosis.

PERICARDIAL DISEASE

Pericarditis

There are 2 kinds of pericarditis, acute and chronic.

- **Acute pericarditis** is characterized by a fibrinous exudate (viral infection or uremia) or by a fibrinopurulent exudate (bacterial infection).
- **Chronic pericarditis** can occur when acute pericarditis does not resolve and adhesions form.

Pericardial Effusion

Pericardial effusion may be serous (secondary to heart failure or hypoalbuminemia), serosanguineous (due to trauma, malignancy, or rupture of the heart or aorta) or chylous (due to thoracic duct obstruction or injury).

Tumors of the Pericardium

Primary pericardial tumors are rare. Metastases from the breast and lung may spread to the pericardium.

- **Sarcoma** occurs more commonly as the synovial sarcoma type.
- **Mesothelioma** arising in pericardium is rarely associated with asbestos exposure.
- **Solitary fibrous tumors** are benign but may recur.
- **Germ cell tumors** occur in the pediatric population.

Tumors of the lung and breast may spread by **direct extension** to the pericardia.

KP00710.indb 117 13/10/22 1:52 PM

14 Pulmonary Pathology

LEARNING OBJECTIVES

- ❑ Explain information related to congenital cystic lung lesions
- ❑ Demonstrate understanding of atelectasis
- ❑ Solve problems concerning pulmonary infections
- ❑ Demonstrate understanding of sarcoidosis
- ❑ Answer questions about obstructive versus restrictive lung disease
- ❑ Answer questions about vascular disorders of the lungs
- ❑ Demonstrate understanding of pulmonary and laryngeal neoplasia
- ❑ Explain information related to diseases of the pleural cavity

CONGENITAL LUNG MALFORMATIONS

Congenital Pulmonary Airway Malformation

Congenital pulmonary airway malformation (previously known as congenital cystic adenomatoid malformation) is a developmental defect in the pulmonary parenchyma that communicates with the tracheobronchial tree. It assumes a variety of gross features ranging from a single, large (3–10 cm) cyst to multiple smaller cysts to a mass without grossly evident cysts. It can be diagnosed prenatally with ultrasound. Rarely, it can be asymptomatic into adulthood. Symptomatic cases causing recurrent infection and pneumothorax are treated prenatally with surgical resection. Severe cases causing hydrops and mediastinal shift have been treated with prenatal surgery.

Bronchopulmonary Sequestration

Bronchopulmonary sequestration is an intralobar (with pulmonary artery blood supply) or extralobar (with descending artery blood supply) malformation of pulmonary tissue that does not communicate with the tracheobronchial tree. Cases presenting with pleural effusion can require intrauterine treatment. Most cases regress spontaneously. Some cases remain undiagnosed until adulthood.

KP00710.indb 119 13/10/22 1:52 PM

ATELECTASIS

Atelectasis refers to an area of collapsed or nonexpanded lung. It is reversible, but areas of atelectasis predispose for infection due to decreased mucociliary clearance.

- **Obstruction/resorption atelectasis** is collapse of lung due to resorption of air distal to an obstruction; examples include aspiration of a foreign body, chronic obstructive pulmonary disease (COPD), and postoperative atelectasis.
- **Compression atelectasis** is atelectasis due to fluid, air, blood, or tumor in the pleural space.
- **Contraction (scar) atelectasis** is due to fibrosis and scarring of the lung.
- **Patchy atelectasis** is due to a lack of surfactant, as occurs in hyaline membrane disease of newborn or acute (adult) respiratory distress syndrome (ARDS).

PULMONARY INFECTIONS

Pneumonia

BRIDGE TO ANATOMY

Pores of Kohn are collateral connections between alveoli through which infections and neoplastic cells can spread.

In **bacterial pneumonia**, acute inflammation and consolidation (solidification) of the lung are due to a bacterial agent. Clinical signs and symptoms include fever and chills; productive cough with yellow-green (pus) or rusty (bloody) sputum; tachypnea; pleuritic chest pain; and decreased breath sounds, rales, and dullness to percussion.

Studies typically show elevated WBC count with a left shift (an increase in immature leukocytes). Chest x-ray for lobar pneumonia typically shows lobar or segmental consolidation (opacification), and for bronchopneumonia typically shows patchy opacification. Pleural effusion may also be picked up on chest x-ray.

In general, the keys to effective therapy are identification of the organism and early treatment with antibiotics.

Lobar pneumonia is characterized by consolidation of an entire lobe. The infecting organism is typically *Streptococcus pneumoniae* (95%) or *Klebsiella*. The lancet-shaped diplococcus *Streptococcus pneumoniae* is alpha-hemolytic, bile soluble, and optochin sensitive.

The **4 classic phases** of lobar pneumonia are **congestion** (active hyperemia and edema); **red hepatization** (neutrophils and hemorrhage); **gray hepatization** (degradation of RBCs); and **resolution** (healing). In today's antibiotic era, these changes are not generally observed in practice.

Bronchopneumonia is characterized by scattered patchy consolidation centered on bronchioles; the inflammation tends to be bilateral, multilobar, and basilar, and particularly susceptible populations include the young, old, and terminally ill. Infecting organisms exhibit more variation than in lobar pneumonia, and include *Staphylococci, Streptococci, Haemophilus influenzae, Pseudomonas aeruginosa,* etc. Microscopic examination of tissue shows acute inflammation of

KP00710.indb 120 13/10/22 1:52 PM

bronchioles and surrounding alveoli. The diagnosis can often be established with sputum Gram stain and sputum culture, but will sometimes require blood cultures.

Complications of pneumonia include fibrous scarring and pleural adhesions, lung abscess, empyema (pus in a body cavity), and sepsis.

Treatment of pneumonia is generally initial empiric antibiotic treatment, modified by the results of cultures and organism sensitivities.

Lung abscess is a localized collection of neutrophils (pus) and necrotic pulmonary parenchyma. The etiology varies with the clinical setting. **Aspiration** is the most common cause. It tends to involve right lower lobe and typically has mixed oral flora (often both anaerobic and aerobic) for infecting organisms.

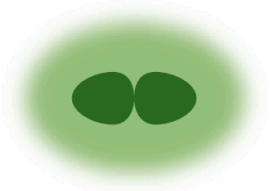
Lung abscess may also occur following a pneumonia, especially one due to *S. aureus* or *Klebsiella*. Lung abscesses may also occur following airway obstruction (postobstructive) or deposition of septic emboli in the lung.

Complications of lung abscess include empyema, pulmonary hemorrhage, and secondary amyloidosis.

Atypical pneumonia is the term used for interstitial pneumonitis without consolidation. It is more common in children and young adults. Infecting organisms that can cause atypical pneumonia include *Mycoplasma pneumoniae, influenza virus, parainfluenza virus, respiratory syncytial virus* (RSV) (which is especially important in young children), *adenovirus, cytomegalovirus* (CMV) (which is especially important in the immunocompromised), varicella virus, and many others.

Diagnosis. Chest x-ray typically shows diffuse interstitial infiltrates. An elevated cold agglutinin titer specifically suggests *Mycoplasma* as a cause, which is important to identify since antibiotic therapy for *Mycoplasma* exists. Lung biopsy, if performed, typically shows lymphoplasmacytic inflammation within the alveolar septa.

Complications include superimposed bacterial infections and Reye syndrome (potentially triggered by viral illness [influenza/varicella] treated with aspirin).



Streptococcus pneumoniae

Tuberculosis (TB)

The number of cases of TB is declining in the United States, but the proportion of cases in people born outside the country is rising. In this clinical setting, a positive PPD skin test may demonstrate that the person has been exposed to the mycobacterial antigens. Individuals who have received the BCG vaccine in some foreign countries may have a positive PPD test without being infected. In such cases chest x-ray and sputum smears and cultures are done.

Infection is usually acquired by inhalation of aerosolized bacilli.

The **clinical presentation** of Mycobacterium tuberculosis includes fevers and night sweats, weight loss, cough, and hemoptysis.

NOTE

BCG (Bacillus Calmette-Guérin) is a tuberculosis vaccine prepared from a strain of attenuated live bovine tuberculosis bacillus, *Mycobacterium bovis*.

KP00710.indb 121 13/10/22 1:52 PM

Primary pulmonary TB develops on initial exposure to the disease. The Ghon focus of primary TB is characterized by subpleural caseous granuloma formation, either above or below the interlobar fissure. The term **Ghon complex** refers to the combination of the Ghon focus and secondarily-involved hilar lymph nodes with granulomas. Most primary pulmonary tuberculosis lesions (95%) will undergo fibrosis and calcification.

Progressive pulmonary TB can take several forms, including cavitary tuberculosis, miliary pulmonary tuberculosis, and tuberculous bronchopneumonia.

Secondary pulmonary TB (also known as postprimary or reactivation TB) occurs either with reactivation of an old, previously quiescent infection or with reinfection secondary to a second exposure to the mycobacteria. In secondary pulmonary TB, the infection often produces a friable nodule at the lung apex (Simon focus) secondary to the high oxygen concentration present at that site, since the upper parts of the lung typically ventilate more efficiently than the lower parts. Biopsy of affected tissues will typically show AFB-positive caseating granulomas.

Additionally, **dissemination to other organ systems** can occur in advanced TB via a hematogenous route that often results in a miliary pattern within each affected organ. Sites that may become involved include meninges; cervical lymph nodes (scrofula) and larynx; liver/spleen, kidneys, adrenals, and ileum; lumbar vertebrae bone marrow (Pott disease); and fallopian tubes and epididymis.

Nontuberculous mycobacteria. *M. avium* complex (MAC) typically occurs in AIDS patients with CD4 counts <50 cells/mm3 and presents as disseminated disease.

The diagnosis of TB requires identification of the bacilli. Positive sputum smear necessitates culture for species identification. Adequate treatment requires drug susceptibility testing.

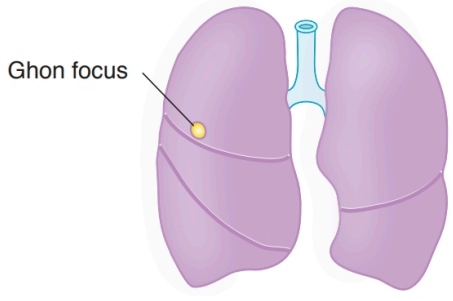


Figure 14-1. Primary Tuberculosis

SARCOIDOSIS

Clinicopathologic Features

Sarcoidosis is a systemic granulomatous disease of uncertain etiology. The disease affects females more than males, with typical age 20–60. It is most common in African American women. Clinical presentation varies. It may be asymptomatic,

14_Preclinical_Pathology_Ch14.indd 122 10/6/22 8:53 PM

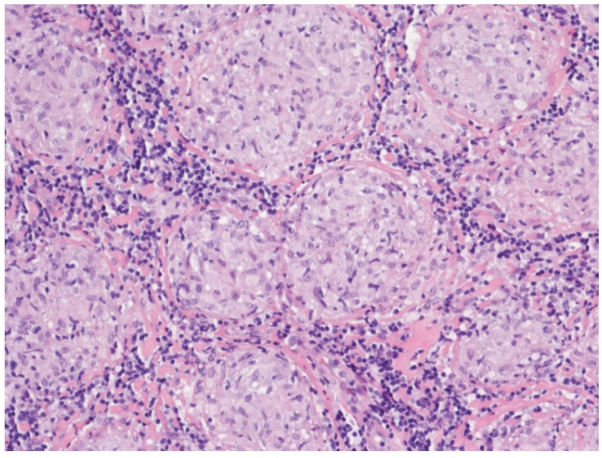
or presenting symptoms may include cough and shortness of breath; fatigue and malaise; skin lesions; eye irritation or pain; and fever or night sweats. Most often, the disease is first detected on chest x-ray as bilateral hilar lymphadenopathy or parenchymal infiltrates.

The noncaseating granulomas that are characteristic of sarcoidosis may occur in **any organ of the body**. In the lung, they typically form diffuse scattered granulomas; lymph node involvement may cause hilar and mediastinal adenopathy. Skin, liver and/or spleen, heart, CNS, bone marrow, and gastrointestinal tract are also frequent targets of the disease. Eye involvement can be seen in Mikulicz syndrome (involvement of the uvea and parotid).

Diagnosis of Sarcoidosis

Sarcoidosis is considered to be a **diagnosis of exclusion**. In practice, this means that the diagnosis is considered when a biopsy shows features characteristic of sarcoidosis (such as **noncaseating granulomas, Schaumann bodies** [laminated dystrophic calcification], and **asteroid bodies** [stellate giant cell cytoplasmic inclusions]). There are no pathognomonic microscopic features though, and the diagnosis requires clinicopathologic correlation.

The diagnosis of sarcoidosis can be suggested by clinical studies. In the laboratory, serum angiotensin converting enzyme (ACE), which is synthesized by endothelial cells and macrophages, may be elevated. X-ray studies frequently show **bilateral hilar lymphadenopathy**.



© Gregg Barré, MD Used with permission.

Figure 14-2. Noncaseating Sarcoid Granulomas

The prognosis is favorable with a variable clinical course. Most patients completely recover but some succumb to respiratory compromise.

OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is a general term used to indicate chronic decreased respiratory function due to chronic bronchitis or emphysema. Both diseases are associated with smoking.

KP00710.indb 123 13/10/22 1:52 PM

Chronic Bronchitis

Chronic bronchitis is a clinical diagnosis made when a patient has a persistent cough and copious sputum production for at least 3 months in 2 consecutive years. It is highly associated with smoking (90%). Clinical findings include cough, sputum production, dyspnea, frequent infections, hypoxia, cyanosis, and weight gain.

Microscopic examination demonstrates hypertrophy and hyperplasia of bronchial mucous glands (Reid index equals the submucosal gland thickness divided by the bronchial wall thickness between the pseudostratified columnar epithelium and the perichondrium; normal ratio is ≤ 0.4).

Complications include increased risk for recurrent infections; secondary pulmonary hypertension leading to right heart failure (cor pulmonale) and lung cancer.

Emphysema

Emphysema is the term used when destruction of alveolar septa results in enlarged air spaces and a loss of elastic recoil. The 4 types of emphysema are named for the anatomical distribution of the septal damage.

- In **centrilobular emphysema**, the damage is in the proximal portion of the acinus and the cause is cigarette smoking.
- In **panacinar emphysema**, the damage affects the entire acinus and the common cause is alpha-1 antitrypsin deficiency.
- In **distal acinar emphysema** (unknown cause), extension to the pleura causes pneumothorax.
- In **irregular emphysema**, post-inflammatory scarring involves the acinus in an irregular distribution.

The etiology of emphysema involves a **protease/antiprotease imbalance**. On gross examination, the lungs are overinflated and enlarged, and have enlarged, grossly visible air spaces. Clinical findings include progressive dyspnea, pursing of lips and use of accessory respiratory muscles to breathe, barrel chest (increased anterior-posterior diameter), and weight loss.

Table 14-1. Manifestations of Emphysema 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, air pollution	α-1-antitrypsin deficiency
Distribution: worse in apical segments of upper lobes	Distribution: entire lung; worse in bases of lower lobes

Asthma

Asthma is due to hyperreactive airways, which undergo episodic bronchospasm when triggered by certain stimuli.

KP00710.indb 124 13/10/22 1:52 PM

- **Atopic (type I IgE-mediated hypersensitivity reaction) asthma** (most common form) usually affects children and young adults. There is often a positive family history.
- **Nonatopic asthma** is triggered by processes including respiratory infections (usually viral), stress, exercise, or cold temperatures.
- **Drug-induced asthma** affects about 10% of adults with a diagnosis of asthma. Aspirin is a key example of a precipitating drug.
- **Occupational asthma** is caused by workplace triggers including fumes and dusts.

An asthma attack is characterized by wheezing, severe dyspnea, and coughing. Problems with expiration cause lung overinflation. Status asthmaticus is a potentially fatal unrelenting attack of asthma.

Microscopic examination of sputum cytology may show **Curschmann spirals** (twisted mucus plugs admixed with sloughed epithelium), eosinophils, or **Charcot-Leyden crystals** (protein crystalloids from broken down eosinophils).

In patients dying from disease, autopsy findings include **mucous plugs**, increased mucous glands with goblet cell hyperplasia, inflammation (especially with eosinophils), edema; **hypertrophy and hyperplasia of bronchial wall smooth muscle**, and thickened basement membranes.

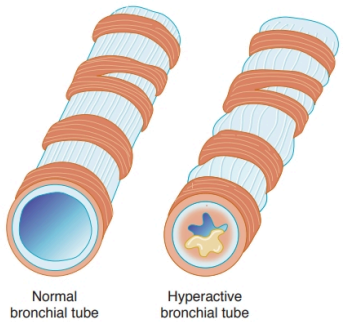


Figure 14-3. Bronchial Changes in Asthma

Bronchiectasis

Bronchiectasis is an abnormal permanent airway dilatation due to chronic necrotizing inflammation. Clinical findings include cough, fever, malodorous purulent sputum, and dyspnea. Causes are diverse, and include bronchial obstruction by foreign body, mucus, or tumor, necrotizing pneumonias, cystic fibrosis, and Kartagener syndrome.

- **Cystic fibrosis** patients often develop lung abscesses as a consequence of bronchiectasis. (See the chapter on genetic disorders.)
- **Kartagener syndrome** is an autosomal recessive condition caused by immotile cilia due to a defect of dynein arms (primary ciliary dyskinesia). It is characterized clinically by bronchiectasis, chronic sinusitis, and situs inversus (a congenital condition where the major visceral organs are anatomically reversed compared with their normal anatomical positions).

14_Preclinical_Pathology_Ch14.indd 125 10/6/22 8:53 PM

On gross examination, bronchiectasis shows dilated bronchi and bronchioles extending out to the pleura. These changes may also be appreciated on chest x-ray. Complications include abscess, septic emboli, cor pulmonale, and secondary amyloidosis.



Figure 14-4. Cross-Section of Bronchiectasis

OBSTRUCTIVE VERSUS RESTRICTIVE LUNG DISEASE

Table 14-2. Obstructive Versus Restrictive Lung Disease

Obstructive Airway Disease	Restrictive Lung Disease
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

KP00710.indb 126 13/10/22 1:52 PM

Table 14-3. Summary of Obstructive Versus Restrictive Pattern

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

INFILTRATIVE RESTRICTIVE LUNG DISEASES (DIFFUSE INTERSTITIAL DISEASES)

Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) refers to diffuse damage of alveolar epithelium and capillaries, resulting in progressive respiratory failure that is unresponsive to oxygen treatment. Clinicians use the term *ARDS*, while pathologists use the term *diffuse alveolar damage (DAD)* to describe the pathologic changes.

ARDS may be caused by shock, sepsis, trauma, gastric aspiration, radiation, oxygen toxicity, drugs, or pulmonary infection. Activated neutrophils mediate cell damage. Clinically, patients show dyspnea, tachypnea, hypoxemia, cyanosis, and use of accessory respiratory muscles. X-rays show bilateral lung opacity ("white out").

On gross pathologic examination affected lungs are heavy, stiff, and noncompliant. Microscopically, there is intra-alveolar edema, and hyaline membranes line the alveolar spaces. In resolving cases there is proliferation of type II pneumocytes and interstitial inflammation and fibrosis.

Treatment is based on treating the underlying cause and on supporting respiration with mechanical ventilation. The prognosis is problematic even with good care, with overall mortality 40%.

BRIDGE TO ANATOMY

Type II pneumocytes repopulate the alveolar epithelium in response to injury.

Respiratory Distress Syndrome of the Newborn

Respiratory distress syndrome of the newborn (hyaline membrane disease) is caused by a deficiency of surfactant. It is associated with prematurity (gestational age of <28 weeks has a 60% incidence), maternal diabetes, multiple births, male gender, and cesarean section delivery. Clinically, infants are normal at birth but within a few hours develop increasing respiratory effort, tachypnea, nasal flaring, use of accessory muscles of respiration, an expiratory grunt, and cyanosis. Chest radiograph may demonstrate bilateral "ground-glass" reticulogranular densities. Autopsy findings include atelectasis and hyaline membranes.

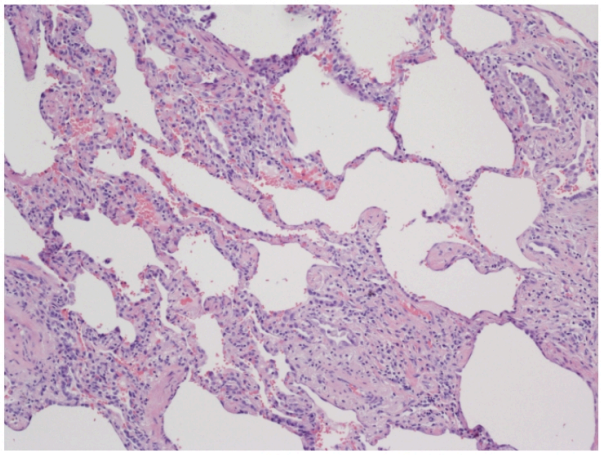
KP00710.indb 127 13/10/22 1:52 PM

Treatment is surfactant replacement, mechanical ventilation, and continuous positive airway pressure (CPAP). Respiratory distress syndrome of the newborn can sometimes be prevented if labor can be delayed and if corticosteroids are used to mature the lung. With improved therapies, now >90% of babies survive.

Chronic Interstitial Lung Disease

Chronic interstitial lung disease is a term describing heterogeneous lung disorders, which share similar symptomology but vary in prognosis. Patients present with dyspnea and cough. Lung biopsy findings can be paired with clinical information to aid in therapeutic management/palliative care.

- **Idiopathic pulmonary fibrosis (IPF)** is a fatal disease. It shows patchy interstitial fibrosis and inflammation. "Honeycomb fibrosis" refers to dilated cystic spaces lined with type II pneumocytes; this histology is consistent with end-stage lung. Pathologists use the term *usual interstitial pneumonia* for IPF.
- **Nonspecific interstitial pneumonia** has a better prognosis than IPF. There is a cellular pattern and a fibrosing pattern.
- **Cryptogenic organizing pneumonia** responds to steroids. Histologically, there are plugs of connective tissue inside the alveolar spaces.
- **Collagen vascular disease pneumonitis** has varied patterns of parenchymal and pleural involvement. The prognosis is poor.



© Gregg Barré, MD Used with permission.

Figure 14-5. Honeycomb Lung (Idiopathic Pulmonary Fibrosis)

- **Smoking-related pneumonitis.** Several entities have been identified.
  - Desquamative interstitial pneumonia features alveolar macrophages.
  - Respiratory bronchiolitis features bronchiolocentric macrophages.
  - Smoking-related interstitial fibrosis shows septal collagen deposition without significant associated inflammation.

KP00710.indb 128 13/10/22 1:52 PM

- **Hypersensitivity pneumonitis.** After exposure to a sensitizing agent such as moldy hay, patients present with a febrile acute reaction or a chronic disease with weight loss. Biopsy shows peribronchiolar acute and chronic interstitial inflammation +/− noncaseating granulomas. The disease is immunologically mediated.
- **Eosinophilic pneumonia** describes a group of diseases with varying clinical features but a common histologic finding of a mixed septal inflammatory infiltrate and eosinophils within alveolar spaces. **Loeffler's syndrome** is a self-limiting type of eosinophilic pneumonia with peripheral blood eosinophilia.

Occupation-Associated Lung Disease

Occupation-associated lung disease is a common cause of chronic interstitial pneumonitis. It is considered separately here to show the full spectrum of disease since neoplasia may occur during its course. **Pneumoconioses** are fibrosing pulmonary diseases caused by inhalation of an aerosol (mineral dusts, particles, vapors, or fumes). Key factors affecting their development include the type of aerosol and its ability to stimulate fibrosis; the dose and duration of exposure; and the size of the particle, with only particles <10 microns entering the alveolar sac. **Caplan syndrome** is the term when pneumoconiosis (of any type) accompanies rheumatoid arthritis.

- **Coal worker's pneumoconiosis** is an important pneumoconiosis that is due to anthracosis, in which carbon pigment (anthracotic pigment) from coal mining accumulates in macrophages along the pleural lymphatics and interstitium. Clinically, the disease may progress through several stages. The earliest stage is asymptomatic.
  - **Simple coal worker's pneumoconiosis** (black lung disease) is characterized by coal-dust macules and nodules in the upper lobes that produce little pulmonary dysfunction.
  - **Complicated coal worker's pneumoconiosis** is characterized by progressive massive fibrosis that is accompanied by increasing respiratory distress, secondary pulmonary hypertension, and cor pulmonale.
- **Asbestosis** is caused by members of a family of crystalline silicates. Occupations in which asbestos exposure may occur include shipyard work, insulation and construction industries, brake-lining manufacture.
  - **Serpentine asbestos** is composed of curved, flexible fibers, with the most common type of serpentine asbestos being chrysotile.
  - **Amphibole asbestos** is composed of straight, brittle fibers. Important types include crocidolite, tremolite, and amosite. Amphibole asbestos is more pathogenic than serpentine asbestos, and is highly associated with mesotheliomas.
  - **The pulmonary pathology of asbestosis** is a diffuse interstitial fibrosis that begins in the lower lobes; it causes slowly progressive dyspnea which may eventually be complicated by secondary pulmonary hypertension and cor pulmonale. Pulmonary biopsy may demonstrate asbestos bodies that have become coated with iron **(ferruginous bodies)**. Otherwise, the findings are the same as usual interstitial pneumonia.

KP00710.indb 129 13/10/22 1:52 PM

- **Pleural involvement** may take the form of **parietal pleural plaques** (acellular type I collagen deposition) in a symmetrical distribution involving the domes of the diaphragm and posterolateral chest walls on chest x-ray. The apices and costophrenic angles are spared. Plaques on the anterior chest wall may be seen on CT. Fibrous **pleural adhesions** may occur on the visceral pleura.
- **Lung cancer** is the most common tumor in asbestos-exposed individuals; there is a strong synergistic effect between smoking and asbestos exposure.
- **Malignant mesothelioma** is a rare, highly malignant neoplasm associated with occupational exposure to asbestos in 90% of cases. It presents with recurrent pleural effusions, dyspnea, and chest pain. The tumor grossly encases and compresses the lung; microscopic exam exhibits carcinomatous and sarcomatous elements (biphasic pattern), while electron microscopy shows long, thin microvilli on some tumor cells. The prognosis of mesothelioma is poor. Other problems include increased risk of laryngeal, stomach, and colon cancers. Family members also have increased risk of cancer due to the worker bringing home clothing covered with asbestos fibers.

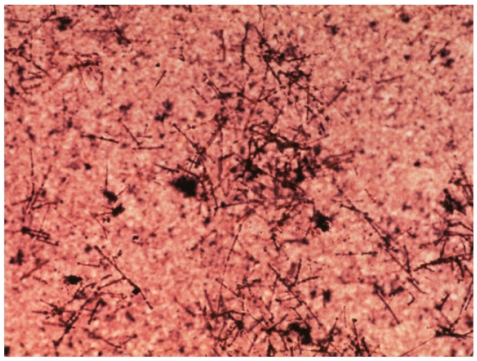


Figure 14-6. Asbestos Fibers in Lung Tissue

- **Silicosis** is due to exposure to silicon dioxide (silica). It is seen most frequently with occupational exposure (sandblasters, metal grinders, miners). The **pulmonary pathology** shows dense nodular fibrosis of the upper lobes which may progress to massive fibrosis; birefringent silica particles can be seen with polarized light. Patients present with insidious onset of dyspnea that is slowly progressive despite cessation of exposure. X-ray shows fibrotic nodules in the upper zones of the lungs. There is an increased risk of TB.
- **Berylliosis** is an allergic granulomatous reaction due to workplace exposure to beryllium in the nuclear, electronics, and aerospace industries. Genetic susceptibility appears to play a role, as does a type IV hypersensitivity reaction, resulting in granuloma formation. Clinically, acute exposure causes acute pneumonitis, while chronic exposure causes pulmonary noncaseating granulomas and fibrosis, hilar lymph node granulomas, and systemic granulomas.

KP00710.indb 130 13/10/22 1:52 PM

VASCULAR DISORDERS

Pulmonary Edema

Pulmonary edema is fluid accumulation within the lungs, usually due to imbalance of Starling forces or endothelial injury.

- Pulmonary edema due to **increased hydrostatic pressure** can be seen in left-sided heart failure, mitral valve stenosis, high altitude pulmonary edema, and fluid overload.
- Pulmonary edema due to **decreased oncotic pressure** can be seen in nephrotic syndrome and liver disease.
- Pulmonary edema due to **increased capillary permeability** can be due to infections, drugs (bleomycin, heroin), shock, and radiation.

The pathology grossly shows wet, heavy lungs (usually worse in lower lobes), while microscopic examination shows intraalveolar fluid, engorged capillaries, and hemosiderin-laden macrophages (heart-failure cells).

NOTE

High altitude pulmonary edema is a hydrostatic-type pulmonary edema. Symptoms (i.e., cough and shortness of breath) resolve with descent and administration of oxygen.

Pulmonary Hypertension

Pulmonary hypertension is increased pulmonary artery pressure, usually due to increased vascular resistance or blood flow.

The etiology varies and can include chronic obstructive pulmonary disease and interstitial disease (hypoxic vasoconstriction); multiple ongoing pulmonary emboli; mitral stenosis and left heart failure; congenital heart disease with left to right shunts (atrial septal defect, ventricular septal defect, patent ductus arteriosus); and primary (idiopathic) pulmonary hypertension, typically in young women.

CLINICAL CORRELATE

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

The pathology includes pulmonary artery atherosclerosis, small artery medial hypertrophy and intimal fibrosis, and plexogenic pulmonary arteriopathy. Pulmonary hypertension may also damage the heart, leading to right ventricular hypertrophy and then failure (cor pulmonale).

For a discussion of pulmonary embolus (PE) and pulmonary infarction, see the circulatory pathology chapter.

PULMONARY TUMORS

Lung Cancer

Lung cancer is the leading cause of cancer death among both men and women; it has been increasing in women (increased smoking) in the past few decades. It occurs most commonly age 50–80. Major risk factors include cigarette smoking, occupational exposure (asbestosis, uranium mining, radiation, etc.), passive smoking, and air pollution. Clinical features include cough, sputum production, weight loss, anorexia, fatigue, dyspnea, hemoptysis, and chest pain. Obstruction may produce focal emphysema, atelectasis, bronchiectasis, or pneumonia.

Intrathoracic spread of lung cancer is to lymph nodes, particularly hilar, bronchial, **tracheal**, and **mediastinal; pleura (adenocarcinoma)**; and lung apex causing **Horner syndrome** (**Pancoast tumor**).

KP00710.indb 131 13/10/22 1:52 PM

NOTE

Horner Syndrome causes ipsilateral:

- Ptosis
- Miosis
- Anhidrosis
- Enophthalmos

- Obstruction of the superior vena cava by tumor causes **superior vena cava syndrome**, characterized by distended head and neck veins, plethora, and facial and upper arm edema.
- **Esophageal obstruction** can cause dysphagia.
- Recurrent laryngeal **nerve involvement** causes hoarseness, while phrenic nerve damage causes diaphragmatic paralysis.

Extrathoracic sites of metastasis include adrenal (>50%), liver, brain, and bone.

Treatment of non–small cell lung cancer is with surgery, and treatment of small cell lung cancer is with chemotherapy and radiation. Despite treatment, the prognosis is poor, with overall 5-year survival 16%.

Common **genetic mutations** in lung cancer involve the oncogenes *MYCL* (small cell carcinomas) and *KRAS* (adenocarcinomas); tumor suppressor genes: *TP53* and *RB1*.

Adenocarcinoma is more commonly seen in women and nonsmokers. Grossly, it causes a peripheral gray-white mass, and the tumor may develop in areas of parenchymal scarring (scar carcinoma). Microscopically, common patterns include acinar, papillary, mucinous, and solid. The precursor lesion—atypical adenomatous hyperplasia—progresses to adenocarcinoma in situ (noninvasive well-differentiated tumor <3 cm) and to minimally invasive tumor (invasion no more than 5 mm) before progressing to invasive adenocarcinoma.

Squamous cell carcinoma (SCC) is strongly related to smoking and affects males more than females. Squamous cell carcinoma arises from bronchial epithelium after a progression:

metaplasia → dysplasia → carcinoma *in situ* → invasive carcinoma

Pathologically, the tumor grossly causes a gray-white bronchial mass, usually centrally located. Microscopically, well-differentiated tumors show invasive nests of squamous cells with intercellular bridges (desmosomes) and keratin production ("squamous pearls").

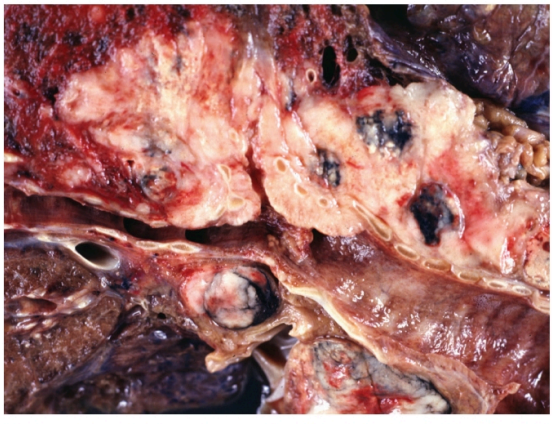
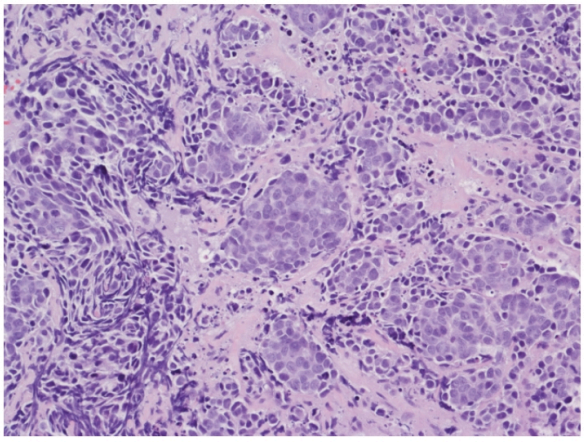


Figure 14-7. Squamous Cell Carcinoma of the Lung

KP00710.indb 132 13/10/22 1:52 PM

Small cell carcinoma has a strong association with smoking, and affects males more than females. This neuroendocrine tumor is very aggressive, with rapid growth and early dissemination. Small cell carcinoma is commonly associated with paraneoplastic syndromes.



© Gregg Barré, MD Used with permission.

Figure 14-8. Small Cell Carcinoma with Crush Artifact in the Lower Left Field

Pathologically, gross examination demonstrates central, gray-white masses. Microscopic examination shows small round or polygonal cells in clusters, and electron microscopy shows cytoplasmic dense-core neurosecretory granules.

Large cell carcinoma has large anaplastic cells without evidence of differentiation.

Carcinoid

Bronchial carcinoids occur in a younger age group (mean age 40 years) and typically produce a polypoid intrabronchial mass or plaque; it is characterized on light microscopy by small, round, uniform cells growing in nests (organoid pattern), and on electron microscopy by cytoplasmic dense-core **neurosecretory granules. Atypical carcinoid** is more aggressive than typical carcinoid.

Metastatic Tumors

Metastatic carcinoma is the most common malignant neoplasm in the lung. It typically causes multiple, bilateral, scattered nodules; common primary sites include breast, stomach, pancreas, and colon.

Hamartomas

Hamartomas are benign tumors; they occur more commonly in middle-aged adults but also occur in children. They can appear as coin lesions on chest x-ray. Microscopically, they are comprised of nonencapsulated fibromyxoid tissue. **Carney triad** is the finding of a hamartoma with a predominantly cartilaginous component (pulmonary chondroma), an extra-adrenal paraganglioma and a gastric gastrointestinal stromal tumor.

BRIDGE TO PHARMACOLOGY

Erlotinib, a tyrosine-kinase inhibitor that inhibits the epidermal growth factor receptor (EGFR), is used to treat non–small cell lung cancer, pancreatic cancer, and other types of cancer that may fail chemotherapy. The drug targets EGFR tyrosine kinase, which is highly expressed and mutated in some cancers.

KP00710.indb 133 13/10/22 1:52 PM

Laryngeal Cancer

- **Risk factors** are related to lifestyle habits. Tobacco use and consumption of alcohol are significant factors, and cigarette smoking is the most consistently reported risk. Given these risk factors, secondary aerodigestive tract primary tumors are not uncommon.
- **Symptoms** include hoarseness, vocal changes, chronic sore throat, difficulty swallowing, ear pain, and weight loss.
- **Histology.** Biopsy is required for diagnosis, and most cancers of the larynx are squamous carcinomas.
- **Treatment.** Stage of disease dictates treatment plan. Treatment modalities include total laryngectomy and/or chemoradiation. Even with treatment, prognosis is poor: The 5-year survival rate is 60%.

DISEASES OF THE PLEURAL CAVITY

Fluid in the Pleural Space

Pleural effusion is the accumulation of fluid in the pleural cavity.

- **Exudative pleural effusion** exists if laboratory analysis of thoracentesis fluid shows the following values: pleural fluid protein/serum protein ratio >0.5, pleura fluid lactate dehydrogenase (LDH)/serum LDH ratio >0.6, pleural fluid LDH level > two-thirds the upper limit of normal value for serum LDH. Conditions causing an exudative pleural effusion include infections (TB), malignancy, and pulmonary embolism.
- **Transudative pleural effusions** are sometimes assessed clinically, without laboratory pleural fluid analysis. These effusions occur in clinical settings including left ventricular failure and cirrhosis.

Hemothorax is the presence of blood in the pleural cavity. Trauma is a common cause. There may be hypotension and shift of the trachea to the unaffected side.

Chylothorax is lymphatic fluid in the pleural cavity. Malignancy is a common cause.

Air in the Pleural Space

Pneumothorax is the term used for air in the pleural cavity. It can be due to traumatic penetrating chest wall injuries or spontaneous rupture of apical blebs in typically tall young adults (spontaneous pneumothorax). The term **tension pneumothorax** is used if a life-threatening shift of thoracic organs across midline occurs.

KP00710.indb 134 13/10/22 1:52 PM



Figure 14-9. Densely Black Appearance on Chest x-Ray of a Pneumothorax

Mesothelioma (*See* section on asbestosis earlier in this chapter.)

KP00710.indb 135 13/10/22 1:52 PM

Renal Pathology 15

LEARNING OBJECTIVES

- ❑ Demonstrate understanding of congenital anomalies of the kidney
- ❑ Use knowledge of cystic disease to solve problems
- ❑ Answer questions about nephritic/nephrotic syndrome, secondary/chronic glomerulonephritis, tubulointerstitial nephritis, and acute tubular injury
- ❑ Describe epidemiology and course of urolithiasis
- ❑ Solve problems concerning chronic renal failure
- ❑ Solve problems concerning tumors of the kidney
- ❑ Explain information related to ureteral disorders
- ❑ Explain information related to urinary bladder pathology

CONGENITAL ANOMALIES OF THE KIDNEY

Renal Agenesis

- **Bilateral agenesis** is incompatible with life. Ultrasound shows oligohydramnios. Affected fetuses typically also have **Potter facies** (flattened nose, posteriorly rotated ears, and recessed chin); talipes equinovarus (talus [ankle]+ pes [foot] and equino [heel] + varus [turned upward] = clubfoot); and pulmonary hypoplasia.
- In **unilateral agenesis**, the remaining kidney undergoes compensatory hypertrophy. Patients often have adequate renal function and are asymptomatic.

Hypoplasia is failure of a kidney (usually unilateral) to develop to normal weight; the hypoplastic kidney has a decreased number of calyces and lobes.

Horseshoe kidney is a common congenital anomaly that is found in 1 in 600 abdominal x-rays. The kidneys show fusion, usually at the lower pole; affected individuals have normal renal function but may be predisposed to renal calculi.

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

NOTE

Oligohydramnios (Potter) Sequence

Renal agenesis

↓

Oligohydramnios

↓

Fetal compression

↓

Flattened facies and positional abnormalities of hands and feet

KP00710.indb 137 13/10/22 1:52 PM

CYSTIC DISEASE

Genetic Cystic Disease

Autosomal recessive polycystic kidney disease (also called infantile polycystic kidney disease or renal dysgenesis Potter type I) is a rare autosomal recessive disease that presents in infancy with progressive and often fatal renal failure. A mutation in the *PKHD1* gene is implicated.

The kidneys are bilaterally enlarged and have a spongelike cut surface. The liver may have multiple hepatic cysts and cirrhosis may develop in childhood. Pulmonary hypoplasia is present to varying degrees.

Autosomal dominant polycystic kidney disease (also called adult polycystic kidney disease or renal dysgenesis Potter type III) is an autosomal dominant disease that affects 1 in 1,000. There is most frequently a mutation of the *PKD1* gene on chromosome 16 which produces a transmembrane protein called polycystin 1. Other mutations involve *PKD2* and polycystin 2.

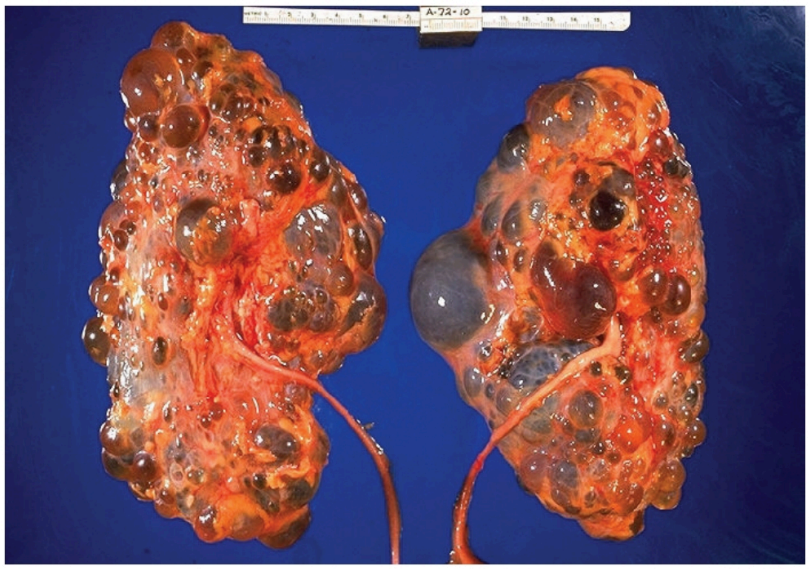
CLINICAL CORRELATE

The cysts in autosomal dominant (adult) PKD involve <10% of nephrons, but they gradually expand and compress the rest of the kidney, interfering with its function. This is why kidney function can remain normal for many years.

Clinically, patients are asymptomatic with normal renal function until middle age, and then present with renal insufficiency, renal stones, hematuria, and hypertension or with abdominal masses and flank pain. Diagnosis is established with U/S and CT scan. Most patients develop end-stage renal failure by decade 7.

On gross pathologic examination, the kidneys have massive bilateral enlargement with large bulging cysts filled with serous, turbid, or hemorrhagic fluid. Microscopic examination shows functioning nephrons present between the cysts; the cysts arise from the tubular epithelial cells of the kidney.

Extrarenal manifestations include cysts of the liver, pancreas, and lungs; berry aneurysms of the circle of Willis; mitral valve prolapse; and colonic diverticula.



© cdc.gov.

Figure 15-1. Gross Pathology of Polycystic Kidneys

KP00710.indb 138 13/10/22 1:52 PM

Developmental Cystic Disease

Renal dysplasia is the most common renal cystic disease in children, in whom it causes an enlarged renal mass with cartilage and immature collecting ducts. It may progress clinically to renal failure.

Acquired Cysts

- **Acquired polycystic disease** is seen in renal dialysis patients and is associated with a small risk of developing renal adenomas and renal cell carcinoma.
- **Simple retention cysts** of the kidney are common in adults and occasionally cause hematuria.

Medullary Diseases with Cysts

- **Medullary sponge kidney** can cause nephrolithiasis but is otherwise innocuous. Some cases are genetic.
- **Nephronophthisis-medullary cystic disease complex** presents as polyuria and polydipsia; it can progress to chronic renal failure in young adults. There are autosomal recessive forms. The cysts are in the cortex and the medulla.

GLOMERULAR DISEASES

Immune mechanisms play a role in the pathogenesis of most glomerular diseases, either via deposition of immune complexes or injury from antibodies. Glomerular diseases may be divided into those originating in the kidney and those caused by systemic disease (secondary).

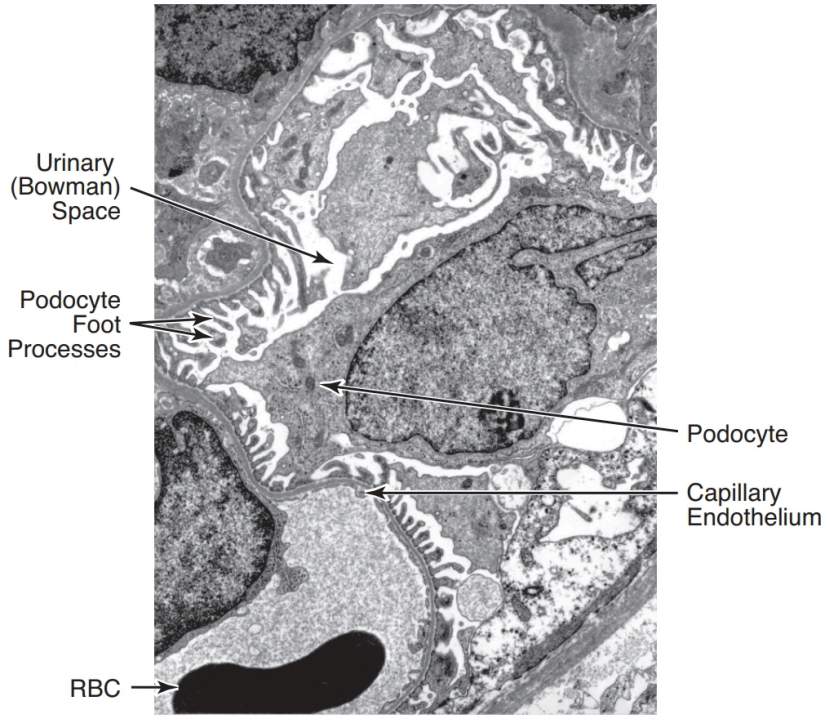
Glomerular disease may present clinically as **nephrotic** or **nephritic syndrome**. Their clinical features are different.

Table 15-1. 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

Renal biopsy can yield a definitive diagnosis when light microscopy features are considered in concert with immunofluorescence (IF) and electron microscopy (EM).

KP00710.indb 139 13/10/22 1:52 PM



© Gold Standard Multimedia, Inc. Used with permission.

Figure 15-2. Transmission Electron Micrograph Demonstrating Podocytes

Primary Glomerulopathies Causing Nephritic Syndrome

Acute poststreptococcal glomerulonephritis (APSGN) (or acute proliferative glomerulonephritis or postinfectious glomerulonephritis) is an immune complex disease that typically occurs 2–4 weeks after a streptococcal infection of the throat or skin. There is a decreasing incidence in the United States; children are affected more often than adults.

CLINICAL CORRELATE

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

The infecting organism is most commonly β-hemolytic group A *streptococci*, but APSGN can also be caused by other bacteria, viruses, parasites, and even systemic diseases (SLE and polyarteritis nodosa). Clinically, it presents with nephritic syndrome with elevated antistreptolysin O (ASO) titers (when related to streptococcal infection) and low C3.

- **Renal biopsy.** Light microscopy shows an infiltrate of neutrophils in the glomeruli; the process is diffuse, that is, it involves all the glomeruli. Immunofluorescence shows granular deposits of IgG and C3 throughout the glomerulus within the capillary walls and some mesangial areas. Electron microscopy shows subepithelial immune complex deposits (humps).
- **Treatment** is conservative fluid management. Most children (>95%) have a good prognosis, with complete recovery, but severe disease can also occur (RPGN 1% and chronic glomerulonephritis 2%). In adults, 15–50% develop end-stage disease.

KP00710.indb 140 13/10/22 1:52 PM

Rapidly progressive glomerulonephritis (RPGN) (crescentic glomerulonephritis) is a group of diseases characterized by glomerular crescents and a rapid deterioration of renal function.

- **Anti-glomerular basement membrane antibody-mediated crescentic glomerulonephritis** has a peak incidence at age 20-40, and males are affected more frequently than females.
- Pulmonary involvement is called **Goodpasture syndrome**. These patients have pulmonary hemorrhage and hemoptysis.
- **Renal biopsy findings** include hypercellularity, crescents, and fibrin deposition in glomeruli. Immunofluorescence shows a smooth and linear pattern of IgG and C3 in the glomerular basement membrane (GBM). By electron microscopy, there are no deposits, but there is glomerular basement membrane disruption.
- Even with **treatment** (plasma exchange, steroids, and cytotoxic drugs), the prognosis is poor because of risks of severe and life-threatening pulmonary hemorrhage and renal failure. Early aggressive treatment may prevent end-stage renal failure.

Immune-complex mediated crescentic glomerulonephritis

- Any of the immune complex nephritides can cause crescent formation.
- IF shows a granular pattern and EM shows discrete deposits.

Pauci-immune crescentic glomerulonephritis

- Antineutrophilic cytoplasmic antibodies (ANCA) are present in serum.
- IF and EM are negative for immunoglobulins and complement components.

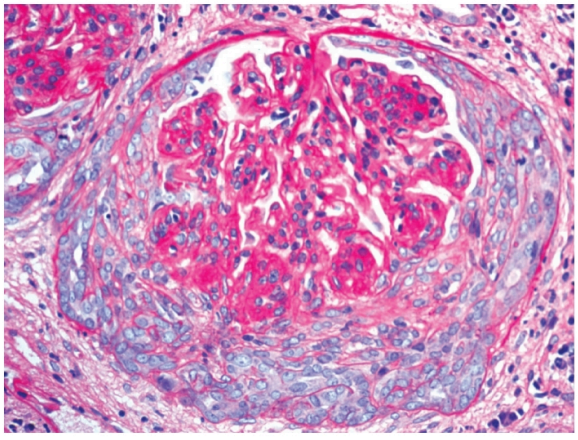


Figure 15-3. Crescent Formation in Rapidly Progressive Glomerulonephritis, as Seen with Trichrome Stain

IgA nephropathy (Berger disease) is the most common cause of glomerulonephritis in the world, being particularly common in France, Japan, Italy, and Austria. It affects children and young adults (mostly males).

NOTE

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

KP00710.indb 141 13/10/22 1:52 PM

NOTE

Henoch-Schönlein Purpura

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

NOTE

MPGN type II is now called dense deposit disease, and is increasingly considered its own entity.

- Most patients have an autoantibody called C3 nephritic factor
- This antibody stabilizes C3 convertase, which leads to enhanced degradation and low serum levels of C3

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.

- **Clinical findings.** IgA nephropathy is characterized by recurrent gross hematuria (a predominately nephritic presentation), whose onset may follow a respiratory infection. IgA nephropathy can be associated with celiac sprue and Henoch-Schönlein purpura or can be secondary to celiac sprue or liver disease.
- The **pathogenesis** is unknown, but may be related to a possible entrapment of circulating immune complexes with activation of the alternate complement pathway; it may also be related to a genetic predisposition.
- **Renal biopsy.** Light microscopy may show normal glomeruli or mesangial proliferation. Immunofluorescence shows mesangial deposits of IgA and C3. Electron microscopy shows mesangial immune complex deposits.
- Many cases slowly progress to **renal failure** over 25 years.

Membranoproliferative glomerulonephritis (MPGN) is a form of glomerular disease that affects both the glomerular mesangium and the basement membranes; it occurs in 2 types, Type I and Type II (dense deposit disease).

- The clinical presentation is variable, and may be nephritic, nephrotic, or mixed. MPGN may be secondary to many systemic disorders (systemic lupus erythematosus, endocarditis), chronic infections (HBV, HCV, HIV), and malignancies (chronic lymphocytic leukemia).
- Laboratory studies show decreased serum C3 and the presence of C3 nephritic factor (MPGN type II).
- Light microscopy demonstrates a lobulated appearance of the glomeruli due to mesangial and endothelial cell proliferation and/or deposition of subendothelial immune complex deposits. Splitting of the basement membrane ("**tram-tracking**") may be seen with a silver or periodic acid-Schiff (PAS) stain.
- **Immunofluorescence** in type I MPGN shows a granular pattern of C3 often with IgG, C1q, and C4; in type II, immunofluorescence shows a granular and linear pattern of C3 deposition.
- **Electron microscopy** in type I shows subendothelial and mesangial immune complex deposits, and in type II shows dense deposits within the glomerular basement membrane.
- MPGN typically has a **slowly progressive** course, resulting in chronic renal failure over the course of 10 years. There is a high incidence of recurrence in transplants.

Alport syndrome is a rare X-linked disorder caused by a defect in type IV collagen. It is characterized by hereditary nephritis, hearing loss, and ocular abnormalities. The most common mutation causing Alport is in the *COL4A5* gene coding for the alpha-3, -4, and -5 chain of type IV collagen.

- **Clinical features.** Gross or microscopic hematuria begins in childhood. Hearing loss (leading to sensorineural deafness) and various ocular abnormalities of the lens and cornea can occur. Alport is a progressive disease that ultimately results in renal failure.
- **Electron microscopy** shows alternating thickening and thinning of basement membrane with splitting of the lamina densa, causing a "basketweave" appearance.

KP00710.indb 142 13/10/22 1:52 PM

Primary Glomerulopathies Causing Nephrotic Syndrome

Membranous glomerulonephritis is a common cause of nephrotic syndrome in adults that is mediated by immune complexes.

- **Etiologies.** Most cases (85%) are idiopathic; in most of these cases, autoantibodies cross-react with podocyte antigens. Membranous glomerulonephritis may also be caused by drugs (penicillamine), infections (hepatitis virus B and C, syphilis, etc.), and systemic diseases (SLE, diabetes mellitus, etc.). It has also been associated with malignant carcinomas of the lung and colon, and there may be a genetic predisposition.
- **Renal biopsy** shows diffuse thickening of the capillary walls. Basement membrane projections ("spikes") are seen on silver stains. Immunofluorescence shows a granular and linear pattern of IgG and C3. Electron microscopy shows subepithelial deposits along the basement membranes with effacement of podocyte foot processes.
- The **clinical course** is variable and may lead to spontaneous remission, persistent proteinuria, or end-stage renal disease.

Minimal change disease (also called lipoid nephrosis and nil disease) is the most common cause of nephrotic syndrome in children. Peak incidence is age 2–6.

- The **diagnosis** is one of exclusion. Light microscopy shows normal glomeruli with lipid accumulation in proximal tubule cells (lipoid nephrosis). Immunofluorescence is negative, with no immune deposits. Electron microscopy shows effacement of epithelial (podocyte) foot processes, microvillous transformation, and no immune complex deposits.
- The **prognosis** is excellent because treatment with corticosteroids produces a dramatic response in children. The majority have a complete recovery.

Focal segmental glomerulosclerosis is a very common cause of nephrotic syndrome that occurs in all ages. African Americans are affected more frequently than Caucasians.

- **Etiologies.** The condition may be idiopathic (primary), or it may be related to a wide variety of predisposing conditions including loss of renal tissue; preexisting glomerular diseases (such as IgA nephropathy); sickle cell anemia; heroin use; AIDS; or morbid obesity. Inherited and congenital forms occur.
- **Renal biopsy.** Light microscopy shows focal segmental sclerosis and hyalinization of glomeruli; focal segmental glomerulosclerosis initially affects the glomeruli along the medullary border. Immunofluorescence shows IgM and C3 deposits in the sclerotic segments. Electron microscopy shows effacement of foot processes in nonsclerotic regions and increased mesangial matrix in sclerotic segments.
- **Clinical course.** There is frequently a poor response to steroids, with the overall prognosis being poor (most progressing to chronic renal failure), though children do better than adults. There is a high rate of recurrence in renal transplants. A variant form, collapsing glomerulopathy, has a worse prognosis.

NOTE

Focal: Only some of the glomeruli are affected.

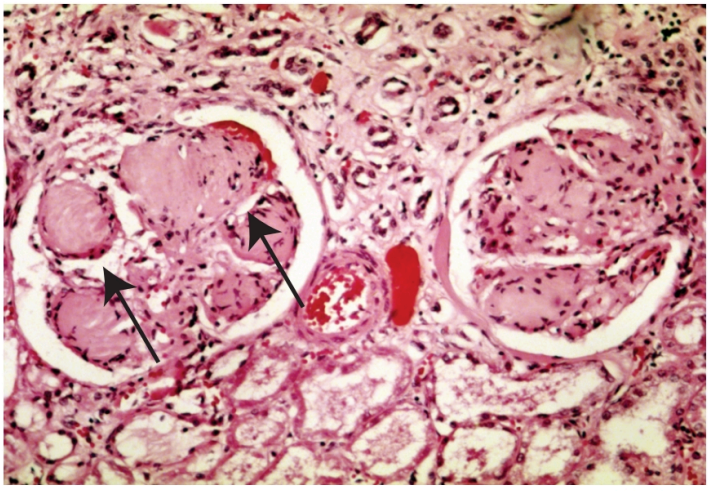
Segmental: Only a portion of the glomerular tuft exhibits sclerosis.

KP00710.indb 143 13/10/22 1:52 PM

Secondary Glomerulonephritis

Secondary glomerulonephritis is glomerular disease that is secondary to other disease processes.

- **Diabetes** causes nodular glomerulosclerosis, hyaline arteriolosclerosis, and diabetic microangiopathy. Clinically, diabetic patients may develop microalbuminuria that can progress to nephrotic syndrome.



© cdc.gov.

Figure 15-4. Sclerotic Nodules (arrows) of Nodular Glomerulosclerosis (Kimmelstiel-Wilson Syndrome) Associated with Diabetes

- **Systemic lupus erythematosus** can cause various patterns of damage to the kidney with clinical features that can include hematuria, nephritic syndrome, nephrotic syndrome, hypertension, and renal failure.

CHRONIC GLOMERULONEPHRITIS

Chronic glomerulonephritis can result from the other acute forms of glomerulonephritis. In some cases the cause remains unknown.

Clinicopathologic Features

Clinical features include anemia, anorexia, malaise, proteinuria, hypertension, and azotemia. Gross examination shows small and shrunken kidneys. Microscopically, there is hyalinization of glomeruli, interstitial fibrosis, tubular atrophy, and a lymphocytic interstitial infiltrate.

Possible Outcomes

- Chronic kidney disease, assessed on the basis of GFR and albuminuria
- End-stage renal disease

KP00710.indb 144 13/10/22 1:52 PM

Treatment

Treatment varies depending on the cause and may include dialysis or kidney transplantation.

TUBULOINTERSTITIAL NEPHRITIS

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

Acute Pyelonephritis

Acute pyelonephritis refers to bacterial infections involving the renal pelvis, tubules, and interstitium. Pyelonephritis affects females much more than males, but the incidence increases in older males with prostatic hyperplasia.

- **Ascending infection** is the most common route of infection. Causative organisms include gram-negative enteric bacilli, *Escherichia coli, Proteus, Klebsiella,* and *Enterobacter.* Predisposing factors include urinary obstruction, vesicoureteral reflux, pregnancy, urethral instrumentation, diabetes mellitus, benign prostatic hyperplasia, and other renal pathology. Symptoms can include fever, chills, and malaise; dysuria, frequency, and urgency; and costovertebral angle tenderness. Urinalysis shows **pyuria** and **WBC casts**.
- The kidney may be enlarged, and the cortical surface may show abscesses. Microscopically there is a neutrophilic interstitial infiltrate. **Parenchymal abscesses** may be present. The tubules contain **neutrophil casts**.

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.

Chronic Pyelonephritis

Chronic pyelonephritis can occur from chronic obstruction or in the setting of vesicoureteral reflux. Scarring can be seen at the upper and lower poles of the kidney, with associated calyceal blunting. Microscopically there is interstitial fibrosis and inflammation with thyroidization of the tubule. Some patients develop glomerulosclerosis. Renal insufficiency develops gradually.

Drug-Induced Tubular Interstitial Nephritis

Drug-induced tubular interstitial nephritis is commonly caused by penicillins, other antibiotics, diuretics, and NSAIDs. Interstitial inflammation is characteristic and granulomas may be seen. This hypersensitivity reaction presents a couple of weeks after drug exposure with fever, eosinophilia, rash, and hematuria. Minimal proteinuria may be present. Recovery is expected after withdrawal of the drug.

Urate Nephropathy

Urate nephropathy is caused by a deposition of urate crystals (secondary to leukemia treatment, lead poisoning, and gout) in renal tubules and interstitium. It may produce acute renal failure.

KP00710.indb 145 13/10/22 1:52 PM

ACUTE TUBULAR INJURY

Acute tubular injury (ATI) is acute renal failure associated with potentially reversible injury to the tubular epithelium. It is the most common cause of acute renal failure in the United States. It is characterized by oliguria with elevation of blood urea nitrogen (BUN) and creatinine; metabolic acidosis and hyperkalemia; and dirty brown granular casts and epithelial casts on urinalysis.

Types of ATI

- **Ischemic acute tubular injury** is the most common cause of ATI. The condition is due to decreased blood flow caused by severe hemorrhage, severe renal vasoconstriction, hypotension, dehydration, or shock.
- **Toxic acute tubular injury** has a large number of causes, including drugs (e.g., polymyxin, methicillin, gentamicin, sulfonamides); radiographic contrast agents; heavy metals (e.g., mercury, lead, gold); organic solvents (e.g., carbon tetrachloride, chloroform, methyl alcohol); ethylene glycol (antifreeze); mushroom poisoning; phenol; pesticides; and myoglobin.

Prognosis

The prognosis is excellent if the patient survives the underlying disease, and if the patient had no preexisting kidney disease.

UROLITHIASIS

Renal calculi occur in up to 6% of the population; men are affected more often than women.

Stone Composition

NOTE

- **Calcium oxalate stones** form in people with alkaline urine.
- **Uric acid** and **cystine stones** form in people with acidic urine.

- Most (75%) stones are calcium oxalate stones.
- Magnesium ammonium phosphate ("struvite") stones are associated with infection by urea-splitting bacteria (*Proteus*), and these stones often form large staghorn calculi.
- Uric acid stones are seen in gout, leukemia, and in patients with acidic urine.
- Cystine stones are uncommon.

KP00710.indb 146 13/10/22 1:52 PM



Figure 15-5. Struvite (Magnesium Ammonium Phosphate) Stone Forming Staghorn Calculi

Clinicopathologic Features

- **Pathology.** Most stones are unilateral stones that are formed in the calyx, pelvis, and urinary bladder.
- **Clinical features.** Calcium stones are radiopaque and can be seen on x-ray. Renal colic may occur if small stones pass into the ureters. Stones may cause hematuria, urinary obstruction, and predispose to infection.
- **Treatment of stones** is with lithotripsy or endoscopic removal.

CHRONIC KIDNEY DISEASE

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

VASCULAR DISORDERS OF THE KIDNEY

Renal Artery Stenosis

Renal artery stenosis of any etiology causes decreased blood flow to the involved kidney, with resulting secondary hypertension that is often not responsive to antihypertensive medications. Treatment is usually surgical.

- Atheromatous plaque is the most common cause of renal artery stenosis.

KP00710.indb 147 13/10/22 1:52 PM

- Dysplastic lesions ("fibromuscular dysplasia") are an important additional cause of renal artery stenosis. All 3 lesion types occur in middle-aged adults.
  - Medial fibroplasia with aneurysms (most common) causes alternating stenosis and aneurysms in "string of beads"-pattern on arteriography
  - Perimedial fibroplasia involves the outer media
  - Medial hyperplasia
- Miscellaneous diseases that can affect the renal arteries (with or without stenosis) include congenital anomalies, Takayasu arteritis, and radiation injuries.



© Lily Chu, National Naval Medical Center Bethesda.
Used with permission.

Figure 15-6. Renal Artery Stenosis as Demonstrated by Angiogram

Other Vascular Disorders

Benign nephrosclerosis is caused by hypertension. The kidneys have a finely granular external surface and on microscopy show hyaline arteriolosclerosis, tubular atrophy, interstitial fibrosis, and glomerulosclerosis. Lab findings include mild proteinuria, hematuria, and azotemia.

Malignant (accelerated) hypertension can damage the kidney, causing fibrinoid necrosis of arterioles, glomerulitis, and hyperplastic arteriolosclerosis. Clinically, it causes cerebral edema, papilledema, retinal hemorrhage, intracerebral hemorrhage, and oliguric acute renal failure. The cortical surface shows pinpoint petechial hemorrhages ("flea-bitten" look).

Renal infarction is due to thrombi from the left side of the heart, atheroembolic disease, and vasculitis. It presents with sudden onset of flank pain and hematuria. Small infarcts may be asymptomatic.

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

KP00710.indb 148 13/10/22 1:52 PM

Diffuse cortical necrosis can cause anuria; the condition can occur with obstetric emergencies and disseminated intravascular coagulation.

TUMORS OF THE KIDNEY

Benign Tumors

- **Cortical adenomas** are small, encapsulated cortical nodules measuring <3 cm; they are a common finding at autopsy. They may be composed of tubular or papillary structures. The papillary adenomas share the same chromosomal gains as papillary renal cell carcinoma.
- **Angiomyolipomas** are hamartomas composed of fat, smooth muscle, and blood vessels, common in patients with tuberous sclerosis.
- **Oncocytomas** are large, benign tumors that are resected to rule out renal cell carcinoma when they are found incidentally on imaging studies. They are brown on cut surface and have abundant pink cytoplasm on microscopy.

Renal Cell Carcinoma

Renal cell carcinoma (RCC) is most common age 50–70, with males affected more than females.

Risk factors include cigarette smoking, chronic analgesic use, asbestos exposure, chronic renal failure, acquired cystic disease, and von Hippel-Lindau disease (VHL tumor suppressor gene).

In 10% of cases, the "classic" triad occurs:

- Hematuria
- Palpable mass
- Flank pain

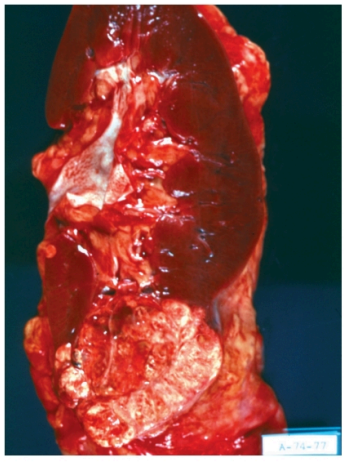


Figure 15-7. Renal Cell Carcinoma

KP00710.indb 149 13/10/22 1:52 PM

A variety of paraneoplastic syndromes from ectopic hormone production can occur:

- Polycythemia (erythropoietin production)
- Hypertension (renin production)
- Cushing syndrome (corticosteroid synthesis)
- Hypercalcemia (PTH-like hormone)
- Feminization or masculinization (gonadotropin release)

Renal cell carcinoma may also cause secondary amyloidosis, a leukemoid reaction, or eosinophilia.

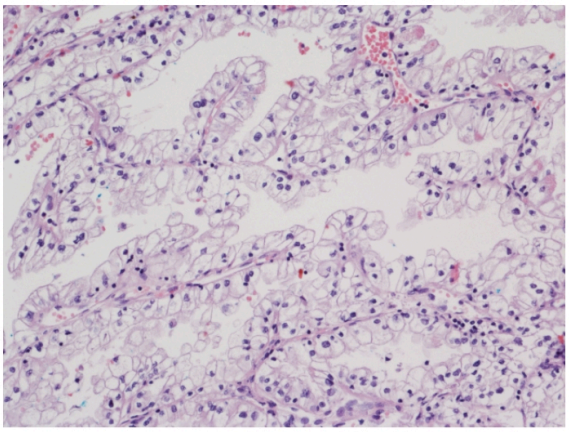
There is a high incidence of metastasis on initial presentation. The clinical course is unpredictable.

Gross examination typically demonstrates a large, solitary yellow mass found most commonly in the upper pole. Areas of necrosis and hemorrhage are commonly present. The tumor often invades the renal vein and may extend into the inferior vena cava and heart.

Histologic types of RCC are as follows:

- **Clear cell RCC (most common)**
  - Often invades renal venous system
  - May have loss of genetic material in 3p
  - A small percent occur in association with von Hippel-Lindau disease
  - Microscopically, there is an alveolar growth pattern with microcysts
  - Tumor is resistant to chemotherapy and radiotherapy
- **Papillary RCC**
  - Tends to be bilateral and multifocal
  - Cut surface is granular
  - Microscopically, the papillae have a single layer of cells
  - Gains of chromosome 7 and 17 are common
  - Duplications of chromosome 7 increase dosage of protooncogene *MET*
- **Chromophobe RCC (rare)**
  - Have cells that stain more darkly than clear cell RCC
  - Have loss of multiple chromosomes
  - Least aggressive of the RCCs

KP00710.indb 150 13/10/22 1:52 PM



© Gregg Barré, MD Used with permission.

Figure 15-8. Renal Cell Carcinoma

Wilms Tumor

Wilms tumor (nephroblastoma) typically presents age 2–5 as a large abdominal mass. Patients with WAGR, DDS, or BWS syndrome are at increased risk of Wilms tumor.

- **WAGR syndrome** is the cluster of Wilms tumor, aniridia, genital anomalies, and mental retardation.
- **Beckwith-Wiedemann syndrome (BWS)** is an overgrowth disorder with characteristic features and an attendant increased risk of cancer.
- **Denys-Drash syndrome (DDS)** affects the genitalia and kidneys.

Both WAGR and DDS are associated with deletions and mutations, respectively, of the *WT1* gene. BWS arises through imprinting abnormalities at the *WT2* locus.

Pathologically, Wilms tumor causes a large, solitary tan mass. Microscopic examination reveals a tumor containing 3 elements: metanephric blastema, epithelial elements (immature glomeruli and tubules), and stroma.

Treatment is surgery, chemotherapy, and radiation, which as a combined therapy yields an excellent prognosis. Long-term survival rate is 90%.

OBSTRUCTIVE DISORDERS OF THE URINARY SYSTEM

Hydronephrosis is a common complication of urinary tract obstruction. It is characterized by dilation of the ureter and renal pelvis. Specific causes include renal stones, retroperitoneal fibrosis, benign prostatic hyperplasia, and cervical cancer.

- In **unilateral hydronephrosis**, the kidney may enlarge to 20 cm. It may be found incidentally on physical exam. The parenchyma becomes compressed. If complete obstruction occurs suddenly, **necrosis of the renal papillae** may result.
- **Bilateral obstruction** that is complete presents as anuria; incomplete bilateral obstruction may present as polyuria.

KP00710.indb 151 13/10/22 1:52 PM

URETERAL DISORDERS

Congenital anomalies include double ureters and congenital megaureter.

Ureteropelvic junction (UPJ) obstruction is the most common cause of hydronephrosis in infants and children. **Congenital UPJ obstruction** can also be identified in adults. It is often seen with other congenital anomalies. Treatment is surgical.

Ureteritis cystica describes chronic inflammation which causes formation of small mucosal cysts in the ureter. This condition can predispose for adenocarcinoma of the ureter.

Renal stones commonly lodge in the ureters.

Retroperitoneal fibrosis is usually an idiopathic condition causing severe fibrosis of the retroperitoneal area, which can entrap the ureters. Some cases show sclerosing conditions in other body sites and are associated with elevated serum IgG4.

Transitional cell carcinoma is the most common ureteral carcinoma.

URINARY BLADDER PATHOLOGY

Nonneoplastic Bladder Pathology

Congenital anomalies of the bladder

Exstrophy of the bladder is a developmental failure of the formation of the abdominal wall and bladder that leaves the bladder open at the body surface. **Urachal cyst remnants** may permit drainage of urine from a newborn's umbilicus, and may also be a cause of bladder adenocarcinoma.

Cystitis. The etiology of cystitis varies; important causes include organisms, notably from fecal flora (*Escherichia coli, Proteus, Klebsiella, Enterobacter*); radiation cystitis (may follow radiation therapy); and chemotherapy agents such as cyclophosphamide (hemorrhagic cystitis).

Clinically, cystitis affects females far more than males. Symptoms include frequency, urgency, dysuria, and suprapubic pain; systemic signs such as fever and malaise are uncommon. Predisposing factors include benign prostatic hypertrophy, bladder calculi, and cystocele.

Acquired diverticula can complicate urinary tract outlet obstruction due to benign prostatic hyperplasia or other causes.

Cystocele is the term used for prolapse of the bladder into the vagina. It is common in middle-aged to elderly women.

Cystitis cystica et glandularis causes formation of small cysts and glands in the bladder mucosa related to chronic inflammation. It is associated with an increased risk of adenocarcinoma.

KP00710.indb 152 13/10/22 1:52 PM

Neoplastic Bladder Pathology

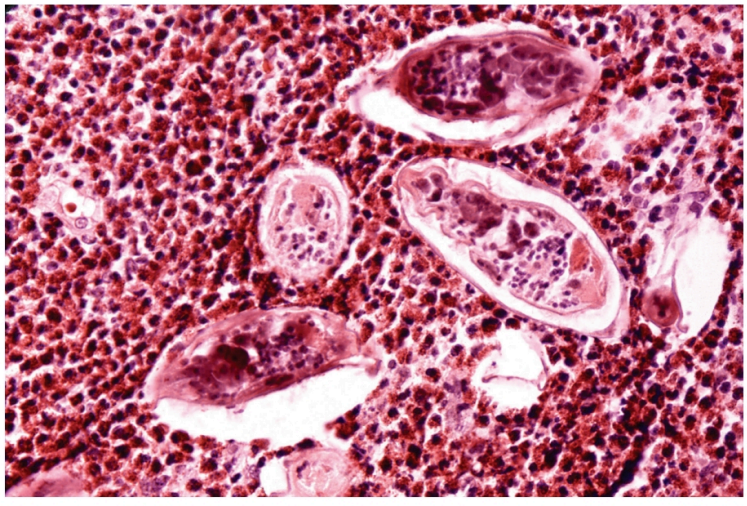
The incidence of bladder cancer is rising. Males are affected more than females, with peak incidence age 40-60. Risk factors include:

- Cigarette smoking (most important risk factor)
- Chronic inflammation

Transitional cell carcinoma (TCC) is the most common histologic type of bladder cancer. Precursors of invasive TCC can arise from a flat or papillary lesion:

- **Carcinoma in situ (CIS)** is a high-grade lesion with cytologic atypia in the full thickness of the epithelium. It is frequently multifocal. In 50-75% of untreated cases, it progresses to invasive cancer.
- Papillary precursors to invasive carcinoma include **papilloma ⇒ papillary urothelial neoplasia of low malignant potential ⇒ low-grade urothelial carcinoma ⇒ high-grade urothelial carcinoma**.

Squamous cell carcinoma occurs more commonly in the Middle East, where infection with *Schistosoma haematobium* is endemic.



© cdc.gov.

Figure 15-9. Migratory Eggs of *Schistosoma haematobium* Surrounded by Dense Inflammation in the Bladder Wall

Adenocarcinoma tends to occur as a focal lesion, and it arises adjacent to areas of glandular metaplasia or cystitis cystica. Microscopically, the tumor resembles colonic epithelium and may contain mucin.

Malakoplakia is a bladder inflammatory pattern associated with a defect in macrophage function. The cause is unknown. Macrophages contain **Michaelis-Gutmann bodies**, laminated basophilic structures.

KP00710.indb 153 13/10/22 1:52 PM

Gastrointestinal Tract Pathology 16

LEARNING OBJECTIVES

- ❑ Answer questions about esophagus, stomach, small and large intestines
- ❑ Solve problems concerning gastric lymphoma

ESOPHAGUS

Congenital and Mechanical Disorders

Tracheoesophageal fistula may arise as a congenital connection between the esophagus and trachea that is often associated with esophageal atresia. It is often discovered soon after birth because of aspiration. In adults the condition can occur secondary to malignancy, trauma, or iatrogenic causes.

Esophageal webs are web-like protrusions of the esophageal mucosa into the lumen which typically present with dysphagia. Plummer-Vinson syndrome is a disease of middle-aged women characterized by esophageal webs, iron deficiency anemia, and increased risk of carcinoma. Schatzki rings are web-like narrowings at the gastroesophageal junction.

Achalasia is a failure of the lower esophageal sphincter (LES) to relax with swallowing. The etiology is unknown in most cases; in South America, achalasia may be caused by Chagas disease. Presentation is with progressive dysphagia. The esophagus is characteristically dilated proximal to the lower esophageal sphincter; barium swallow shows a "bird-beak" sign. Microscopically, there is a loss of ganglion cells in the myenteric plexus. Treatment is LES balloon dilation or myotomy. Achalasia carries an increased risk for esophageal carcinoma.

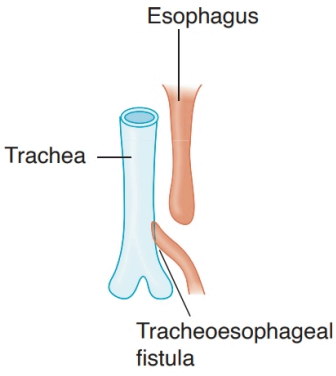
Hematemesis and Esophageal Bleeding

Mallory-Weiss syndrome is esophageal bleeding due to linear lacerations at the gastroesophageal junction from severe prolonged vomiting; the most common cause is acute alcohol ingestion and/or chronic alcoholism. Esophageal rupture (Boerhaave syndrome) may result.

Esophageal varices are dilated submucosal veins in the lower third of the esophagus, usually secondary to portal hypertension. The most common cause is cirrhosis. Clinically, the presentation is asymptomatic, though there is massive hematemesis when the varices are ruptured. Complications include potentially fatal hemorrhage. Treatment is generally band ligation, sclerotherapy, or balloon tamponade.

CLINICAL CORRELATE

The most common type of tracheoesophageal fistula:



CLINICAL CORRELATE

Chagas disease, a tropical parasitic disease common in South America, is caused by *Trypanosoma cruzi*. It is transmitted by reduviid or "kissing" bugs and can cause:

- Romaña's sign (unilateral swelling of the eyelid)
- Cardiomyopathy
- Megaesophagus and megacolon

16_Preclinical_Pathology_Ch16.indd 155 10/6/22 8:57 PM

NOTE

Both **Mallory-Weiss tears** and **esophageal varices** are associated with alcohol abuse and can present with hematemesis. However,

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

NOTE

The incidence of Barrett esophagus is increasing in the United States.

NOTE

Tylosis is an autosomal dominant syndrome. The phenotypic hallmarks are oral leukoplakia and hyperkeratosis of the palms and soles. SCC of the esophagus is seen in up to 95% of affected individuals.

Esophagitis

Gastroesophageal reflux disease (reflux esophagitis) (GERD) is esophageal irritation and inflammation due to reflux of gastric secretions into the esophagus. Reflux typically presents with heartburn and regurgitation. Complications include bleeding, stricture, bronchospasm and asthma, and Barrett esophagus.

Barrett esophagus is a metaplasia of the squamous esophageal mucosa to a more protective columnar type (intestinal metaplasia). It occurs because of chronic exposure to gastric secretions, usually in the setting of GERD. The endoscopic appearance is of an irregular gastroesophageal junction with tongues of red granular mucosa extending up into the esophagus. Barrett esophagus has an increased risk for dysplasia and esophageal adenocarcinoma.

Esophageal Carcinoma

Squamous cell carcinoma (SCC) of the esophagus is the most common type of esophageal cancer in the world. Men > women, and African Americans > Caucasians; typical age >50. Risk factors include:

- Heavy smoking and alcohol use
- Achalasia
- Plummer-Vinson syndrome
- Tylosis
- Lye ingestion

The presentation of squamous cell carcinoma of the esophagus varies; it is often asymptomatic until late in the course. When symptoms do develop they may include progressive dysphagia, weight loss and anorexia, bleeding, hoarseness, and cough. Diagnosis is by endoscopy with biopsy. Treatment is surgery though the prognosis is poor.

Adenocarcinoma of the esophagus affects Caucasians more than African Americans. It arises in the distal esophagus. The progression from Barrett metaplasia to dysplasia and eventually to invasive carcinoma occurs due to the stepwise accumulation of genetic and epigenetic changes. The prognosis is poor.

In the United States, adenocarcinoma and squamous cell carcinoma of the esophagus occur with equal frequency.

STOMACH

Congenital Disorders

CLINICAL CORRELATE

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

Pyloric stenosis is a congenital stenosis of the pylorus due to marked muscular hypertrophy of the pyloric sphincter, resulting in gastric outlet obstruction. It affects male infants more than females. It is associated with Turner and Edwards syndromes. Presentation is the onset of regurgitation and vomiting in week 2 of life; waves of peristalsis are visible on the abdomen and there is a palpable oval abdominal mass. Treatment is surgical.

Congenital diaphragmatic hernia occurs when a congenital defect is present in the diaphragm, resulting in herniation of the abdominal organs into the thoracic cavity. The stomach is the most commonly herniated organ due to left-sided

KP00710.indb 156 13/10/22 1:52 PM

congenital diaphragmatic hernia. Congenital diaphragmatic hernia is often associated with intestinal malrotation. It may be complicated by significant lung hypoplasia.

Hypertrophic Gastropathy

Ménétrier disease is a rare disease of middle-aged men. It is caused by profound hyperplasia of surface mucous cells, accompanied by glandular atrophy. It is characterized by enlarged rugal folds in the body and fundus; clinically, patients experience decreased acid production, protein-losing enteropathy, and increased risk of gastric cancer.

Zollinger-Ellison syndrome. See discussion of gastrinoma in the Pancreas chapter.

Acute Inflammation and Stress Ulcers

Acute hemorrhagic gastritis causes acute inflammation, erosion, and hemorrhage of the gastric mucosa, secondary to a breakdown of the mucosal barrier and acid-induced injury. The etiology is diverse, with initiating agents including chronic aspirin or NSAID use, alcohol use, smoking, recent surgery, burns, ischemia, stress, uremia, and chemotherapy. Patients present with epigastric abdominal pain, or with gastric hemorrhage, hematemesis, and melena.

Gastric stress ulcers are multiple, small, round, superficial ulcers of the stomach and duodenum. Predisposing factors include:

- NSAID use
- Severe stress
- Sepsis
- Shock
- Severe burn or trauma
- Elevated intracranial pressure (Cushing ulcers)

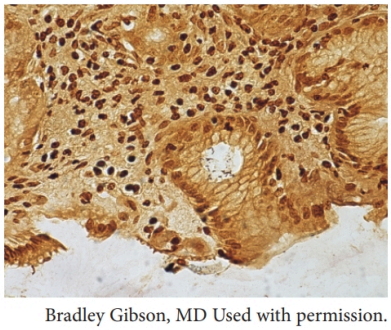
ICU patients have a high incidence of gastric stress ulcer. These ulcers may be complicated by bleeding.

Chronic Gastritis

Chronic gastritis is chronic inflammation of the gastric mucosa, eventually leading to atrophy (chronic atrophic gastritis).

Fundic type chronic gastritis is an autoimmune atrophic gastritis that involves the body and the fundus. It is caused by autoantibodies directed against parietal cells and/or intrinsic factor. The result is loss of parietal cells, decreased acid secretion, increased serum gastrin (G-cell hyperplasia), and pernicious anemia (megaloblastic anemia due to lack of intrinsic factor and B12 malabsorption). Women are affected more than men.

Grossly, one sees a loss of rugal folds in the body and fundus. Microscopically, mucosal atrophy is seen with loss of glands and parietal cells, chronic lymphoplasmacytic inflammation, and intestinal metaplasia. Patients are at increased risk for gastric carcinoma.



Bradley Gibson, MD Used with permission.

Helicobacter pylori, Warthin-Starry stain.

KP00710.indb 157 13/10/22 1:52 PM

CLINICAL CORRELATE

The 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.

Antral type chronic gastritis (also called *Helicobacter pylori* gastritis) is the most common form of chronic gastritis in the United States. The *H. pylori* organisms are curved, gram-negative rods which produce urease. The risk of infection increases with age. Infection is also associated with duodenal/gastric peptic ulcer, and gastric carcinoma with intestinal type histology.

Microscopically, *H. pylori* organisms are visible in the mucous layer of the surface epithelium. Other microscopic features include foci of acute inflammation, chronic inflammation with lymphoid follicles, and intestinal metaplasia.

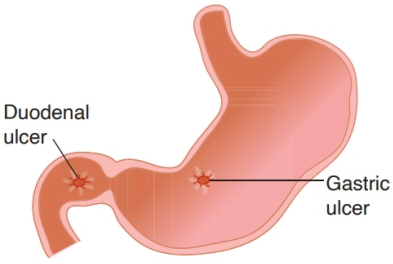
Chronic Peptic Ulcer

Peptic ulcers are ulcers of the distal stomach and proximal duodenum caused by gastric secretions (hydrochloric acid and pepsin) and impaired mucosal defenses. Predisposing factors include the following:

- Chronic NSAID and aspirin use
- Steroid use
- Smoking
- *H. pylori* infection

Patients present with burning epigastric pain. Diagnosis is by endoscopy with or without biopsy. Treatment is acid suppression (H2 blocker, proton pump inhibitor, etc.) and eradication of *H. pylori*.

Complications of peptic ulcer include hemorrhage, iron deficiency anemia, penetration into adjacent organs, perforation (x-ray shows free air under the diaphragm), and pyloric obstruction.



Duodenal peptic ulcers are more common than gastric peptic ulcers. Associations include the following:

- *H. pylori* (~100%)
- Increased gastric acid secretion
- Increased rate of gastric emptying
- Blood group O
- Multiple endocrine neoplasia (MEN) type I
- Zollinger-Ellison syndrome
- Cirrhosis
- Chronic obstructive pulmonary disease

Most duodenal peptic ulcers are located in the anterior wall of the proximal duodenum.

Gastric peptic ulcers are associated with *H. pylori* (75%). Most are located in the lesser curvature of the antrum. Grossly, they are small (<3 cm), sharply demarcated ('punched out'), solitary with round/oval shape, smooth borders, and radiating mucosal folds.

16_Preclinical_Pathology_Ch16.indd 158 10/6/22 8:57 PM

Gastric Neoplasia

Gastric adenocarcinoma is more common in Japan than in the United States, and has a decreasing incidence in the United States. Dietary factors can be risk factors:

- Smoked fish and meats
- Pickled vegetables
- Nitrosamines
- Benzpyrene
- Reduced intake of fruits and vegetables

Other risk factors include *H. pylori* infection, chronic atrophic gastritis, smoking, blood type A, bacterial overgrowth in the stomach, prior subtotal gastrectomy, and Ménétrier disease.

Gastric carcinoma is often (90%) asymptomatic until late in the course, when it can produce weight loss and anorexia. It can also present with epigastric abdominal pain mimicking a peptic ulcer, early satiety, and occult bleeding with iron-deficiency anemia.

Most gastric carcinomas are located in the lesser curvature of the antrum. They are large (>3 cm) ulcers with heaped-up margins and a necrotic ulcer base. They may also occur as a flat or polypoid mass. Several histological types occur.

- The **intestinal type** shows gland-forming adenocarcinoma microscopically.
- The **diffuse type** shows diffuse infiltration of stomach by poorly differentiated tumor cells, numerous signet-ring cells (whose nuclei are displaced to the periphery by intracellular mucin), and *linitis plastica* (thickened "leather bottle"–like stomach) gross appearance.

Gastric carcinoma may specifically metastasize to the left supraclavicular lymph node (Virchow sentinel node) and to the ovary (Krukenberg tumor).

Diagnosis is by endoscopy with biopsy; treatment is gastrectomy. The prognosis is poor, with overall 5-year survival ~30%.

Gastric lymphoma can arise from mucosa-associated lymphoid tissue (MALT). Extranodal marginal zone B-cell lymphomas are frequently associated with *Helicobacter pylori* gastritis. Diffuse, large B-cell lymphoma can also occur in the stomach.

SMALL AND LARGE INTESTINES

Mechanical Obstruction

Volvulus is a twisting of a segment of bowel on its vascular mesentery, causing intestinal obstruction and infarction. It is often associated with congenital abnormalities such as intestinal malrotation. Common locations include the sigmoid colon and small bowel; complications include infarction and peritonitis.

Intussusception is the telescoping of a proximal segment of the bowel into the distal segment. It is most common in infants and children. Children present with vomiting, abdominal pain, passage of blood per rectum, and lethargy; a sausage-shaped mass is often palpable in the right hypochondrium.

KP00710.indb 159 13/10/22 1:52 PM

NOTE

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

In adults, intussusception may be caused by a mass or tumor. The intussuscepted segment can become infarcted.

Incarcerated hernia is a segment of bowel that is imprisoned within a hernia; the condition can become complicated by intestinal obstruction and infarction.

Motility Disorders

Hirschsprung disease (or congenital aganglionic megacolon) is caused by congenital absence of ganglion cells in the rectum and sigmoid colon, resulting in intestinal obstruction. The condition affects males more than females, and can be associated with Down syndrome. Hirschsprung may present with delayed passage of meconium, or with constipation, abdominal distention, and vomiting.

BRIDGE TO ANATOMY

Auerbach plexus = myenteric ganglia

Meissner plexus = submucosal ganglia

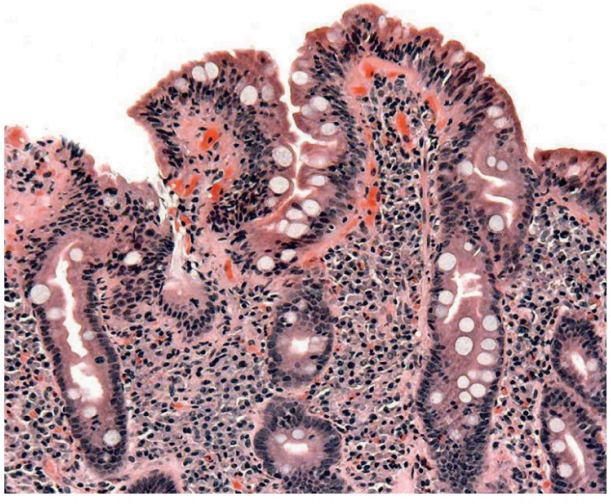
Grossly, the affected segment is narrowed, and there is dilation proximal to the narrow segment (megacolon). Microscopically, there is an absence of ganglion cells in Auerbach and Meissner plexuses, and the diagnosis is established when rectal biopsy demonstrates the absence of ganglion cells. Treatment is resection of the affected segment.

Irritable bowel syndrome is a diagnosis of exclusion based on symptoms of diarrhea and/or constipation.

Malabsorption Syndromes

Celiac sprue (or gluten-sensitive enteropathy and nontropical sprue) is caused by hypersensitivity to gluten (and gliadin), resulting in loss of small bowel villi and malabsorption. HLA-DQ2 and/or -DQ8 are carried by most patients. Microscopic exam demonstrates a loss of villi, with increased intraepithelial lymphocytes and increased plasma cells in the lamina propria.

Clinically, it often presents in childhood with malabsorption. Symptoms include abdominal distention, bloating, and flatulence, along with diarrhea, steatorrhea, and weight loss. Dermatitis herpetiformis may occur age >20. In adults, celiac presents between decades 4-7. Treatment is dietary restriction of gluten. There is an increased risk of gastrointestinal cancer.



wikimedia.org.

Figure 16-1. Celiac Disease

KP00710.indb 160 13/10/22 1:52 PM

Environmental enteropathy (previously known as **tropical sprue**) is a malabsorption disease of unknown etiology (infection and/or nutritional deficiency). It affects residents of low-income countries. Biopsy shows blunting of villi and a lymphocytic infiltrate.

Whipple disease is a rare infectious disease involving many organs, including small intestines, joints, lung, heart, liver, spleen, and CNS. It typically affects Caucasian males age 30-50.

The infecting organism is *Tropheryma whipplei.* Microscopically, the small bowel lamina propria is filled with macrophages stuffed with the PAS-positive, gram-positive, rod-shaped bacilli. Patients present with malabsorption, weight loss, and diarrhea. Treatment is antibiotics.

Inflammatory Bowel Disease (IBD)

There are 2 categories of IBD:

- **Crohn disease (CD)** (or regional enteritis)
- **Ulcerative colitis (UC)**

Colitis of indeterminate type describes cases that cannot be clearly classified.

Caucasians develop IBD more frequently than non-Caucasians. The incidence of IBD is increasing.

Age distribution varies with the disease:

- CD has a bimodal distribution with peaks at age 10–30 and 50–70
- UC peaks at age 20–30

IBD can present with episodes of bloody diarrhea or stools with mucus, crampy lower abdominal pain, or fever. CD may present with malabsorption or extraintestinal manifestations. It may mimic appendicitis. CD may cause perianal fistulas.

Diagnosis of IBD requires endoscopic biopsy and clinicopathologic correlation.

New studies indicate that risk of colorectal carcinoma (CRC) in CD and UC are equivalent for similar extent and duration of disease; the risk of CRC is not as high as previous studies suggested.

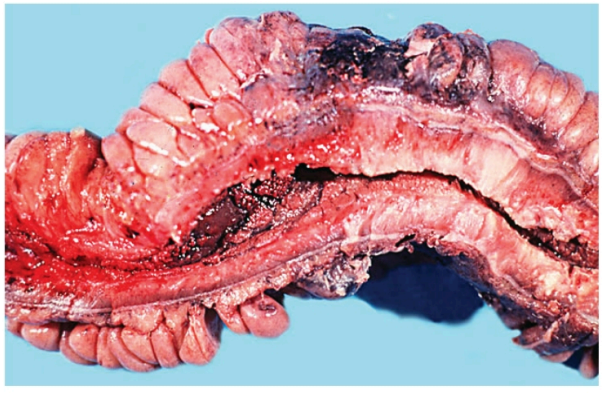


Figure 16-2. Narrowed Colon Segment in Crohn Disease

NOTE

Damage to the ileal mucosa can cause deficiencies of vitamin B12 and folate.

KP00710.indb 161 13/10/22 1:52 PM

Table 16-1. 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 appearance • 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	Common (e.g., migratory polyarthritis, ankylosing spondylitis, primary sclerosing cholangitis, erythema nodosum, pyoderma gangrenosum, uveitis)	Common (e.g., migratory arthritis, ankylosing spondylitis, primary sclerosing cholangitis, erythema nodosum, pyoderma gangrenosum, uveitis)

Other Inflammatory Diseases

Pseudomembranous colitis (antibiotic-associated colitis) is an acute colitis characterized by the formation of inflammatory pseudomembranes in the intestines. It is usually caused by *Clostridium difficile* infection (often brought on by a course of broad-spectrum antibiotics, especially clindamycin and ampicillin), but it can be caused by ischemic bowel disease.

Gross examination shows yellow-tan mucosal membranes. Microscopic exam shows the pseudomembranes are composed of an adherent layer of acute inflammatory cells, mucus and necrotic debris overlying sites of colonic mucosal injury. Presentation is with diarrhea, fever, and abdominal cramps. Diagnosis is established with detection of *C. difficile* toxin in the stool. Treatment of clostridial pseudomembranous colitis is vancomycin or metronidazole.

KP00710.indb 162 13/10/22 1:52 PM

Appendicitis is most commonly caused by obstruction of the appendix by a fecalith. It often starts with periumbilical pain that subsequently localizes to the right lower quadrant. Nausea, vomiting, and fever may also be present. Lab studies show an elevated WBC count. A complication is appendiceal rupture leading to peritonitis. Grossly, a fibrinopurulent exudate may be seen on the appendiceal serosa; microscopically, neutrophils are present within the mucosa and muscular wall (muscularis propria) of the appendix.

Vascular Disorders

Ischemic bowel disease is caused by decreased blood flow and ischemia of the bowel, secondary to atherosclerosis with thrombosis, thromboembolism, or reduced cardiac output from shock. It is most common in older individuals. Typical presentation is with abdominal pain and bloody diarrhea. The disease distribution tends to involve watershed areas (e.g., splenic flexure), and affected areas typically show hemorrhagic infarction.

Treatment is surgical resection, but the prognosis is poor, with >50% mortality.

Hemorrhoids are tortuous, dilated anal submucosal veins caused by increased venous pressure. Risk factors include constipation and prolonged straining during bowel movements, pregnancy, and cirrhosis. Complications include painful thrombosis and streaks of bright red blood on hard stool.

Angiodysplasia is the most common vascular malformation of the GI tract. Individuals age >55 are most commonly affected, presenting with multiple episodes of rectal bleeding. It is associated with Osler-Weber-Rendu and CREST syndromes.

Melanosis Coli

Melanosis coli is associated with laxative use; it causes black pigmentation of the colon due to the ingestion of the laxative pigment by macrophages in the mucosa and submucosa. It can mimic colitis or malignancy.

Diverticula

Meckel diverticulum is a congenital small bowel diverticulum caused by persistence of a remnant of the vitelline (omphalomesenteric) duct (*see* Anatomy Lecture Notes). With Meckel, the "rule of 2s" applies:

- 2% of the normal population
- 2 feet from the ileocecal valve
- Length 2 cm
- Age ≤2 years at time of diagnosis

Most Meckel diverticula are asymptomatic but they may contain rests of ectopic gastric mucosa and present with intestinal bleeding.

BRIDGE TO ANATOMY

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

NOTE

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

KP00710.indb 163 13/10/22 1:52 PM

NOTE

Given that only 2 layers of the bowel wall are involved, these acquired outpouchings are technically pseudodiverticula.

Colonic diverticulosis is an acquired outpouching of the bowel wall, characterized by herniation of the mucosa and submucosa through the muscularis propria (pseudodiverticulum). It is extremely common in the United States.

- Incidence increases with age
- Major risk factor is a low-fiber diet, which leads to increased intraluminal pressure
- Most common location is sigmoid colon

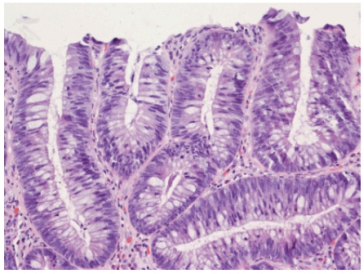
Many cases are asymptomatic and picked up on screening colonoscopy. When symptomatic, it can cause constipation alternating with diarrhea, left lower quadrant abdominal cramping and discomfort, occult bleeding and an iron deficiency anemia, or lower gastrointestinal tract hemorrhage. Complications include diverticulitis, fistulas, and perforation with accompanying peritonitis.

Polyps

Hamartomatous polyps include nonfamilial juvenile polyps and polyps associated with a familial (Peutz-Jeghers) syndrome. Nonsyndromic polyps do not have malignant potential.

Hyperplastic polyps are the most common histologic type; they occur most often in the left colon and are usually <5 mm. Although previously considered not to have malignant potential, newer studies suggest they are part of a group of polyps with serrated histology and risk of progression to cancer. **Serrated polyps** occur more often in the right colon.

Tubular and villous adenomas have long been known to have malignant potential. Microscopically, they show cellular dysplasia and either pure tubular, pure villous or tubulovillous histology.



© Gregg Barré, MD Used with permission.

Tubular Adenoma

Familial Syndromes

Familial adenomatous polyposis (FAP), also called adenomatous polyposis coli (APC), is due to an autosomal dominant mutation of the *APC* gene on chromosome 5q21.

Affected individuals may develop **thousands of colonic adenomatous polyps**; the diagnosis is made with discovery of >100 adenomatous polyps on endoscopy. **Complications:** by age 40, virtually 100% will develop an invasive adenocarcinoma and increased risks for developing duodenal adenocarcinoma and adenocarcinoma of the papilla of Vater.

Gardner syndrome is an autosomal dominant variant of familial adenomatous polyposis characterized by numerous colonic adenomatous polyps, multiple osteomas, fibromatosis, and epidermal inclusion cysts.

Turcot syndrome is a rare variant of familial adenomatous polyposis characterized by numerous colonic adenomatous polyps and CNS tumors (gliomas).

Hereditary nonpolyposis colorectal cancer (HNPCC), or Lynch syndrome, is due to an autosomal dominant mutation of a DNA nucleotide mismatch repair gene that predisposes for colon cancer. It is associated with an increased risk of cancer at other sites, including the endometrium and the ovary.

KP00710.indb 164 13/10/22 1:52 PM

Peutz-Jeghers syndrome is an autosomal dominant condition characterized by multiple hamartomatous polyps (primarily in the small intestine); melanin pigmentation of the oral mucosa; and increased risk of cancer at numerous sites including the lung, pancreas, breast, and uterus.

Neoplasia

Colonic adenocarcinoma is the third most common tumor in the United States, in terms of incidence and mortality. **Risk factors** include:

- Dietary factors (low fiber, low fruits/vegetables and high in red meat and animal fat)
- Colon polyps (isolated adenomatous polyps, hereditary polyposis syndromes)
- Other colon disease (Lynch syndrome, ulcerative colitis)

Diagnosis of colonic adenocarcinoma is established via endoscopy with biopsy.

Cancer genetics: Mutations of the *APC* gene cause activation of the Wnt pathway, leading β-catenin to translocate to the nucleus where it causes the overexpression of growth-promoting genes. DNA mismatch repair causes microsatellite instability, which is another genetic carcinogenesis pathway.

The pattern of spread in colonic adenocarcinoma includes lymphatic spread to mesenteric lymph nodes, with distant spread to liver, lungs, and bone. Staging is with the TNM system. Treatment can include surgical resection and chemotherapy (for metastatic disease); CEA levels can be used to monitor for disease recurrence.

Screening for colonic adenocarcinoma and other GI neoplasias is recommended for the general population beginning age 50. Current guidelines suggest:

- Colonoscopy every 10 years or annual fecal occult blood test (FOBT), or
- Combination of FOBT (every 3 years) and sigmoidoscopy (every 5 years)

Table 16-2. 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

Carcinoid tumors are neuroendocrine tumors that often produce serotonin. Locations include the appendix (most common) and the terminal ileum. Metastasis to the liver may result in carcinoid heart disease.

NOTE

TNM Staging of Colorectal Cancer

Stage I (T1-2N0M0): tumors that do not penetrate through mucosa (T1) or muscularis (T2)

Stage II (T3N0M0): tumors that have penetrated through the muscularis but have not spread to the lymph nodes

Stage III (TXN1M0): regional lymph node involvement

Stage IV (TXNXM1): metastasis to distant sites

NOTE

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

KP00710.indb 165 13/10/22 1:52 PM

Carcinoid syndrome is characterized by diarrhea, cutaneous flushing, bronchospasm and wheezing, and fibrosis. The diagnosis is substantiated by demonstrating elevated urinary 5-HIAA (5-hydroxyindoleacetic acid).

BRIDGE TO BIOCHEMISTRY

Serotonin is converted to 5-HIAA by monoamine oxidase.

Gastrointestinal stromal tumor (GIST) is the most common sarcoma of the GI tract. Most cases have a *KIT* mutation. The peak incidence is in decade 7. Treatment is resection and a tyrosine-kinase inhibitor.

ANUS

Anal Skin Tags

Anal skin tags are fibroepithelial polyps that arise secondary to inflammation or injury. They can be mistaken clinically for condylomata and hemorrhoids.

Anal Lesions of Inflammatory Bowel Disease

Manifestations of **perianal Crohn disease** include fissures, fistulas, abscesses, and anal canal stenosis. Fistulas can be the first sign of disease.

Hemorrhoids are vascular structures in the anal canal that can become enlarged and inflamed, causing pain and bright red blood per rectum. Above the dentate line (internal hemorrhoids) they are covered by columnar epithelium; below the dentate line they are covered by anoderm and skin.

HPV-Associated Disease

Condyloma acuminatum is the most common tumor of the anal region. It is caused by HPV infection.

Anal intraepithelial neoplasia (AIN) is a precursor to **anal squamous carcinoma**. The incidences of both anal intraepithelial neoplasia and anal cancer are rising in the United States. HPV infection causes the majority of anal cancers. Screening for the disease is recommended in high-risk populations, and anoscopy with biopsy evaluation is useful for early detection.

KP00710.indb 166 13/10/22 1:52 PM

17 Pancreatic Pathology

LEARNING OBJECTIVES

- ❑ Demonstrate understanding of congenital anomalies of the pancreas
- ❑ Use knowledge of inflammation of the pancreas or tumors of the pancreas to solve problems

NONNEOPLASTIC CONDITIONS

Congenital Anomalies of the Pancreas

- **Pancreatic agenesis** is incompatible with life.
- **Pancreatic divisum** is a variant of pancreatic duct anatomy.
- **Annular pancreas** encircles the duodenum and presents as obstruction.
- **Ectopic pancreatic tissue** can hemorrhage, become inflamed, or give rise to a neuroendocrine tumor. It most often arises in the stomach, duodenum, or jejunum.

Inflammation of the Pancreas

Acute pancreatitis is acute inflammation caused by injury to the exocrine portion of the pancreas. The etiology is diverse:

- Gallstones
- Alcohol
- Hypercalcemia
- Drugs
- Shock
- Infections
- Trauma
- Scorpion stings

Pancreatic acinar cell injury results in activation of pancreatic enzymes and enzymatic destruction of the pancreatic parenchyma.

Symptoms include stabbing epigastric abdominal pain radiating to the back. Severe acute pancreatitis can also cause shock. Lab studies show elevated serum amylase and lipase. Complications include acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), pancreatic pseudocyst; pancreatic calcifications, and hypocalcemia. Severe cases have a 30% mortality rate.

NOTE

Pancreatic pseudocyst is a fluid-filled sac adjacent to the pancreas. The wall of granulation tissue lacks an epithelial lining.

KP00710.indb 167 13/10/22 1:52 PM

- Gross pathologic examination shows focal hemorrhage and liquefication in the pancreas, accompanied by chalky, white-yellow fat necrosis of adjacent adipose tissue.
- Microscopically there is liquefactive necrosis of the pancreatic parenchyma with acute inflammation and enzymatic fat necrosis.
- Necrosis of blood vessels causes hemorrhage.

Chronic pancreatitis refers to irreversible changes in pancreatic function with accompanying chronic inflammation, atrophy, and fibrosis of the pancreas secondary to repeated bouts of pancreatitis. Manifestations include abdominal pain, pancreatic insufficiency and malabsorption, pancreatic calcifications, pseudocyst, and secondary diabetes mellitus (late complication).

It is common in middle-aged male alcoholics. Pathology shows grossly firm, white, and fibrotic pancreas. Microscopically there is extensive fibrosis with parenchymal atrophy and chronic inflammation.

Autoimmune pancreatitis can occur in association with IgG4-associated fibrosing disorders; this variant responds to steroid therapy.

PANCREATIC NEOPLASMS

Neuroendocrine Tumors

Pancreatic neuroendocrine tumors (islet cell tumors) are less common than exocrine tumors. Most are considered low-grade malignancies. Some patients lack laboratory evidence of hormone overproduction. These tumors are not distinguishable from each other on the basis of gross appearance or histology.

- **Insulinoma (β-cell tumor)** (most common type of islet cell tumor)
  - Produces insulin
  - Can cause hypoglycemia, sweating, hunger, confusion, and insulin coma
  - Surgical excision is curative
- **Gastrinoma (G-cell tumor)**
  - Produces gastrin
  - Excess gastrin manifests as Zollinger-Ellison syndrome, which is characterized by thick gastric folds, elevated serum gastrin, gastric hyperacidity, and intractable peptic ulcers
  - Gastrinomas may arise outside the pancreas
  - May be associated with MEN I
- **Glucagonoma** (α-cell tumor)
  - Produces glucagon
  - Excess glucagon causes hyperglycemia (diabetes), anemia, and skin rash
- **Somatostatinoma** (δ-cell tumor)
  - Produces somatostatin
  - Excess somatostatin inhibits insulin secretion, leading to diabetes
  - Can also inhibit gastrin secretion (leading to hypochlorhydria) and cholecystokinin secretion (leading to gallstones and steatorrhea)
  - Prognosis is poor

KP00710.indb 168 13/10/22 1:52 PM

- **VIPoma**
  - Produces vasoactive intestinal peptide (VIP)
  - Excess VIP causes WDHA syndrome: watery diarrhea, hypokalemia, and achlorhydria

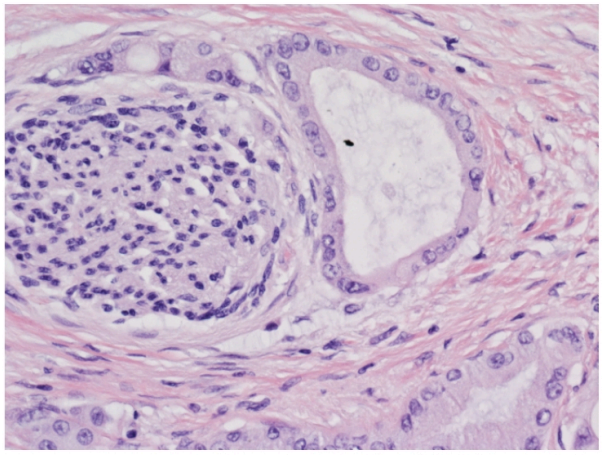
Adenocarcinoma

Pancreatic carcinoma is the third most common cause of cancer death in the United States.

- Most common ages 60–80
- Smoking is a risk factor
- Presents with only vague signs and symptoms until late in course
- When more definitive signs and symptoms develop, they can include abdominal pain, migratory thrombophlebitis, and obstructive jaundice

The tumor may occur in the head (60%), body (15%), and tail (5%). Microscopically, the adenocarcinoma arises from the duct epithelium. Tumor desmoplasia and perineural invasion are common. Tumor markers for pancreatic carcinoma include CEA and CA19-9, but they are not useful screening assays.

Treatment is surgical excision (Whipple procedure). The prognosis is very poor, with 5-year survival only ~5%.



© Gregg Barré, MD Used with permission.

Figure 17-1. Pancreatic Adenocarcinoma with Perineural Invasion

Pancreatic Cystic Neoplasms

Serous neoplasms account for 25% of pancreatic cystic neoplasms; most are benign (cystadenomas) and the tumors carry a mutation of *VHL*.

Mucinous neoplasms: Mucinous cystic neoplasms are common in women and can harbor dysplasia or carcinoma; distal pancreatectomy is curative in most cases. **Intraductal papillary mucinous neoplasms** are common in men and tend to arise in the head of the pancreas; *GNAS* mutations are common and carcinoma may arise in the neoplasm.

KP00710.indb 169 13/10/22 1:52 PM

Gallbladder and Biliary Tract Pathology

18

LEARNING OBJECTIVES

- ❑ Use knowledge of gallstones (cholelithiasis), inflammatory conditions of the gallbladder, and miscellaneous conditions to solve problems
- ❑ Explain information related to biliary tract cancer

GALLSTONES (CHOLELITHIASIS)

Gallstones are frequently asymptomatic but can cause biliary colic (right upper quadrant pain due to impacted stones). Diagnosis is by U/S; the majority of stones are not radiopaque. Complications include cholecystitis, choledocholithiasis (calculi within the biliary tract), biliary tract obstruction, pancreatitis, and cholangitis.

Cholesterol Stones

These stones are composed mostly of cholesterol monohydrate. The incidence increases with age. Risk factors include female gender, obesity, pregnancy, oral contraceptives, and hormone replacement therapy. Native American Pima and Navajo Indians have an increased incidence of cholesterol gallstones.

NOTE

Formation of cholesterol stones involves the precipitation of cholesterol from supersaturated bile.

Pigmented Bilirubinate Stones

These stones are composed of calcium salts and unconjugated bilirubin. Risk factors are chronic hemolytic anemias, cirrhosis, bacterial infection, and parasites (*Ascaris* or *Clonorchis* [*Opisthorchis*] *sinensis*).

INFLAMMATORY CONDITIONS

Acute Cholecystitis

Acute cholecystitis is an acute inflammation of the gallbladder, usually caused by cystic duct obstruction by gallstones. It can present with biliary colic, right upper quadrant tenderness on palpation, nausea and vomiting, low-grade fever, and leukocytosis. Complications include gangrene of the gallbladder, perforation and peritonitis, fistula formation and gallstone ileus (small bowel obstruction by a large gallstone). Acute acalculous cholecystitis is associated with surgery, trauma, and sepsis.

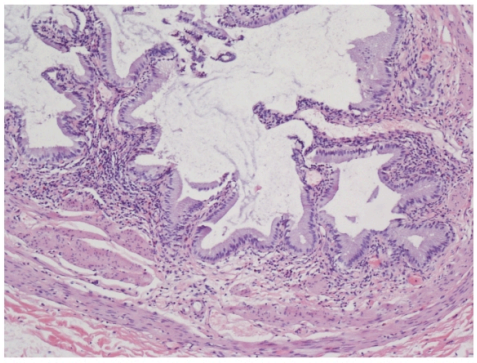
CLINICAL CORRELATE

Murphy's sign is inspiratory arrest in response to palpation of the right subcostal area during deep inspiration. It is seen in patients with pain due to cholecystitis.

KP00710.indb 171 13/10/22 1:52 PM

Chronic Cholecystitis

Chronic cholecystitis is ongoing chronic inflammation of the gallbladder, usually caused by gallstones. Well-developed examples show stromal and mural lymphocytic and plasmacytic infiltrates. Macrophages and granulomas may also be present. The wall is thickened.



© Gregg Barré, MD Used with permission.

Figure 18-1. Chronic Cholecystitis

CLINICAL CORRELATE

Charcot's triad is RUQ pain, jaundice, and fever, characteristic of acute cholangitis.

Ascending Cholangitis

Ascending cholangitis is a bacterial infection of the bile ducts ascending up to the liver, usually associated with obstruction of bile flow oftentimes from bile duct stones. It presents with biliary colic, jaundice, high fever, and chills. The infecting organisms are usually gram-negative enteric bacteria.

MISCELLANEOUS CONDITIONS

Cholesterolosis

Cholesterolosis refers to an accumulation of cholesterol-laden macrophages within the mucosa of the gallbladder wall. Gross examination shows yellow speckling of the red-tan mucosa ("strawberry gallbladder"). Microscopic examination shows lipid-laden macrophages within the lamina propria.

Hydrops of the Gallbladder

Hydrops of the gallbladder (mucocele) occurs when 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).

KP00710.indb 172 13/10/22 1:52 PM

BILIARY TRACT CANCER

Gallbladder Cancer

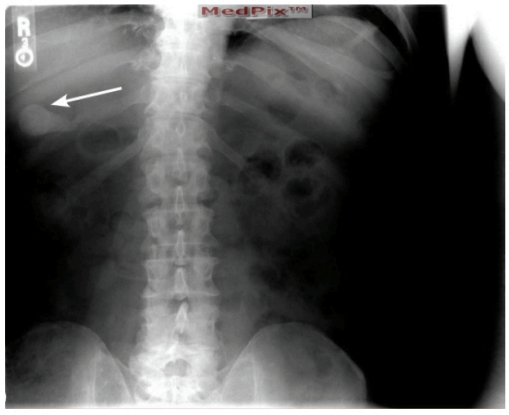
Gallbladder cancer is frequently asymptomatic until late in the course. When the tumor does present, it may be with cholecystitis, enlarged palpable gallbladder, or biliary tract obstruction (uncommon). X-ray may show a calcified "porcelain gallbladder." Microscopically, the tissues show adenocarcinoma. The prognosis for gallbladder cancer is poor; 5-year survival rate is ~12%.

Bile Duct Cancer

Bile duct cancer. Bile duct carcinoma is carcinoma of the **extrahepatic** bile ducts, while cholangiocarcinoma is carcinoma of the **intrahepatic** bile ducts. Klatskin tumor is a carcinoma of the bifurcation of the right and left hepatic bile ducts. Risk factors for bile duct cancer include *Clonorchis (Opisthorchis) sinensis* (liver fluke) in Asia and primary sclerosing cholangitis. Bile duct cancer typically presents with biliary tract obstruction. Microscopic examination shows adenocarcinoma arising from the bile duct epithelium. The prognosis is poor.

Adenocarcinoma of the Ampulla of Vater

Adenocarcinoma of the ampulla of Vater may exhibit duodenal, biliary, or pancreatic epithelium. Patients present with painless jaundice. The 5-year survival rate is <50% in spite of resection.



© Gloria Jicha: Tripler Army Medical Center.
Used with permission.

Figure 18-2. X-Ray Showing Calcified (Porcelain) Gallbladder

CLINICAL CORRELATE

Courvoisier law is a palpable gallbladder more likely to be caused by obstruction due to malignancy than by stones.

"Porcelain gallbladder" is a calcification of the gallbladder due to chronic inflammation; recent studies have cast doubt on its association with carcinoma.

KP00710.indb 173 13/10/22 1:52 PM

19 Liver Pathology

LEARNING OBJECTIVES

- ❑ Solve problems concerning jaundice, cirrhosis, viral hepatitis, amebic liver abscess, and alcoholic liver disease
- ❑ Differentiate metabolic liver disease from hemodynamic liver disease
- ❑ Solve problems concerning liver tumors

NONNEOPLASTIC LIVER DISEASE

Liver Dysfunction

Dysfunction of the liver may be divided into 4 categories that may coexist:

- **Hepatic failure** occurs in the setting of hepatic necrosis secondary to acute liver failure, chronic liver disease, and hepatocyte dysfunction.
- **Portal hypertension** occurs in the setting of cirrhosis or increased portal venous blood flow.
- **Cholestasis** occurs in the setting of impaired bile flow due to hepatocyte dysfunction or biliary obstruction.
- **Cirrhosis** occurs in the setting of hepatocyte injury and is usually an irreversible nodular regeneration that is end-stage.

Jaundice

Clinical jaundice occurs with bilirubin levels >2–3 mg/dL. The classic presentation is yellow skin (jaundice) and sclera (icterus). Causes of jaundice include overproduction of bilirubin, defective hepatic bilirubin uptake, defective conjugation, and defective excretion.

Table 19-1. 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-Najjar syndromes)	Hereditary (Dubin-Johnson and Rotor syndromes)
	Liver disease (cirrhosis and hepatitis)

KP00710.indb 175 13/10/22 1:52 PM

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).

Increased RBC turnover. RBCs are the major source of bilirubin. Jaundice related to overproduction of bilirubin can be seen in hemolytic anemia and ineffective erythropoiesis (thalassemia, megaloblastic anemia, etc.). Laboratory studies show increased unconjugated bilirubin. Chronic hemolytic anemia patients often develop pigmented bilirubinate gallstones. The most common cause of marked jaundice in the newborn is blood group incompatibility (most commonly ABO) between mother and child, causing **hemolytic disease of the newborn**.

Physiologic jaundice of the newborn is a transient unconjugated hyperbilirubinemia due to the immaturity of the liver. Risk factors include prematurity and hemolytic disease of the newborn (erythroblastosis fetalis). Physiologic jaundice of the newborn can be complicated by kernicterus; treatment is phototherapy. Jaundice also occurs in newborns who have infections.

Hereditary hyperbilirubinemias

When hyperbilirubinemia is prolonged in the newborn, a mutation affecting bilirubin conjugation enters the differential diagnosis.

- **Gilbert syndrome** is a common benign inherited disorder that causes unconjugated hyperbilirubinemia due to bilirubin UDP-glucuronosyltransferase (UGT) deficiency. Kernicterus rarely occurs and the treatment is phenobarbital.
- **Crigler-Najjar syndrome** causes unconjugated hyperbilirubinemia due to bilirubin glucuronosyltransferase (UGT) absence or deficiency. Treatment for type 1 is gene replacement therapy and liver transplantation. For a milder type 2, phenobarbital is used.
- **Dubin-Johnson syndrome** is a benign autosomal recessive disorder characterized by decreased bilirubin excretion due to a defect in the canalicular cationic transport protein. It produces conjugated hyperbilirubinemia and a distinctive black pigmentation of the liver, but has no clinical consequences.
- **Rotor syndrome** is an autosomal recessive conjugated hyperbilirubinemia that is similar to Dubin-Johnson syndrome, but without liver pigmentation. There are no clinical consequences.

Biliary tract obstruction may have multiple etiologies, including gallstones; tumors (pancreatic, gallbladder, and bile duct); stricture; and parasites (liver flukes—*Clonorchis [Opisthorchis] sinensis*). The presentation can include jaundice and icterus; pruritus due to increased plasma levels of bile acids; abdominal pain, fever, and chills; dark urine (bilirubinuria); and pale clay-colored stools. Lab studies show elevated conjugated bilirubin, elevated alkaline phosphatase, and elevated 5′-nucleotidase.

Primary biliary cirrhosis (PBC) is a chronic liver disease that is characterized by inflammation and granulomatous destruction of intrahepatic bile ducts. Females have 10 times the incidence of primary biliary cirrhosis compared to males; the peak incidence is age 40–50.

Presentation includes obstructive jaundice and pruritus; xanthomas, xanthelasmas, and elevated serum cholesterol; fatigue; and cirrhosis (late complication). Most patients have another autoimmune disease (scleroderma, rheumatoid arthritis or systemic lupus erythematosus).

KP00710.indb 176 13/10/22 1:52 PM

Laboratory studies show elevated conjugated bilirubin, elevated alkaline phosphatase, and elevated 5′-nucleotidase. Treatment with oral ursodeoxycholic acid slows disease progression. **Antimitochondrial autoantibodies** (AMA) are present in >90% of cases, which further supports an autoimmune basis. Microscopically, lymphocytic and granulomatous inflammation involves interlobular bile ducts.

Primary sclerosing cholangitis (PSC) is a chronic liver disease characterized by segmental inflammation and fibrosing destruction of intrahepatic and extrahepatic bile ducts. The exact etiologic mechanism is not known but growing evidence supports an immunologic basis.

The male to female ratio is 2:1; peak age is 20–40. Most cases of PSC are associated with ulcerative colitis. The presentation is similar to PBC. Complications include biliary cirrhosis and cholangiocarcinoma.

Microscopically, there is periductal chronic inflammation with concentric fibrosis around bile ducts and segmental stenosis of bile ducts. Cholangiogram shows "beaded appearance" of bile ducts.

Cirrhosis

Cirrhosis is end-stage liver disease characterized by disruption of the liver architecture by bands of fibrosis which divide the liver into nodules of regenerating liver parenchyma.

Causes of cirrhosis include alcohol, viral hepatitis, biliary tract disease, hemochromatosis, cryptogenic/idiopathic, Wilson disease, and α-1-antitrypsin deficiency.

On gross pathology, micronodular cirrhosis has nodules <3 mm, while **macronodular** cirrhosis has nodules >3 mm; mixed micronodular and macronodular cirrhosis can also occur. At the end stage, most diseases result in a mixed pattern, and the etiology may not be distinguished based on the appearance.

Cirrhosis has a multitude of **consequences**, including portal hypertension, ascites, splenomegaly/hypersplenism, esophageal varices, hemorrhoids, caput medusa, decreased detoxification, hepatic encephalopathy, spider angiomata, palmar erythema, gynecomastia, decreased synthetic function, hepatorenal syndrome and coagulopathy.

CLINICAL CORRELATE

Prothrombin time, not partial thromboplastin time, is used to assess the coagulopathy due to liver disease.

Viral Hepatitis

Viral hepatitis can be asymptomatic or it can present with malaise and weakness, nausea and anorexia, jaundice, or dark urine. Lab studies show markedly elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Diagnosis is by serology.

Acute viral hepatitis is viral hepatitis with signs and symptoms for <6 months. It can be caused by any of the hepatitis viruses.

Microscopically, the liver shows lobular disarray, hepatocyte swelling (balloon cells), apoptotic hepatocytes (Councilman bodies), lymphocytes in portal tracts and in the lobule, hepatocyte regeneration, and cholestasis.

CLINICAL CORRELATE

Non-hepatitis viruses that may infect the liver include:

- *Epstein-Barr virus* (EBV)—infectious mononucleosis
- *Cytomegalovirus* (CMV)
- Herpes
- Yellow fever

KP00710.indb 177 13/10/22 1:52 PM

CLINICAL CORRELATE

Hepatitis D requires hepatitis B to propagate.

Chronic viral hepatitis is viral hepatitis with signs and symptoms for >6 months. It can be caused by hepatitis viruses B, C, and D.

- Microscopically, **chronic persistent hepatitis** shows inflammation confined to portal tracts.
- **Chronic active hepatitis** shows inflammation spilling into the parenchyma, causing interface hepatitis (piecemeal necrosis of limiting plate).

Hepatitis B often has "ground glass" hepatocytes (due to cytoplasmic HBsAg).

Table 19-2. 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	*Hepatovirus* nonenveloped capsid RNA	*Hepadnavirus* enveloped DNA	*Flavivirus* enveloped RNA	Defective enveloped circular RNA	*Hepevirus* nonenveloped capsid RNA
Transmission	Fecal-oral	Parenteral, sexual, perinatal	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)	• 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 EIA for anti-HCV	Anti-HDV ELISA	Tests not routinely available
Prevention	Vaccine, hygiene	Vaccine			Hygiene
Treatment	Supportive	Antivirals, interferons, transplant	Antivirals, interferons, transplant	See hepatitis B	Supportive

KP00710.indb 178 13/10/22 1:52 PM

Table 19-3. Hepatitis B Terminology and Markers

Abbreviation	Name and Description
HBV	Hepatitis B virus, a hepadnavirus (enveloped, partially doublestranded 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 19-4. Hepatitis A Serology

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

Table 19-5. 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

Amebic Liver Abscess

Amebic liver abscess is rare in the United States except in those who have traveled to/from tropical areas with poor sanitation. The causative organism is *Entamoeba histolytica*. The presentation, which may occur years after travel, includes RUQ pain, fever, and hepatic tenderness.

Detection of a space-occupying liver lesion with positive serology is diagnostic. Treatment is antibiotics. Drainage is rarely necessary.

KP00710.indb 179 13/10/22 1:52 PM

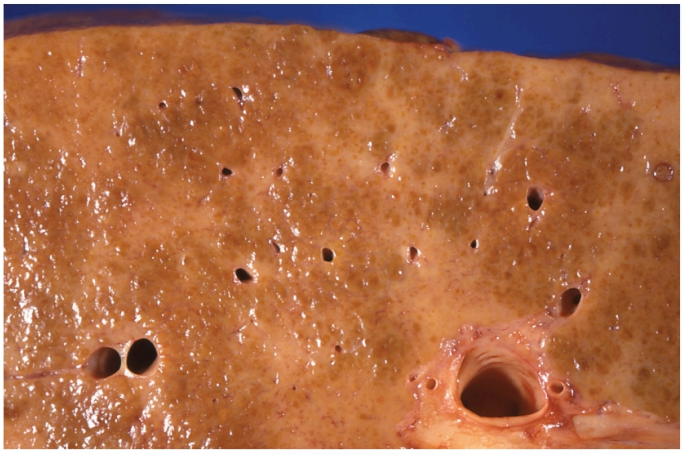
Alcoholic Liver Disease

Fatty change (steatosis) is reversible with abstinence. The gross appearance is of an enlarged, yellow, greasy liver. Microscopically, the liver initially shows centrilobular macrovesicular steatosis (reversible) that can eventually progress to fibrosis around the central vein (irreversible).

Alcoholic hepatitis is an acute illness that usually follows a heavy drinking binge. Some patients have no symptoms and others develop RUQ pain, hepatomegaly, jaundice, malaise, anorexia, or even fulminant liver failure.

Microscopically, the liver shows hepatocyte swelling (ballooning) and necrosis, Mallory bodies (cytokeratin intermediate filaments), neutrophils, fatty change, and eventual fibrosis around the central vein. The prognosis can be poor, since each episode has a 20% risk of death, and repeated episodes increase the risk of developing cirrhosis.

Alcoholic cirrhosis develops in 15% of alcoholics, and is typically a micronodular or Laennec cirrhosis.



© cdc.gov.

Figure 19-1. Alcoholic Cirrhosis, Liver

Metabolic Liver Disease

Wilson disease (hepatolenticular degeneration) is a genetic disorder of copper metabolism resulting in the accumulation of toxic levels of copper in various organs. It affects the liver (fatty change, chronic hepatitis, and micronodular cirrhosis), cornea (Kayser-Fleischer rings [copper deposition in Descemet's membrane]), and brain (neurological and psychiatric manifestations, movement disorder).

Diagnosis is established by demonstrating decreased serum ceruloplasmin levels, increased tissue copper levels (liver biopsy), and increased urinary copper excretion. Treatment includes copper chelators (D-penicillamine); liver transplantation is curative.

The disease is autosomal recessive, and the WD gene (*ATP7B* on chromosome 13) codes for a hepatocyte canalicular copper-transporting ATPase. Damage to the

KP00710.indb 180 13/10/22 1:52 PM

gene leads to a decreased biliary excretion of copper. Wilson disease presents in children or adolescents with liver disease.

Hemochromatosis is a disease of increased levels of iron, leading to tissue injury. **Hereditary (primary) hemochromatosis** is a recessive disorder of the *HFE* gene on chromosome 6p. The most common mutation of the *HFE* gene is the C282Y mutation, which increases small intestine absorption of iron. **Secondary hemochromatosis** can follow transfusions for chronic anemias. Hemochromatosis affects 5 times as many males as females, and the disease is common in people of Northern European descent.

Hemochromatosis can cause micronodular cirrhosis and hepatocellular carcinoma (200 times the normal risk ratio); secondary diabetes mellitus; hyperpigmented skin ("bronzing"); congestive heart failure and cardiac arrhythmias; and hypogonadism. Diagnosis is established by demonstrating markedly elevated serum iron and ferritin or increased tissue iron levels (Prussian blue stain) on liver biopsy. Treatment is phlebotomy.

α-1-antitrypsin deficiency is an 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.

- α1-AT is produced by the *SERPINA1* gene (chromosome 14); >75 gene variants are described. Normal individuals are homozygous *PiMM*. Heterozygotes have intermediate levels of the enzyme. Homozygous *PiZZ* have severe reductions (10% of normal) in enzyme levels.
- α-1-antitrypsin deficiency affects the liver (micronodular cirrhosis and an increased risk of hepatocellular carcinoma) and lungs (panacinar emphysema). Microscopically, PAS positive, eosinophilic cytoplasmic globules are found in hepatocytes. Treatment includes smoking abstinence/cessation to prevent emphysema; liver transplantation is curative.

Reye syndrome is a rare, potentially fatal disease that occurs in young children with viral illness (varicella or influenza) treated with aspirin. The disease mechanism is unknown; mitochondrial injury and dysfunction play an important role. Reye causes hepatic fatty change (microvesicular steatosis) and cerebral edema/encephalopathy. There is complete recovery in 75% of patients, but those that do not recover may experience permanent neurologic deficits. Coma and death may result. Treatment is supportive.

Nonalcoholic fatty liver disease is a disease of lipids accumulating in hepatocytes that is not associated with heavy alcohol use. It occurs equally in men and women, and is strongly associated with obesity, hyperinsulinemia, insulin resistance, and type 2 diabetes mellitus.

The pathogenesis involves lipid accumulation in hepatocytes that can progress to steatohepatitis (NASH—nonalcoholic steatohepatitis) and finally cirrhosis. Nonalcoholic fatty liver disease is a diagnosis of exclusion.

Hemodynamic Liver Diseases

Budd-Chiari syndrome (hepatic vein thrombosis) refers to occlusion of the hepatic vein by a thrombus, often resulting in death. While a few cases are idiopathic, more often there is an underlying process predisposing for the thrombosis e.g., polycythemia vera, pregnancy, oral contraceptives, paroxysmal

NOTE

Protease-Antiprotease Imbalance

α-1-antitrypsin is an important protease inhibitor.

- Responsible for inhibiting neutrophil elastase
- Inhibits trypsin, chymotrypsin, and bacterial proteases

KP00710.indb 181 13/10/22 1:52 PM

nocturnal hemoglobinuria, or hepatocellular carcinoma. It presents with abdominal pain, hepatomegaly, ascites, jaundice, splenomegaly, and in some cases, death.

The initial diagnostic test is ultrasonography. Microscopically, the liver shows centrilobular congestion and necrosis. In the chronic form, fibrosis develops. Treatment includes supportive care and treatment of the underlying condition. Some patients require lifelong anticoagulation.

Chronic passive congestion of the liver refers to a "backup of blood" into the liver, usually due to right-sided heart failure. Grossly, the liver characteristically has a nutmeg pattern of alternating dark (congested central areas) and light (portal tract areas) liver parenchyma. Microscopically, the liver shows centrilobular congestion.

Complications include centrilobular necrosis, which is an ischemic necrosis of centrilobular hepatocytes. Long-standing congestion can lead to centrilobular fibrosis, which can eventually become cardiac cirrhosis (sclerosis).

LIVER TUMORS

Benign Tumors

Hemangioma is the most common primary tumor of the liver, mostly affecting women. It is a benign vascular tumor that typically forms a subcapsular, red, spongy mass. It is often asymptomatic and detected incidentally on CT or MRI. Resection is rarely indicated, and liver biopsy carries the risk of bleeding.

Hepatocellular adenoma (HCA) affects young women and is related to oral contraceptive use. Half of cases are asymptomatic. Symptoms include abdominal pain or spontaneous intraperitoneal hemorrhage (25% of cases). Due to the risk of transformation to HCC, resection is often recommended.

There are 3 subtypes of HCA:

- **H-HCA** is a solitary or multiple tan steatotic nodule with rare transformation into HCC
  - Mutation of hepatocyte nuclear factor 1
- **b-HCA** can resemble HCC histologically and transforms to HCC in some cases
  - Was named for the associated beta-catenin mutations
- **I-HCA** shows inflammatory infiltrates, sinusoidal dilatation, and thick-walled arteries
  - Acute inflammatory markers are elevated; malignant transformation occurs less frequently

Focal nodular hyperplasia is a subcapsular lesion often discovered incidentally by the radiologist. Laboratory values are generally normal. It is a nodular proliferation in response to a vascular anomaly. There is a central, stellate scar. Excision is generally not required due to the characteristic appearance on imaging.

KP00710.indb 182 13/10/22 1:52 PM

Malignant Tumors

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver in adults. The incidence is higher in Asia and Japan than in the United States. Risk factors include cirrhosis, hepatitis B and C viruses, alcohol, aflatoxin B1.

HCC has a tendency for hematogenous spread and invasion of portal and hepatic veins. The tumor marker is α-fetoprotein (AFP).

The fibrolamellar variant affects younger age, has fibrous bands, and has a better prognosis.

Angiosarcoma is a rare, fatal tumor associated with exposure to vinyl chloride.

Hepatoblastoma is the most common hepatic malignancy in infants and children. Lobectomy is the standard of care. Histology shows immature precursor cells.

Metastatic tumors are the most common tumors found within the liver. Common primary sites include the colon, breast, and lung. Metastatic tumors tend to occur as multiple well-circumscribed masses.

KP00710.indb 183 13/10/22 1:52 PM

Central Nervous System Pathology 20

LEARNING OBJECTIVES

- ❑ Solve problems concerning infections across the blood-brain barrier
- ❑ Answer questions about cerebrovascular disease, CNS trauma, and brain herniation
- ❑ Use knowledge of developmental abnormalities and perinatal brain injury
- ❑ Explain information related to demyelinating disorders
- ❑ Solve problems concerning degenerative and dementing disorders
- ❑ Describe CNS tumors

INFECTIONS

Meningitis

Meningitis is inflammation of the 2 inner meningeal layers, the pia and the arachnoid.

Acute aseptic (viral) meningitis is caused by leptomeningeal inflammation due to viruses (enterovirus most frequent); the inflammation produces a lymphocytic infiltration of leptomeninges and superficial cortex. Patients present with fever, signs of meningeal irritation, and depressed consciousness. Mortality is low. Viral meningitis carries a better prognosis than bacterial meningitis.

Acute viral meningitis is the most common neurologic symptom associated with primary HIV infection; it presents around the time of seroconversion with an acute confusional state. Symptoms resolve after 1 month with supportive care.

Acute purulent (bacterial) meningitis is a purulent leptomeningeal inflammation.

- *Streptococcus pneumoniae* is the most common cause of meningitis in infants, young children, and adults.
- Neonates are infected most frequently with group B streptococci, but *Escherichia coli* causes a greater number of fatalities.
- *Neisseria meningitidis* is seen in teens and young adults and is often associated with a maculopapular rash.
- The incidence of *Listeria monocytogenes* increases after age 50. This pathogen also tends to infect people with poor cell-mediated immunity.

The leptomeninges are opaque on gross examination. Microscopic examination shows neutrophilic infiltration of the leptomeninges, extending variably to cortex. Diffuse cerebral edema carries a risk of fatal herniations. The classic triad of bacterial meningitis is fever, nuchal rigidity, and altered mental status.

KP00710.indb 185 13/10/22 1:52 PM

Mycobacterial meningitis can be caused by *Mycobacterium tuberculosis* or atypical mycobacteria. It occurs in patients who have reactivation of latent infection and immunocompromised patients such as AIDS patients (*Mycobacterium avium-intracellulare*). Diagnosis requires microscopy/culture of large volumes of CSF. MRI is the imaging test of choice and shows basal meningeal enhancement and hydrocephalus. It usually involves the basal surface of the brain and may cause characteristic tuberculomas within the brain and dura mater. When infection spreads into the parenchyma, the condition is known as **meningoencephalitis**.

Fungal meningitis. *Candida*, *Aspergillus*, *Cryptococcus*, and *Mucor* species are the most frequent agents. *Aspergillus* and *Mucor* have a marked tropism for blood vessels, which leads to vasculitis, rupture of blood vessels, and hemorrhage. *Cryptococcus* causes diffuse meningoencephalitis, which leads to invasion of the brain through the Virchow-Robin space (a continuation of the subarachnoid space around blood vessels entering the neuropil) and soap bubble lesions.

Table 20-1. 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 or decreased	Normal or slightly increased (>50)	Normal or slightly elevated
Granulomatous (mycobacterial/fungal)	100–1,000 most lymphocytes	Decreased (<45)	Increased (>50)	Moderately elevated

Encephalitis

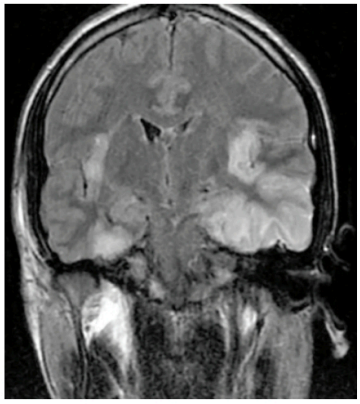
Encephalitis is inflammation of the brain.

The **viral encephalitides** have common features of perivascular cuffs, microglial nodules, neuron loss, and neuronophagia. Clinical manifestations are variable and can include mental status change, fever, and headache, often progressing to coma.

- Arthropod-borne forms can be due to St. Louis, Eastern and Western equine, and Venezuelan encephalitides.
- Herpes simplex type 1 produces a characteristic **hemorrhagic necrosis of temporal lobes**. Cowdry type A bodies are intranuclear inclusions seen in neurons and glial cells.
- **Rabies** has characteristic Negri bodies in the cytoplasm of hippocampal and Purkinje cells.
- **HIV encephalopathy** shows histopathology of microglial nodules and diagnostic multinucleated giant cells. Spinal involvement leads to vacuolar myelopathy, which is similar to vitamin B12 deficiency–associated subacute combined degeneration. **HIV-associated neurocognitive disorder (HAND)** presents as cognitive decline with behavioral changes and motor symptoms. Diagnosis is based on clinical features and the exclusion of other etiologies.

KP00710.indb 186 13/10/22 1:52 PM

- **Progressive multifocal leukoencephalopathy (PML)** is caused by JC polyomavirus. It occurs in immunocompromised patients and patients taking immunomodulatory therapies. Neurologic symptoms are varied and include impairment of cognition and motor function. There is no specific antiviral drug, and mortality is high. Tissue sections show areas of demyelination and enlarged oligodendrocytes.
- **Subacute sclerosing panencephalitis** is a rare complication of measles (rubeola) virus infection. Persistent immune-resistant measles virus infection causes slow-virus encephalitis. The typical scenario is a child who had measles age <2 and then 6–15 years later develops progressive mental deterioration with seizures. Subacute sclerosing panencephalitis may be fatal in 1–2 years once it develops.



© Paul J. Shogan, National Capital Consortium.
Used with permission.

Figure 20-1. MRI Showing Edema of Bilateral Temporal Lobes, Related to Herpes Simplex Encephalitis

Cerebral Abscess

Cerebral abscess can occur as a result of either hematogenous dissemination or direct spread from contiguous foci. **Systemic predisposing conditions** include acute bacterial endocarditis, cyanotic heart disease (right-to-left shunt), and chronic pulmonary abscesses. **Local predisposing conditions** include mastoiditis, paranasal sinusitis, acute otitis, open fracture, and previous neurosurgery. CT/MRI scan characteristically shows a ring-enhancing lesion. Clinical manifestations include signs of increased intracranial pressure (headache, vomiting, and papill-edema). Focal neurological deficits vary depending on the site of lesion.

Toxoplasmosis is caused by the protozoan parasite *Toxoplasma gondii*. It is common in AIDS patients, and the condition causes **cerebral abscess** with central necrosis and chronic inflammation. MRI/CT scan shows a characteristic ring-enhancing lesion.

KP00710.indb 187 13/10/22 1:52 PM

Prion Infections

Creutzfeldt-Jakob disease (CJD) is the most common human transmissible spongiform encephalopathy due to a prion (a protein with the capacity to be an infectious agent) that can change the conformation of normal prion protein(s). This can lead to rapidly progressive dementia, memory loss, personality changes, and hallucinations.

- The **prion protein** (PrP) is a 30-kD protein normally present in neurons. It is encoded by a single-exon gene on chromosome 20. Its normal conformation is an α-helix: **PrP^{c}**. In disease states, PrPc changes to a β-pleated sheet conformation: **PrP^{sc}**. A low rate of spontaneous change results in sporadic cases of CJD. Mutations of PrP result in hereditary cases of CJD. PrP^{sc} facilitates conformational change of other PrP^{c} molecules into PrP^{sc}.
- PrP^{sc} is responsible for **cerebral pathologic changes**, characteristically resulting in spongiform change. This change is a fine vacuolization of the neuropil in the gray matter (especially cortex), which is due to large membrane-bound vacuoles within neuronal processes. There is an associated neuronal loss and astrogliosis. Kuru plaques are deposits of amyloid composed of altered PrP protein.
- About 85% of Creutzfeld-Jakob cases are sporadic, and 15% are familial. Affected patients are typically middle-aged to elderly patients who develop rapidly progressive dementia and memory loss with startle myoclonus or other involuntary movements. Typical EEG changes may be diagnostic. Death occurs within 6–12 months.

Variant Creutzfeldt-Jacob disease occurs in younger patients and results from exposure to bovine spongiform encephalopathy.

Table 20-2. Prion Diseases

Disease	Infectious Agent	Host	Comments
Kuru	Prion	Human	Subacute spongiform encephalopathy (SSE); Fore Tribe in New Guinea; consuming infected brains
Creutzfeldt-Jakob	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

KP00710.indb 188 13/10/22 1:52 PM

CEREBROVASCULAR DISEASE

General Concepts

Cerebrovascular disease is the third most frequent cause of death in industrialized countries; it is the leading cause of serious disability in the United States. Risk factors are similar to CAD.

- **Global cerebral ischemia** (diffuse ischemic encephalopathy) is caused by a fall in blood flow to the brain, due to processes such as shock, cardiac arrest, and hypotensive episodes. While the entire brain can be damaged, some regions have selective vulnerability, including Purkinje neurons, hippocampus, CA1 (Sommer sector), and pyramidal neurons of cortex. The pathology often includes infarcts in watershed areas, cortical laminar necrosis, and diffuse ischemic necrosis of neocortex. Global cerebral ischemia may lead to brain death.
- **Transient ischemic attack** (TIA) is due to small platelet thrombi or atheroemboli and is characteristically reversible, with symptoms lasting less <24 hours.
- **Stroke** can be due to infarction (85% of all stroke cases) or hemorrhage (15% of all stroke cases).

BRIDGE TO ANATOMY

The brain is highly dependent on a constant supply of oxygen and glucose from the cerebral arteries, which have collateral blood flow at the circle of Willis.

CLINICAL CORRELATE

Strokes frequently occur in the middle cerebral artery territory.

Infarction

Infarction causes 85% of all stroke cases.

- Types:
  - Can be due to **thrombotic occlusion** in the setting of atherosclerosis of the cerebral arteries; the thrombotic infarction is characteristically an anemic (white) infarct.
  - Can be due to **embolic occlusion**, most often due to thromboemboli from cardiac chambers and less frequently due to atheroemboli. Embolic infarction produces a hemorrhagic infarct. Small-vessel disease is a cause of small, lacunar infarcts or lacunae, and it is related to hypertension, resulting in hyaline arteriolosclerosis.
  - **Atherosclerotic aneurysms** are fusiform, involve the basilar artery, and present with infarction.
- **Morphologic features.** The pathology of infarction is illustrated in the following table. Clinical manifestations depend on the affected arterial distribution.

KP00710.indb 189 13/10/22 1:52 PM

Table 20-3. 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
Years	Old cyst surrounded by gliotic scar	Astrogliosis surrounding a cyst

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

Hemorrhage

Hemorrhage causes 15% of strokes.

- **Intracerebral (intraparenchymal) hemorrhage** causes severe headache, frequent nausea/vomiting, steady progression of symptoms over 15–20 minutes, and coma. It is most frequently due to hypertension, and in those instances, it most commonly involves the basal ganglia, cerebellum, pons, and centrum semiovale. Other causes include vascular malformations (especially arteriovenous malformations), cerebral amyloid angiopathy, neoplasms, vasculitides, abnormal hemostasis, hematological malignancies, infections, and diabetes mellitus.
- **Subarachnoid hemorrhage** is most frequently caused by ruptured berry aneurysm. Less frequent causes include extension of an intracerebral or subdural hematoma, vascular malformations, trauma, abnormal hemostasis, and tumors. Subarachnoid hemorrhage causes sudden headache ("worst headache of my life"), nuchal rigidity, neurological deficits on one side, and stupor.
  - **Berry aneurysms** are thin-walled saccular outpouchings, consisting of intima and adventitia only. They are the most frequent cause of subarachnoid hemorrhage. The most frequent sites are the anterior circle of Willis at branching points. Rupture is precipitated by a sudden increase in blood pressure; the prognosis after rupture is that one-third die, one-third recover, and one-third rebleed. The pathogenesis involves a congenital focal weakness of vessel media that is not identifiable at birth. Associated disorders include Marfan syndrome, Ehlers-Danlos type 4, and adult polycystic kidney disease. Hypertension and cigarette smoking predispose to formation.

KP00710.indb 190 13/10/22 1:52 PM



© Charles Gould, National Capital Consortium.
Used with permission.

Figure 20-2. Large Berry Aneurysm Seen on Angiography of Circle of Willis

CNS TRAUMA AND HERNIATIONS

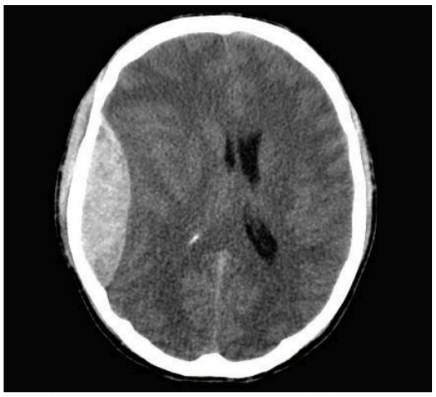
Cranial Cavity and Brain

Concussion is mild traumatic brain injury with a transient loss of brain function. The trauma is commonly due to a change in the momentum of the head (impact against a rigid surface). Concussion causes loss of consciousness and reflexes, temporary respiratory arrest, and amnesia for the event. The pathogenesis is uncertain. Parenchymal injuries may or may not be evident at autopsy.

Contusions are bruises of the brain tissue. Common sites of injury include crests of orbital gyri in frontal and temporal poles, in addition to *coup* (site of injury) and *contrecoup* (site diametrically opposite) injuries. Coup and contrecoup develop when the head is mobile at the time of impact.

- **Acute contusion** is characterized by hemorrhage of brain tissue in a wedge-shaped area.
- **Subacute contusion** shows necrosis and liquefaction of brain.
- **Remote contusion** causes a depressed area of cortex with yellow discoloration ("*plaque jaune*").

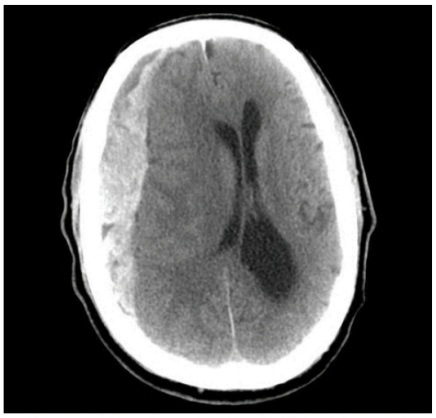
KP00710.indb 191 13/10/22 1:52 PM



© Andrew Mullins, National Naval Medical Center.
Used with permission.

Figure 20-3. Epidural Hematoma

Epidural hematoma (*See* Anatomy Lecture Notes.)



© Brendan T. Doherty, National Capital Consortium.
Used with permission.

Figure 20-4. Subdural Hematoma

Subdural hematoma is caused by the rupture of bridging veins (from the cerebral convexities to the sagittal sinus); it is usually traumatic in older individuals. Predisposing conditions include brain atrophy (due simply to aging) and abnormal hemostasis. Symptoms include headache, drowsiness, focal neurological deficits, and sometimes dementia. It recurs frequently.

Diffuse axonal injury refers to damage to axons at nodes of Ranvier with impairment of axoplasmic flow. It causes coma after trauma without evidence of direct parenchymal injuries. There is a poor prognosis, related to duration of coma. The injury to the white matter is due to acceleration/deceleration forces with shearing of axons.

The histopathology shows axonal swellings appreciable in the white matter. It is diffuse, but with a predilection for the corpus callosum, periventricular white matter, and hippocampus, as well as cerebral and cerebellar peduncles.

KP00710.indb 192 13/10/22 1:52 PM

Spinal cord injuries are usually traumatic, due to vertebral displacement. Symptomatology depends on the interruption of ascending and descending tracts.

- Lesions to thoracic segments or below cause paraplegia.
- Lesions to cervical segments cause tetraplegia.
- Lesions above C4 cause respiratory arrest due to paralysis of the diaphragm.

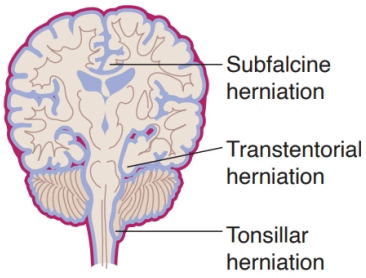
Chronic traumatic encephalopathy is a neurodegenerative disorder that occurs years or decades after a sports career with repetitive brain trauma. Neuropathological changes include neurofibrillary tangles, cerebellar atrophy and gliosis, hypopigmentation of the substantia nigra, and cavum septum pellucidum.

Cerebral Herniations

Subfalcine (cingulate gyrus) herniation occurs when the cingulate gyrus is displaced underneath the falx to the opposite side. Compression of the anterior cerebral artery can occur.

Transtentorial (uncal) herniation occurs when the uncus of the temporal lobe is displaced over the free edge of the tentorium. Clinical features include compression of the third nerve, ipsilateral pupillary dilatation, and infarction of the tissue supplied by the posterior cerebral artery. Advanced stages of transtentorial herniation can cause Duret hemorrhages within the central pons and midbrain.

Cerebellar tonsillar herniation occurs when there is displacement of cerebellar tonsils through the foramen magnum. Compression of the medulla may lead to cardiorespiratory arrest.



Cerebral Herniations

DEVELOPMENTAL ABNORMALITIES AND PERINATAL BRAIN INJURY

Neural tube defects are the most common developmental CNS abnormalities. They result from defective closure of the neural tube, and they tend to occur at the 2 extremities of the neuraxis. Folate deficiency is involved in the pathogenesis.

- **Anencephaly** is the absence of cranial vault. It is incompatible with life; babies die soon after birth.
- **Neural tube defects of the spinal cord** may take a variety of forms. Significant defects lead to paraplegia and urinary incontinence from birth.
  - **Spina bifida occulta** is a bony defect of the vertebral arch.
  - **Meningocele** is a bony defect with outpouching of meninges.
  - **Meningomyelocele** is a defective formation of the bony arch with cystic outpouching of meninges, spinal cord, and spinal roots.
  - **Myelocele** is a defective bony arch with complete exposure of the spinal cord.

20_Preclinical_Pathology_Ch20.indd 193 26/09/22 5:16 PM

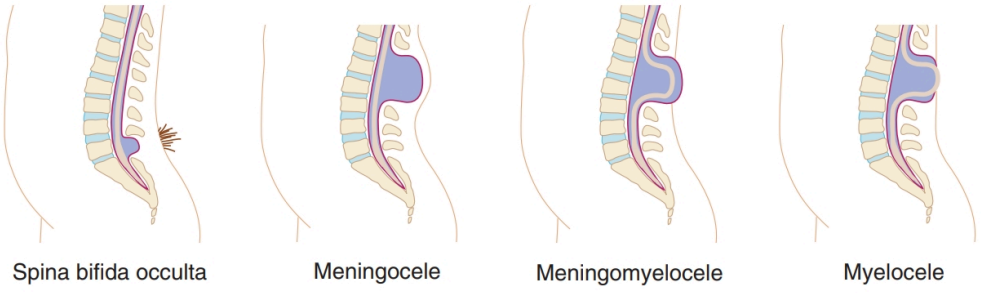
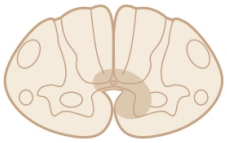


Figure 20-5. Neural Tube Defects of the Spinal Cord



Syringomyelia

Syringomyelia is an ependymal-lined, CSF-filled channel parallel to and connected with the central canal in the spinal cord. (*Hydromyelia* means the central canal is dilated with CSF.) About 90% of cases are associated with Arnold-Chiari type 1; the remaining 10% are posttraumatic or associated with intraspinal tumors. *Syrinx* (the cyst) enlarges progressively and destroys the spinal parenchyma. Symptoms include paralysis and loss of sensory functions. (*See* Anatomy Lecture Notes.)

Perinatal brain injury is injury to the brain during prenatal or immediately postnatal period. This is the most common cause of cerebral palsy, and it occurs most frequently in premature babies.

- **Germinal matrix hemorrhage** is hemorrhage localized in the germinal matrix due to its fragile vessels.
- **Periventricular leukomalacia** causes infarcts in watershed areas (periventricular white matter in the fetus).
- **Multicystic encephalopathy** refers to multiple brain infarcts occurring early in gestation.

Fetal alcohol syndrome is characterized by structural abnormalities (microcephaly, agenesis of the corpus callosum, cerebellar hypoplasia), functional impairments including learning disabilities, and neurological impairments including epilepsy.

Cerebellar Malformations

Cerebellar malformations have chromosomal, single-gene and complex inheritance. *FOXCI* deletions and duplications are associated with cerebellar vermis hypoplasia, mega-cisterna magna and Dandy-Walker malformation, the most common human cerebellar malformation.



Arnold-Chiari Malformation

- **Dandy-Walker malformation** is a non-communicating hydrocephalus with dilation of the fourth ventricle and hypoplasia of the cerebellar vermis.
- **Arnold-Chiari malformations**
  - **Type 1** (common) is a downward displacement of cerebellar tonsils and the medulla through the foramen magnum. This lesion is mostly asymptomatic. Syringomyelia is often seen.
  - **Type 2** is due to a faulty craniospinal junction, resulting in a small posterior fossa, with abnormal development of the cerebellar vermis and medulla leading to downward displacement. It is mostly symptomatic because of compression of the fourth ventricle with obstructive hydrocephalus. Lumbar meningomyelocele (a form of spina bifida) is a classic feature.

20_Preclinical_Pathology_Ch20.indd 194 26/09/22 5:16 PM

DEMYELINATING DISORDERS

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic relapsing-remitting disorder of probable autoimmune origin characterized by recurrent episodes of demyelination in the brain (including optic nerves) and spinal cord; it results in progressive neurological deficits.

- The overall prevalence of MS is 1/1,000, with higher prevalence in northern countries.
- Those who emigrate age >15 from areas of high prevalence to areas of low prevalence maintain their original risk.
- Women have 2× the risk of men.

Genetic and environmental factors contribute to the pathogenesis. HLA DR 15 confers genetic susceptibility. Environmental factors include viral infection, vitamin D deficiency, and smoking.

- **Acute lesions** on gross examination show well-circumscribed gray lesions (plaques), with bilateral distribution that is frequently periventricular. Histology shows chronic inflammation with phagocytosis of myelin by macrophages; axons are initially preserved.
- **Chronic lesions** have no inflammation, with axons showing remyelination. Remyelination is defective because myelin sheaths are thinner with shorter internodes.

During an acute attack, nerve conduction is entirely blocked, leading to acute neurological deficits. Chronic plaques are associated with slower nerve conduction, allowing for partial recovery. Recurrent attacks cause progressive neurological deterioration.

Clinical onset is typically in decades 3–4. About 85% of cases show a relapsing-remitting course; a minority of cases show primary progressive (slow deterioration) or progressive-relapsing (slow progression punctuated by acute exacerbations) course. Recovery from each episode of demyelination occurs in weeks or months.

Early symptoms include sensory problems, paresis, and visual dysfunction. As the disease progresses, other symptoms include fatigue, bladder dysfunction, spasticity and ataxia. Neuropsychological symptoms affect 40–60% of patients.

Diagnosis of MS requires the demonstration of the dissemination of disease in space and time. Clinical history, MRI, CSF studies and electrophysiological studies are important. Treatment is immunomodulatory drugs (e.g., interferon beta), immunosuppressive therapies (e.g., mitoxantrone), and monoclonal antibodies (e.g., natalizumab). The latter is used as monotherapy in cases of relapsing MS; its use is linked to PML.

Central Pontine Myelinolysis

Central pontine myelinolysis (CPM) is a focal demyelination of the central area of the basis pontis. It probably derives from rapid correction of hyponatremia, and the condition is very often fatal. Patients at risk include the severely malnourished and alcoholics with liver disease.

KP00710.indb 195 13/10/22 1:52 PM

DEGENERATIVE AND DEMENTING DISORDERS

Parkinson Disease

Parkinson disease (PD) is a progressive neurodegenerative disease that involves genetic and environmental factors. The *SNCA* gene (alpha-synuclein) has been identified as a risk factor, and gene mutations and multiplications are associated with familial PD, but the majority of cases are sporadic. PD is due to loss of dopaminergic neurons in the substantia nigra, leading to tremor, rigidity, and akinesia.

- **Parkinson disease** is the idiopathic form.
- **Parkinson syndrome** is secondary to known injuries to the substantia nigra (e.g., infection, vascular condition, toxic insult).

Parkinson disease is common, affecting 2% of the population. Clinical onset is typically in decades 5–8. Loss of dopaminergic neurons is still unexplained, though theories emphasize oxidative stress. Pesticides and meperidine have been associated with increased risk, while smoking and caffeine are protective.

On gross examination there is pallor of the substantia nigra. Histology shows loss of pigmented (dopaminergic) neurons in the substantia nigra. Residual neurons show Lewy bodies, which are intracytoplasmic round eosinophilic inclusions that contain α-synuclein. Electron microscopy shows filaments most likely of cytoskeletal origin. There is also a secondary degeneration of dopaminergic axons in the striatum.

Loss of the extrapyramidal nigrostriatal pathway leads to inhibition of movement of proximal muscles and disruption of fine regulation of distal muscles. Involvement of the amygdala, cingulate gyrus, and higher cortical regions causes dementia and psychosis.

About 60% of patients experience dementia 12 years after diagnosis; 50% also experience depression and psychosis. Those treated with medication (combination carbidopa and levodopa) and surgery (deep brain stimulation) will become refractory to therapy.

A clinical diagnosis is difficult to make early in disease because symptoms overlap with other conditions. Early symptoms include hyposmia, constipation, and fatigue. Key features are bradykinesia, rigidity, tremor, and postural instability. Early in the disease course, a response to levodopa can help confirm the diagnosis. Imaging studies are not useful in most cases.

Huntington Disease

Huntington disease (HD) is an autosomal dominant disorder. It is characterized pathologically by the degeneration of GABAergic neurons of the caudate nucleus and clinically by involuntary movements, cognitive decline, and behavioral changes.

- Affects those of northwestern European descent
- Has an incidence in high-prevalence regions of 1/12,000–20,000
- Gene (*HTT*), located on chromosome 4, codes for a protein called huntingtin
- Mutations due to expansion of unstable cytosine-adenine-guanine (CAG) repeats
- Shows features of anticipation and genomic imprinting

KP00710.indb 196 13/10/22 1:52 PM

The pathophysiology is that loss of caudate nucleus GABAergic neurons removes inhibitory influences on extrapyramidal circuits, thus leading to chorea.

Clinical onset is typically in decades 3–5. The chorea is characterized by sudden, unexpected, and purposeless contractions of proximal muscles while awake. Psychiatric symptoms may predate motor symptoms. Disease progression leads to dependency and death.

Gross examination shows atrophy of the caudate nucleus with secondary ventricular dilatation. Histology shows loss of small neurons in the caudate nucleus followed by loss of the larger neurons.

A definitive diagnosis can be based on clinical symptoms with an affected parent. Otherwise, DNA determination is the gold standard. Prenatal diagnosis and preimplantation diagnostics are available. Treatment is medical therapeutics for chorea (dopamine receptor blocking or depleting agents).

Alzheimer Disease

Alzheimer disease (AD) causes 60% of all cases of dementia. It is the most common cause of dementia in people age >65.

- Incidence is 2% at age 65 and doubles every 5 years
- Risk factors include aging and significant head trauma
  - Aluminum is an epiphenomenon, not a risk factor
- Protective factors include high level of education and smoking

About 5–10% of AD cases are hereditary, early onset, and transmitted as an autosomal dominant trait. There are 3 genes that cause autosomal dominant AD:

- *APP* (amyloid precursor protein)
- Presenilin 1 and 2 (*PSEN1* and *2*)

Carriers of *APP* and *PSEN1* mutations develop early-onset AD. Other AD susceptibility genes have been identified. *APOE* is the largest effect locus for late-onset AD.

Table 20-4. Genetics of AD

Genes causing autosomal dominant AD	• *APP* • *PSEN1* • *PSEN2* All can cause early onset disease but *PSEN2* is associated with a broad range of onset ages.
Susceptibility genes	• Apolipoprotein E gene (*APOE*) – ε2 allele: associated with decreased risk – ε3 allele: neutral – ε4 allele: high-risk • *SORL1*

KP00710.indb 197 13/10/22 1:52 PM

AD is characterized by amyloid-β deposition, neurofibrillary tangle formation, and neuronal degeneration.

- **Abnormal proteins**. Aβ amyloid is a 42-residue peptide derived from a normal transmembrane protein, the amyloid precursor protein (APP). There is also an abnormal tau (a microtubule-associated protein).
- **Neuritic plaques** have a core of Aβ amyloid and are surrounded by abnormal neurites.
- **Neurofibrillary tangles** are intraneuronal aggregates of insoluble cytoskeletal elements, mainly composed of abnormally phosphorylated tau forming paired helical filaments.
- **Cerebral amyloid angiopathy** is accumulation of Aβ amyloid within the media of small and medium-size intracortical and leptomeningeal arteries; it may occur by itself and cause intracerebral hemorrhage.
- Additional changes include **granulovacuolar degeneration** and **Hirano bodies,** which develop in the hippocampus and are less significant diagnostically.

Affected areas are involved in learning and memory. Lesions involve the neocortex, hippocampus, and several subcortical nuclei including forebrain cholinergic nuclei (i.e., basal nucleus of Meynert). The earliest and most severely affected are the hippocampus and temporal lobe. Small numbers of neuritic plaques and neurofibrillary tangles also form in intellectually normal aging persons.

Macroscopic changes include atrophy of affected regions, producing brains that are smaller (atrophic), with thinner gyri and wider sulci. Hippocampi and temporal lobes are markedly atrophic.

Clinical manifestations have insidious onset, typically beginning in decades 7–8. They include progressive memory impairment, especially related to recent events; alterations in mood and behavior; progressive disorientation; and aphasia (loss of language skills) and apraxia (loss of learned motor skills). Within 5–10 years patients become mute and bedridden.

No effective **treatment** is available for AD, but there is mild improvement with inhibitors of acetylcholinesterase (e.g., tacrine).

Lewy Body Dementia

Lewy body dementia is a progressive brain disease associated with the formation of Lewy bodies in neurons involving neocortex and subcortical nuclei. The etiopathogenesis is obscure, with no known risk factors; it is the second leading cause of degenerative dementia in the elderly.

The histopathological hallmark is the Lewy body. Neuron loss accompanies Lewy body formation. Sites involved include the neocortex (especially the limbic system and cingulate gyrus), and subcortical nuclei, including basal nucleus of Meynert, amygdala, and substantia nigra.

The involvement of the neocortex and substantia nigra is responsible for cognitive deterioration and parkinsonism. Clinical manifestations include memory loss, parkinsonism, and visual hallucinations. There is a possible treatment benefit from cholinesterase inhibitors.

KP00710.indb 198 13/10/22 1:52 PM

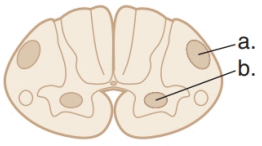
Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is the most common adult-onset, progressive motor neuron disease.

The clinical diagnosis is supported by a biopsy of muscles. The etiopathogenesis is obscure; 5–10% of cases are hereditary, and a small number are caused by mutation of the gene encoding zinc-copper superoxide dismutase on chromosome 21.

- **Loss of upper motor neurons** produces hyperreflexia and spasticity. In some cases, involvement of cranial nerve nuclei also occurs.
- **Loss of lower motor neurons** produces weakness, atrophy, and fasciculations.

There is no cure for ALS. Ultimately, involvement of respiratory muscles will lead to death.



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

Friedreich Ataxia

Friedreich ataxia is an autosomal recessive disorder that leads to degeneration of nerve tissue in the spinal cord, especially those sensory neurons connected to the cerebellum affecting muscle movement of the arms and legs. Mean onset is early childhood (age 10-15).

Friedreich ataxia is caused by the expansion of an unstable triplet nucleotide repeat (GAA repeats in the first intron) in the frataxin gene on chromosome 9. The frataxin protein is essential for mitochondrial function by helping in mitochondrial iron regulation; in the absence of frataxin, mitochondrial iron builds up, leading to free radical damage and mitochondrial dysfunction.

Clinical manifestations include gait ataxia, dysarthria, hand clumsiness, loss of sense of position, impaired vibratory sensation, and loss of tendon reflexes. There is an increased incidence of heart disorders and diabetes. Patients become wheelchair-bound by age 30–45.

METABOLIC AND TOXIC DISORDERS

Metabolic Disorders

Wilson disease (*See* liver pathology chapter.)

Acute intermittent porphyria is an autosomal dominant defect in porphyrin metabolism with deficient uroporphyrinogen synthase. Both porphobilinogen and aminolevulinic acid are increased. Urine is initially colorless but on exposure to light turns dark red. Patients may develop recurrent severe abdominal pain, psychosis, neuropathy, and dementia.

Vitamin B12 deficiency causes megaloblastic anemia, and demyelination of the spinal cord posterior columns and lateral corticospinal tracts (subacute combined degeneration of the spinal tract). It also causes dementia and peripheral neuropathy.

KP00710.indb 199 13/10/22 1:52 PM

Toxic Disorders

Alcohol abuse causes generalized cortical and cerebellar atrophy, as well as Wernicke-Korsakoff syndrome. The neurologic disease is usually related to thiamine deficiency. There can be hemorrhages in the mamillary bodies and the walls of the third and fourth ventricles. Neuronal loss and gliosis may be prominent.

- **Wernicke encephalopathy** has reversible confusion, ataxia, and nystagmus.
- **Korsakoff psychosis** is more severe and has irreversible anterograde and retrograde amnesia.
- **Central pontine myelinolysis** may cause death.

Other neurotoxins include metals, chemicals, and carbon dioxide.

CNS TUMORS

General Concepts

CNS tumors account for 20% of all pediatric tumors. Most pediatric tumors mainly arise in the posterior fossa, while adult tumors arise in the supratentorial region. Factors determining prognosis and response to therapy include the following:

- Age
- Tumor location
- Grade
- Extent of surgical resection
- Molecular subgroupings

The World Health Organization (WHO) grading system assigns grades I–IV, with grade IV tumors the most aggressive. While grade IV glioblastoma patients usually succumb to disease within a year, other patients with treatable grade IV tumors may survive 5 years. Metastasis of CNS tumors is rare.

Table 20-5. Primary Versus Metastatic (CNS) Tumors

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

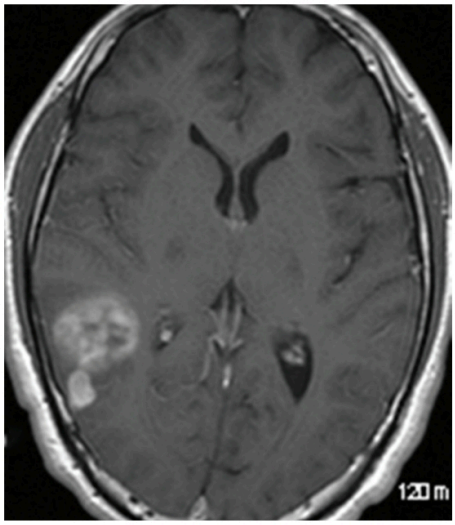
KP00710.indb 200 13/10/22 1:52 PM

Tumors of Neuroepithelial Tissue

Tumors of neuroepithelial tissue are categorized as **astrocytic** tumors, **oligodendroglial** tumors, **ependymal** tumors, and **embryonal** tumors (further broken down as **medulloblastoma** or **CNS primitive neuroectodermal tumor**).

Astrocytoma originates from astrocytes and exhibits fibrillary background, immunoreactivity for glial fibrillary acidic protein (GFAP), and diffuse (ill-demarcated) pattern of growth.

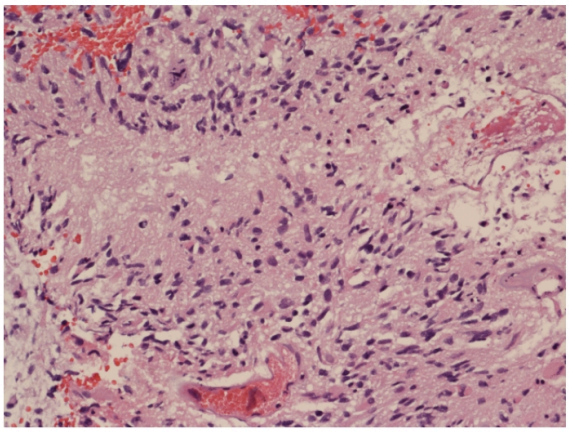
- **Pilocytic astrocytoma** is a well-differentiated, benign astrocytic tumor that arises throughout the neuraxis; it is common in children and young adults. It is the most common benign CNS tumor in children.
- Sites of involvement include posterior fossa (cerebellum) and diencephalon.
  - Radiographically, most show cystic lesion with a mural nodule
  - Histology shows spindly neoplastic astrocytes with long bipolar processes
  - Rosenthal fibers are thick, corkscrew-like eosinophilic structures that derive from hypertrophic processes of astrocytes
  - Posterior fossa tumors have favorable prognosis
  - Activating mutations in *BRAF* are common
- **Fibrillary (diffuse) astrocytoma** is a low-grade tumor that arises in the cerebral hemisphere of young to middle-aged adults and the brainstem of children.
  - IDH1 (immunostain) is positive.
- **Anaplastic astrocytoma** is cellular, pleomorphic, and mitotically active.
- **Glioblastoma** is the most common CNS primary malignancy in adults.
  - Histology shows necrosis and/or vascular proliferation in addition to features seen in anaplastic astrocytoma.



© Steven J. Goldstein, University of Kentucky.
Used with permission.

Figure 20-6. White Mass in the Cerebral Cortex Showing a Glioblastoma Multiforme

KP00710.indb 201 13/10/22 1:52 PM



© Gregg Barré, MD Used with permission.

Figure 20-7. Glioblastoma with Necrosis

NOTE

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

The prognosis of astrocytomas varies.

- Well-differentiated astrocytomas grow slowly; affect younger patients.
- Anaplastic astrocytomas and glioblastoma are aggressive; affect older patients; median survival for glioblastoma is 15 months.

Oligodendroglioma occurs more often in adults than in children. Its cortical location may cause seizures. Histologically, perinuclear halos are a fixation artifact that is not seen on frozen section. This tumor is slow-growing. Tumors with deletions of 1p and 19q respond well to therapy.

Ependymoma is typically located in the fourth ventricle in children, where it presents with obstructive hydrocephalus. In adults the spinal cord is the most common site. Pseudorosettes are a helpful diagnostic feature on microscopic study. Multifocality in the spinal cord is associated with NF2. The prognosis depends on tumor location and adequacy of resection.

Embryonal (primitive) tumors are a group of small round cell tumors that occur predominantly in children. In the cerebellum, they are called medulloblastoma.

- Medulloblastoma is the most common malignant brain tumor in children.
- Molecular subgroupings are proving useful for prognosis; Wnt subgroup has the best prognosis.

Tumors of Cranial and Paraspinal Nerves

Schwannoma originates from Schwann cells of cranial or spinal nerves. The most frequent location is on CN 8 at the cerebellopontine angle (CPA). Schwannoma manifests characteristically with unilateral loss of hearing and tinnitus. The prognosis is good after surgical resection.

NOTE

Bilateral acoustic schwannoma is pathognomonic of neurofibromatosis type 2.

- Has spindly cells arranged in hypercellular Antoni A areas; alternating hypocellular Antoni B areas; and *Verocay bodies*, parallel rows of neoplastic Schwann cells.
- Neoplastic cells are immunoreactive for S-100.

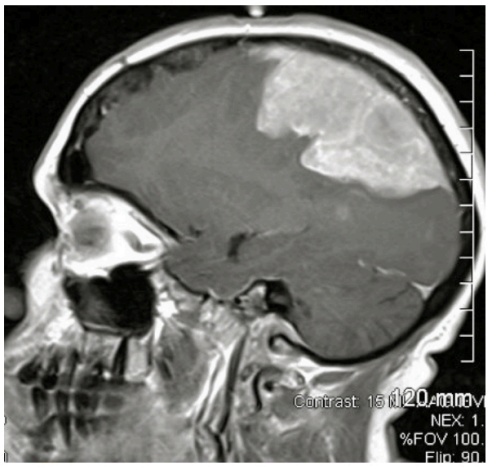
KP00710.indb 202 13/10/22 1:52 PM

Tumors of the Meninges

Meningioma is a tumor that originates from meningothelial cells of the arachnoid. It is common in adults (women > men) and rare in children. It is a dura-based mass that can recur if the brain has been invaded, but invasion is unusual. It has varied clinical features but commonly presents with headache, seizures, and neurological deficits.

- Histology shows cellular whorls and psammoma bodies. Many patterns are seen; the syncytial pattern is common.
- Abnormalities of chromosome 22 are sometimes present.
- Multiple meningiomas occur in NF2 patients.

The prognosis of meningioma is good, though tumors in some locations may not be amenable to complete resection.



© Steven J. Golstein, University of Kentucky.
Used with permission.

Figure 20-8. Large Meningioma Pushing into the Cerebral Cortex.

Note the thin dark shadow around the lesion, which occurs because the tumor is not actually invading the brain.

Tumors of the Sellar Region

Craniopharyngioma arises from rests of odontogenic epithelium within the suprasellar/diencephalic region. It most commonly affects children and young adults. The most common presenting symptoms are headache, hypopituitarism, and visual field disturbances.

- Contains deposits of calcium, evident on x-ray
- Histology shows squamous cells and resembles **adamantinoma**, a bone tumor of unknown histological origin that is the most common tumor of the tooth
- Is benign but tends to recur after resection
- Beta-catenin (*CTNNB1*) gene mutations have been reported

KP00710.indb 203 13/10/22 1:52 PM

Other Neoplasms

- **Lymphomas** are the most common CNS tumors in the immunosuppressed. Primary CNS lymphomas may be multiple, unlike other histologic types. They do not respond well to chemotherapy.
- **Germ cell tumors** are more common in children than adults. The germinoma is the most common histologic type. It resembles the seminoma of the testis and the dysgerminoma of the ovary; the cells are large with a prominent nucleolus. These tumors are radiosensitive.

Metastatic Tumors

About 25–50% of all CNS tumors are metastatic tumors from sources outside the CNS. **Carcinomas** are the most common.

KP00710.indb 204 13/10/22 1:52 PM

Hematopoietic Pathology: White Blood Cell Disorders & Lymphoid and Myeloid Neoplasms

21

LEARNING OBJECTIVES

- ❑ Explain information related to reactive changes in the leukocyte count
- ❑ Describe lymphoid, mature B-cell, peripheral T-cell, and natural killer cell neoplasms
- ❑ Solve problems concerning Hodgkin lymphoma, acute leukemias, B and T lymphoblastic lymphoma/leukemia, and myeloid neoplasms
- ❑ Solve problems concerning diseases of histiocytes and dendritic cells
- ❑ Demonstrate understanding of mast cell diseases
- ❑ Answer questions about diseases of the spleen and thymus

LEUKOCYTE COUNT

Leukocytosis

Leukocytosis is characterized by an elevated WBC count. It has the following features:

- **Increased neutrophils** (neutrophilia)
  - Increased bone marrow production is seen with acute inflammation associated with pyogenic bacterial infection or tissue necrosis
  - Increased release from bone marrow storage pool may be caused by corticosteroids, stress, or endotoxin
  - Increased bands ("left shift") noted in peripheral circulation
  - Reactive changes include Döhle bodies (aggregates of rough endoplasmic reticulum), toxic granulations (prominent granules), and cytoplasmic vacuoles of neutrophils
- **Increased eosinophils** (eosinophilia) occurs with allergies and asthma (type I hypersensitivity reaction), parasites, drugs (especially in hospitals), and certain skin diseases and cancers (adenocarcinomas, Hodgkin disease).
- **Increased monocytes** (monocytosis) occurs with certain chronic diseases such as some collagen vascular diseases and inflammatory bowel disease, and with certain infections, especially TB.

KP00710.indb 205 13/10/22 1:52 PM

- **Increased lymphocytes** (lymphocytosis) occurs with acute (viral) diseases and chronic inflammatory processes.
  - **Infectious mononucleosis**, an acute, self-limited disease, which usually resolves in 4–6 weeks, is an example of a viral disease that causes lymphocytosis. The most common cause is Epstein-Barr virus (a herpesvirus) though other viruses can cause it as well (heterophile-negative infectious mononucleosis is most likely due to cytomegalovirus).
    - Age groups include adolescents and young adults ("kissing disease").
    - The "classic triad" includes fever, sore throat with gray-white membrane on tonsils, and lymphadenitis involving the posterior auricular nodes. Another sign is hepatosplenomegaly.
    - Complications include hepatic dysfunction, splenic rupture, and rash if treated with ampicillin.
    - Diagnosis is often made based on symptoms. Lymphocytosis and a rising titer of EBV antibodies are suggestive of the infection. Atypical lymphocytes may be present in peripheral blood. Monospot test is often negative early in infection.
- **Increased basophils** are seen with chronic myeloproliferative disorders such as polycythemia vera.

Leukopenia

Leukopenia is characterized by a decreased WBC count. It has the following features:

- **Decreased neutrophils** can be due to decreased production (aplastic anemia, chemotherapy), increased destruction (infections, autoimmune disease such as systemic lupus erythematosus), and activation of neutrophil adhesion molecules on endothelium (as by endotoxins in septic shock).
- **Decreased eosinophils** are seen with increased cortisol, which causes sequestering of eosinophils in lymph nodes; examples include Cushing syndrome and exogenous corticosteroids.
- **Decreased lymphocytes** are seen with immunodeficiency syndromes such as HIV, DiGeorge syndrome (T-cell deficiency), and severe combined immunodeficiency (B- and T-cell deficiency); also seen secondary to immune destruction (systemic lupus erythematosus), corticosteroids, and radiation (lymphocytes are the most sensitive cells to radiation).

KP00710.indb 206 13/10/22 1:52 PM

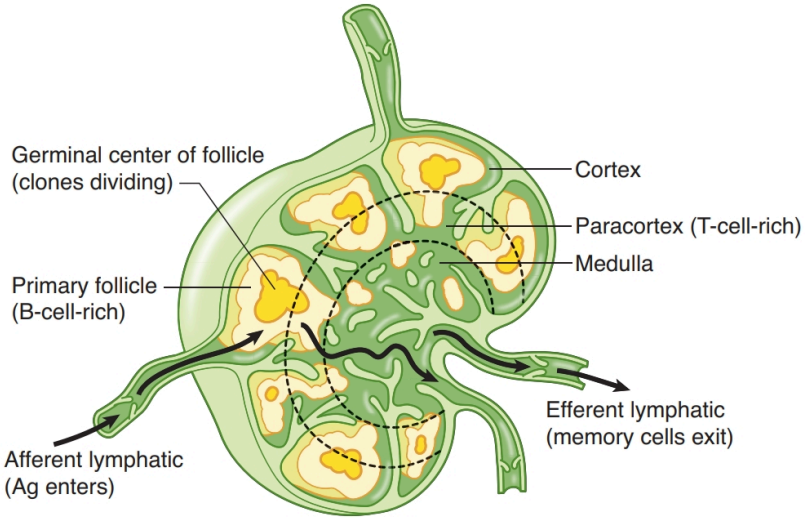


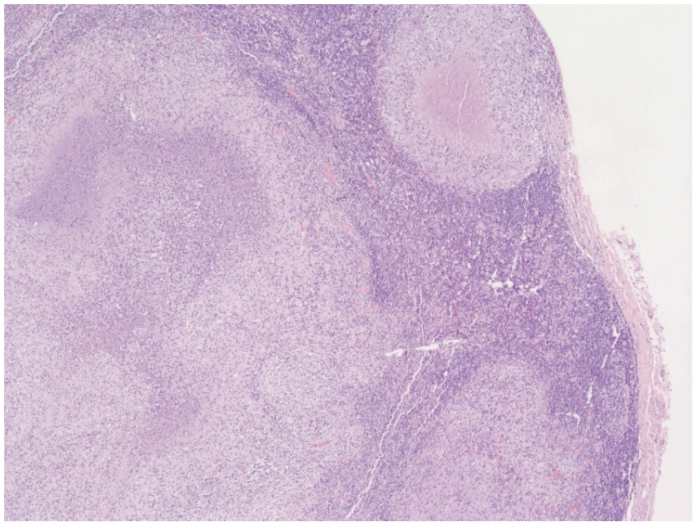
Figure 21-1. Lymph Node

LYMPHADENOPATHY

Lymphadenopathy is lymph node enlargement due to reactive conditions or neoplasia.

Acute Nonspecific Lymphadenitis

Acute nonspecific lymphadenitis produces tender enlargement of lymph nodes; focal involvement is seen with bacterial lymphadenitis. Microscopically, there may be neutrophils within the lymph node. Cat-scratch fever (due to *Bartonella henselae*) causes stellate microabscesses. Generalized involvement of lymph nodes is seen with viral infections.



© Gregg Barré MD Used with permission.

Figure 21-2. Stellate Microabscesses in a Cat-Scratch Fever Lymph Node

KP00710.indb 207 13/10/22 1:53 PM

Chronic Nonspecific Lymphadenitis

Chronic nonspecific lymphadenitis causes nontender enlargement of lymph nodes. Follicular hyperplasia involves B lymphocytes and may be seen with rheumatoid arthritis, toxoplasmosis, and early HIV infections. Paracortical lymphoid hyperplasia involves T cells and may be seen with viruses, drugs (Dilantin), and systemic lupus erythematosus. Sinus histiocytosis involves macrophages and, in most cases, is nonspecific; an example is lymph nodes draining cancers.

Neoplastic Enlargement

Neoplasia usually causes nontender enlargement of lymph nodes. The most common tumor to involve lymph nodes is metastatic cancer (e.g., breast, lung, malignant melanoma, stomach and colon carcinoma), which is initially seen under the lymph node capsule. Other important causes of lymphadenopathy are malignant lymphoma and infiltration by leukemias.

LYMPHOID NEOPLASMS

Lymphoid neoplasia is grouped according to the 2016 WHO classification as follows (note that B and T lymphoblastic lymphoma/leukemia is grouped by the WHO with myeloid neoplasia):

- Mature B-cell neoplasms
- Mature T-cell and NK-cell neoplasms
- Hodgkin lymphoma
- Histiocytic and dendritic cell neoplasms
- Posttransplantation lymphoproliferative disorders

Mature B-Cell Neoplasms

Chronic lymphocytic leukemia (CLL) and **small lymphocytic lymphoma** (SLL) are very similar; they both represent an abnormal proliferation of B cells. Patients who present with **lymph node findings** are classified as having SLL. Patients who present with **blood findings** are classified as having CLL; 50% of CLL patients also have lymph node involvement.

- CLL is the most indolent of all of the leukemias.
- Mean age at time of diagnosis is age 60.
- The malignant cells are nonfunctional, so patients develop hypogammaglobulinemia, leading to an increased risk of infections.
- CLL is associated with warm autoimmune hemolytic anemia (AIHA) (10% of cases), which will cause spherocytes to be observed in peripheral blood.
- CLL rarely transforms into a worse disease such as prolymphocytic leukemia or large cell lymphoma (Richter syndrome).

CLL and SLL can be categorized by the markers present on the B cells:

- **B-chronic lymphocytic leukemia cells** (95% of cases) have B-cell markers, such as CD19 and CD20. One T-cell marker, CD5, is also present. Also important is that the cells are CD23 positive and CD10 negative.
  - SLL occurs only as this type.

KP00710.indb 208 13/10/22 1:53 PM

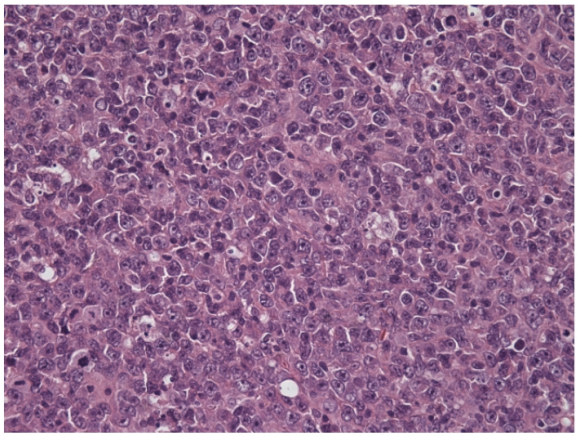
- **T-chronic lymphocytic leukemia cells** (5% of cases) have T-cell markers. The histology of affected lymph nodes reveals only a diffuse pattern (not nodular), but proliferation centers may also be present.
- Peripheral blood findings show increased numbers of normal-appearing lymphocytes. Numerous smudge cells ("parachute cells") are also present; the smudge cells result from the fact that the neoplastic lymphocytes are unusually fragile.
- Bone marrow shows numerous normal-appearing neoplastic lymphocytes.

Hairy cell leukemia is a rare B-cell neoplasm that causes indolent disease in middle-aged Caucasian men. There can be a "dry tap" with bone marrow aspiration. Lymphocytes have "hairlike" cytoplasmic projections; the diagnostic stain is positive tartrate-resistant acid phosphatase (TRAP).

Physical examination shows a markedly enlarged spleen (splenomegaly) due to infiltration of red pulp by malignant cells.

Treatment is 2-chloro-deoxyadenosine (2-CdA), which inhibits adenosine deaminase (ADA) and increases levels of toxic deoxyadenosine.

Diffuse large B-cell lymphoma (DLBCL) (most common lymphoma worldwide) is a heterogeneous neoplasm with clinical and pathologic diversity. The most common type (DLBCL, NOS) occurs mainly in the elderly but can affect all ages; it can present with nodal or extranodal disease. DLBCL is an aggressive neoplasm but cure is possible in most cases with a combination of immunotherapy and chemotherapy.



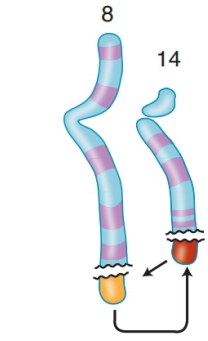
Bradley Gibson, MD Used with permission.

Figure 21-3. Diffuse Large B-Cell Lymphoma

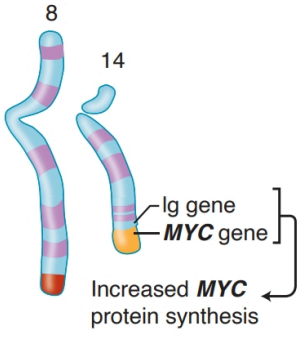
Follicular lymphoma (FL) (second most common lymphoma worldwide) is a neoplasm of germinal center-derived B-cells. Although subtypes exist, most cases have widespread disease with an indolent course; histologic transformation to a more aggressive non-Hodgkin lymphoma can occur.

Most FL cases have a characteristic translocation t(14;18) involving the immunoglobulin heavy chain gene and *BCL2* gene; some subtypes such as pediatric-type follicular lymphoma are t(14;18) negative.

KP00710.indb 209 13/10/22 1:53 PM



Normal Chromosome

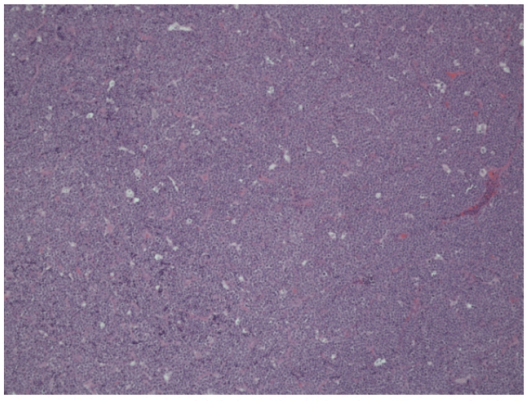


Burkitt Lymphoma

Small noncleaved lymphoma (Burkitt lymphoma) is a high-grade B-cell lymphoma. It is composed of intermediate-sized lymphoid cells with a "starry sky" appearance due to numerous reactive tingible-body macrophages (phagocytosis of apoptotic tumor cells). There is a characteristic t(8;14) translocation juxtaposing MYC to the immunoglobulin heavy chain locus in most cases.

- **African type:** endemic form
  - Involvement of mandible or maxilla is characteristic; is associated with Epstein-Barr virus
- **American type**: nonendemic, sporadic form
  - Involvement of the abdomen (such as bowel, retroperitoneum, or ovaries); has a high incidence in AIDS patients

Both endemic and sporadic forms of Burkitt lymphoma are seen most often in children and young adults.



Bradley Gibson, MD Used with permission.

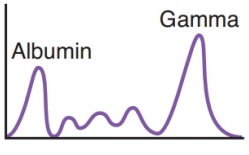
Figure 21-4. "Starry Sky" Appearance of Burkitt Lymphoma

Mantle cell lymphoma (MCL) is a rare B-cell lymphoma in which the tumor cells arise from mantle zone B lymphocytes (positive for CD19, CD20, and CD5; negative for CD23). The characteristic translocation is t(11;14), involving *CCD1* and the heavy chain locus.

Marginal zone lymphoma (MALToma) is a diverse group of B-cell neoplasms that arise within lymph nodes, spleen, or extranodal tissue. It is associated with mucosa-associated lymphoid tissue (MALTomas). The lesion begins as a reactive polyclonal reaction and may be associated with previous autoimmune disorders or infectious disease (e.g., Sjögren disease, Hashimoto thyroiditis, *Helicobacter* gastritis). The lymphoma remains localized for long periods of time.

Multiple myeloma is a malignant neoplasm of plasma cells.

- Most common primary tumor arising in the bone marrow of adults
- Lab studies show increased serum protein with normal serum albumin; an M spike in serum electrophoresis is a monoclonal immunoglobulin spike—most commonly IgG (60%) and next most commonly IgA (20%)
- Bence Jones proteins are light chains that are small and can be filtered into urine.



Serum electrophoresis pattern of IgG myeloma with γ spike and reduced albumin

21_Preclinical_Pathology_Ch21.indd 210 10/6/22 9:00 PM

Histologically, bone marrow shows increased plasma cells (>20% is characteristic). Peripheral blood may show rouleaux formation ("stack of coins"). Multiple lytic bone lesions are due to the osteoclastic activating factor. Lytic bone lesions cause hypercalcemia, bone pain, and increased risk of fracture.

Increased risk of infection is the most common cause of death. Other complications include renal disease (such as myeloma nephrosis) and primary amyloidosis (10% of patients) due to amyloid light (AL) chains. Increased amounts of IL-6 are associated with a poorer prognosis because survival of myeloma cells is dependent on IL-6.

Plasmacytoma is a solitary myeloma within bone or soft tissue.

- **Within bone**: precursor lesion that can later develop into myeloma
- **Outside bone** (extramedullary): usually found within upper respiratory tract

Monoclonal gammopathy of undetermined significance (MGUS) (an old name was benign monoclonal gammopathy). Serum M protein is found in 1–3% of asymptomatic individuals age >50; the incidence increases with increasing age. The annual risk of developing a plasma cell dyscrasia, usually multiple myeloma, is 1–2% per year. MGUS may also evolve into Waldenström macroglobulinemia, primary amyloidosis, B-cell lymphoma, or CLL.

Lymphoplasmacytic lymphoma (Waldenström macroglobulinemia) is a small lymphocytic lymphoma with plasmacytic differentiation. It is a cross between multiple myeloma and SLL.

Like myeloma, it has an M spike (IgM). Like SLL (and unlike myeloma), the neoplastic cells infiltrate many organs (e.g., lymph nodes, spleen, bone marrow). Also unlike multiple myeloma, there are no lytic bone lesions and there is no increase in serum calcium. Russell bodies (cytoplasmic immunoglobulin) and Dutcher bodies (intranuclear immunoglobulin) may be present.

- May have hyperviscosity syndrome, because IgM is a large pentamer
- Visual abnormalities may be due to vascular dilatations and hemorrhages in the retina
- Neurologic symptoms include headaches and confusion
- Bleeding and cryoglobulinemia can be due to abnormal globulins, which precipitate at low temperature and may cause Raynaud phenomenon

Peripheral T-Cell and Natural Killer Cell Neoplasms

Peripheral T-cell lymphoma, unspecified is a "wastebasket" diagnostic category.

Adult T-cell leukemia/lymphoma (ATLL) is a malignant T-cell disorder (CD4-T cells) due to HTLV-1 infection. It is often seen in Japan and the Caribbean. Clinical symptoms include skin lesions, hypercalcemia, enlarged lymph nodes, hepatomegaly, and splenomegaly. Microscopically, characteristic hyperlobated "4-leaf clover" lymphocytes can be found in the peripheral blood.

Mycosis fungoides is a malignant T-cell disorder (CD4+ cells) that has a better prognosis than ATLL. It can present with a generalized pruritic erythematous rash (no hypercalcemia), which develops as a sequence of skin changes:

inflammatory eczematous stage → plaque stage → tumor nodule stage

KP00710.indb 211 13/10/22 1:53 PM

Microscopically, atypical PAS-positive lymphocytes are present in the epidermis (epidermotropism); aggregates of these cells are called Pautrier microabscesses. If there is erythroderma and cerebriform Sézary cells are present in peripheral blood, the condition is called **Sézary syndrome**.

Hodgkin Lymphoma

Hodgkin lymphoma has some characteristics that are different from non-Hodgkin lymphoma.

- May present similar to infection (with fever)
- Spread is contiguous to adjacent node groups
- No leukemic state
- Extranodal spread is uncommon

The malignant cells are the diagnostic **Reed-Sternberg cells**; these malignant cells are intermixed with reactive inflammatory cells. The Reed-Sternberg cell is a large malignant tumor cell that has a bilobed nucleus with a prominent large inclusion-like nucleolus in each lobe.

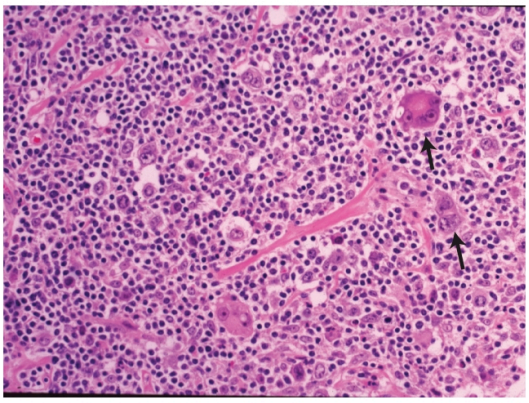


Figure 21-5. Reed-Sternberg Cells (arrows) of Hodgkin Lymphoma Appear as Large Binucleate Cells with Macronucleoli

Hodgkin lymphoma classification:

- **Lymphocyte-rich** type (rare): composed primarily of reactive lymphocytes; associated with Epstein-Barr virus (40% of cases)
- **Lymphocyte-predominant** type: has lymphohistiocytic variants (L&H cells, called "popcorn cells") and a unique phenotype (CD45+, CD15−, CD30−, CD20+)
- **Mixed cellularity** type: occurs in middle-aged and older males; the increased number of eosinophils is related to IL-5 secretion
- **Lymphocyte-depleted** type: presents with abdominal adenopathy; Reed-Sternberg cells predominate

NOTE

The classical Hodgkin lymphomas (nodular sclerosis, mixed cellularity, lymphocyte-rich, lymphocyte-depleted) share the immunophenotype CD45−, CD15+, CD30+.

KP00710.indb 212 13/10/22 1:53 PM

- **Nodular sclerosis** type (most common subtype (65–70% of cases)): only type in which females > males
  - Lymph node has broad collagen bands
  - Reed-Sternberg cell has clear space in the cytoplasm (lacunar cell)

Hodgkin lymphoma has a bimodal age group distribution (age late 20s and >50). Patients usually present with painless enlargement of lymph nodes. Poor prognosis is directly proportional to the number of Reed-Sternberg cells present. Survivors of chemotherapy and radiotherapy have increased risk for secondary non-Hodgkin lymphoma or acute leukemia.

Posttransplant lymphoproliferative disorder (PTLD) is a lymphoid proliferation that arises after solid organ or stem cell transplant. Epstein-Barr virus is involved in the pathogenesis of the majority of cases. There are polymorphic types that regress, but PTLD is more often monomorphic (B-cell lymphoma).

NOTE

Hodgkin lymphoma patients who have symptoms (fever, night sweats, unexplained weight loss > 10%) have a worse prognosis.

Diseases of Histiocytes and Dendritic Cells

Langerhans histiocytosis is common in children. It can affect many sites, including skin, bone, CNS (diabetes insipidus), and lungs. Biopsy is required for diagnosis. The Langerhans cells are CD1a positive and on electron microscopy show cytoplasmic Birbeck granules (tennis racket–shaped organelles).

- Multisystem variant: Letterer-Siwe disease (marrow involvement can be fatal)
- Hand-Schuller-Christian triad is calvarial involvement, diabetes insipidus, and exophthalmos
- Unisystem variant: eosinophilic granuloma (most often found in bone)

MYELOID NEOPLASMS

Acute Myelogenous Leukemia

Acute myelogenous leukemia is a cancer of the myeloid line of blood cells. Median age at diagnosis is age 50. Symptoms include fatigue, unusual bleeding, and infections.

Lab findings: Myeloid blasts or promyelocytes represent at least 20% of the marrow cells. **Auer rods** (linear condensations of cytoplasmic granules) are characteristic of AML and are not found in normal myeloid precursors.

The WHO classification of AML (2008) is as follows:

- AML with recurrent genetic abnormalities (for some of these entities, the karyotype is diagnostic regardless of the blast percentage)
  - Promyelocytic leukemia has t(15;17)(q22;q12) with fusion gene PML/RARA and responds to all-transretinoic acid (ATRA); DIC is common
  - AML with either t(8;21)(q22;q22) or inv(16)(p13.1;q22)
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML, not otherwise specified

CLINICAL CORRELATE

Tumor lysis syndrome is a group of metabolic complications that can occur after treatment of neoplastic disorders. These complications, which include hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, and acute renal failure, are caused by the breakdown products of dying cancer cells. Treatment is hydration and allopurinol.

KP00710.indb 213 13/10/22 1:53 PM

Myelodysplastic Syndromes (MDS)

MDS are classified according to the number of blasts in the marrow. Dysplastic changes include Pelger-Huët cells ("aviator glasses" nuclei), ring sideroblasts, nuclear budding, and "pawn ball" megakaryocytes. MDS are considered preleukemias, so patients are at increased risk for developing acute leukemia.

MDS mainly affect older adults (age 50–70); they also predispose to infection, hemorrhage and anemia. Transformation to AML is common.

Myeloproliferative Neoplasms (MPN)

MPN are clonal neoplastic proliferations of multipotent myeloid stem cells. The bone marrow is usually markedly hypercellular (hence the name *myeloproliferative*). All cell lines are increased in number (erythroid, myeloid, and megakaryocytes).

- **Chronic myelogenous leukemia (CML)** is a clonal proliferation of pluripotent granulocytic precursor stem cells. In most cases it is associated with a *BCR-ABL* fusion gene due to a balanced (9;22) translocation; however, this Philadelphia chromosome is not specific to CML.

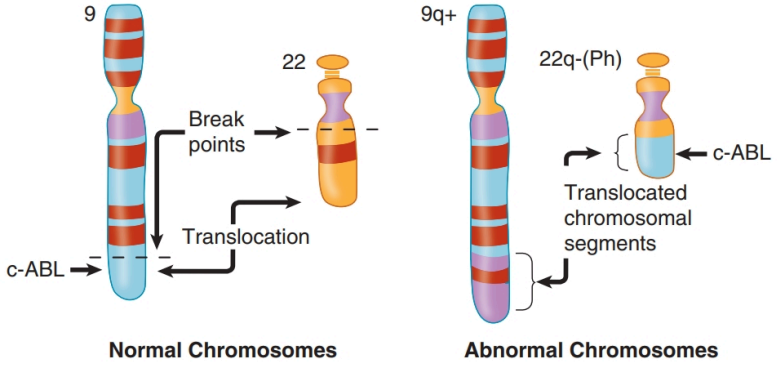


Figure 21-6. Translocation of Chromosomal Segments between Chromosomes 9 and 22

- CML has an insidious onset (i.e., chronic) and causes massive splenomegaly. Progression is typically slow (50% develop accelerated phase <5 years), unless blast crisis develops (very poor prognosis; doesn't respond to chemotherapy). In blast crisis, 70% of cases show myeloid blasts and 30% show lymphoid blasts.
- Microscopically, the bone marrow is hypercellular, with all cell lines increased in number. Peripheral leukocytosis is present, including markedly increased neutrophils (and bands and metamyelocytes), as well as increased eosinophils and basophils (as in the other MPS).
- Treatment is imatinib mesylate, which blocks the P210 tyrosine kinase protein produced by the translocation. Hematopoietic stem cell transplantation is also used.

KP00710.indb 214 13/10/22 1:53 PM

- **Polycythemia vera** is a stem cell disorder with trilineage (erythroid, granulocytic, megakaryocytic) proliferation. It may develop into a "spent phase" with myelofibrosis. It causes an increased risk for acute leukemia. Phlebotomy is therapeutic. Polycythemia vera characteristically shows the following:
  - Increased erythroid precursors with increased red cell mass
  - Increased hematocrit
  - Increased blood viscosity, which can cause deep vein thrombosis and infarcts
  - Decreased erythropoietin, but erythrocytes have increased sensitivity to erythropoietin and overproliferate
  - Increased basophils. Histamine release from basophils can cause intense pruritus and gastric ulcer (bleeding may cause iron deficiency).
  - Increased eosinophils (like all of the MPS)
  - High cell turnover can cause hyperuricemia, resulting in gout. Other clinical characteristics include plethora (redness) and cyanosis (blue).
- **Essential thrombocythemia** is characterized by increased megakaryocytes (and other cell lines) in bone marrow. Peripheral blood smear shows increased platelets, some with abnormal shapes. There are also increased leukocytes. Clinical signs include excessive bleeding and occlusion of small vessels.
- **Myelofibrosis (MF) with myeloid metaplasia** has unknown etiology (agnogenic).
  - Marrow fibrosis is secondary to factors released from megakaryocytes, such as platelet-derived growth factor (PDGF).
  - Bone marrow aspiration may be a "dry tap." The biopsy specimen shows hypocellular marrow with fibrosis (increased reticulin). The fibroblasts are a polyclonal proliferation and are not neoplastic.
  - There is an enlarged spleen due to extramedullary hematopoiesis (myeloid metaplasia). Peripheral smear shows leukoerythroblastosis (immature white cells and nucleated red cells) with teardrop RBCs. High cell turnover causes hyperuricemia and gout.

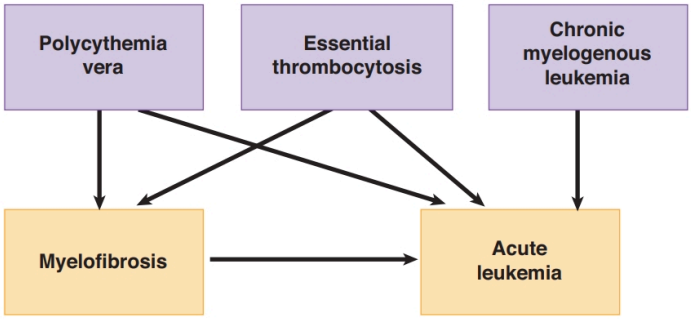


Figure 21-7. Natural History of the Myeloproliferative Syndromes

NOTE

The most common site for extramedullary hematopoiesis is the spleen.

KP00710.indb 215 13/10/22 1:53 PM

B AND T LYMPHOBLASTIC LYMPHOMA/LEUKEMIA

Acute Lymphoblastic Leukemia (ALL)

- **Karyotypic abnormalities**: Most pre-B-cell tumors are hyperdiploid. Translocations are common in both B-ALL and T-ALL.
- **Immunophenotyping**. Most tumors are positive for terminal deoxytransferase (TdT).
  - **B-cell lineage** classification is based on presence or absence of cytoplasmic or surface markers, including surface immunoglobulin (sIg) presence (mature B-ALL) and cytoplasmic μ presence (pre-BALL). The B-cell tumors almost always express B-cell molecules CD19 and CD10.
  - **T-cell lineage**: The majority of T-ALLs stain with CD2, CD3, CD5, and CD7.

B-ALL is more common in children; symptoms include fever, anemia, and bleeding. **T-ALL** is more common in adolescent males, who present with a mediastinal mass.

NOTE

In **acute leukemias**, the peripheral blood has decreased mature forms and increased immature forms called **blasts**, which have immature chromatin with nucleoli. The bone marrow has increased immature cells (blasts). Acute symptoms are secondary to marrow failure, which can produce decreased erythrocytes (causing anemia and fatigue), decreased leukocytes (permitting infections and fever), and decreased platelets (inducing bleeding).

Lymphoblastic Lymphoma

Most cases of lymphoblastic lymphoma are T-cell neoplasms that are aggressive and rapidly progressive. Most patients are young men with a mediastinal mass (think thymus). The leukemic phase of lymphoblastic lymphoma is similar to T-ALL and some consider them the same entity. Most cells are CD1+, CD2+, CD5+, and CD7+.

NOTE

With some exceptions, lymphoblasts stain with PAS; myeloblasts are myeloperoxidase (MPO) positive.

CLINICAL CORRELATE

ALL is associated with infiltration of the CNS and testes (**sanctuary sites**). Thus, prophylactic radiation and/or chemotherapy to the CNS is used because malignant cells in the brain are protected from chemotherapy by the blood–brain barrier.

Mast Cell Diseases

Mastocytosis occurs from birth to adulthood; adult-onset cases are more severe. The WHO separates mastocytosis into 3 categories:

- **Cutaneous mastocytosis**, seen in children, regresses over time. Mast cell degranulation enzymes (histamine and tryptase) cause pruritus.
- **Systemic mastocytosis** is a clonal proliferation of mast cells associated with a KIT mutation; ≥1 organs are involved, as are the skin and bone marrow. The WHO now classifies systemic mastocytosis as one of the myeloproliferative neoplasms.
  - Variants include some rare leukemias.
  - Diagnosis is made with bone marrow biopsy and molecular analysis.
- **Localized extracutaneous mast cell neoplasms** can be benign (mastocytoma) or malignant (sarcoma).

KP00710.indb 216 13/10/22 1:53 PM

DISEASES OF THE SPLEEN AND THYMUS

Splenic Enlargement and Dysfunction

Splenomegaly (splenic enlargement) can be caused by multiple things:

- Vascular congestion (portal hypertension)
- Reactive hyperplasia of white pulp (autoimmune disorder, infectious mononucleosis, malaria)
- Infiltrative disease (metastatic non-Hodgkin lymphoma, primary amyloidosis, leukemia)
- Accumulated macrophages in red pulp (Gaucher, Niemann-Pick disease)
- Extravascular hemolysis
- Extramedullary hematopoiesis in splenic sinusoids

Hypersplenism will result in thrombocytopenia.

Splenic dysfunction will result in a loss of ability to remove damaged red cells, which leads to Howell-Jolly bodies in peripheral RBCs. Splenectomized, asplenic, and hyposplenic individuals are at risk for infection (sepsis, peritonitis), particularly due to *Streptococcus*, *Haemophilus*, and *Salmonella*.

Thymomas and Thymic Hyperplasia

Thymomas are low-grade tumors of the thymic epithelium with many histologic patterns. Recent large case series have shown that tumor behavior does not always correlate with histopathological features.

True thymic hyperplasia is enlargement of a histologically normal thymus; it can occur as a complication of chemotherapy.

Thymic lymphoid hyperplasia shows germinal center hyperplasia.

KP00710.indb 217 13/10/22 1:53 PM

Female Genital Pathology 22

LEARNING OBJECTIVES

- ❑ Demonstrate understanding of the pathology of the vulva, vagina, cervix, uterus, and ovary
- ❑ Solve problems concerning the placenta

VULVA

Nonneoplastic Disorders

- **Lichen sclerosus** is caused by epidermal thinning and dermal changes that cause pale skin in postmenopausal women. There is a small risk of progression to squamous cell carcinoma (SCC).
- In **lichen simplex chronicus**, a chronic scratch/itch cycle produces the white plaques seen clinically. These plaques are characterized microscopically by squamous cell hyperplasia and dermal inflammation.

Infections

- **Human papillomavirus (HPV)** causes warty lesions (condylomata acuminata) and precursor dysplastic lesions of squamous cell carcinoma called vulvar intraepithelial neoplasia (VIN). Vulvar HPV is commonly subtype 6 and 11 and therefore has low oncogenic potential.
- **Herpes simplex virus (HSV)**. Most cases of vulvar herpes are caused by HSV-2. Painless vesicles progress to pustules and painful ulcers.
- **Syphilis** is a sexually transmitted disease caused by *Treponema pallidum*. The primary lesion is a chancre, a painless ulcer that does not scar after healing.
- **Molluscum contagiosum** is a viral disease caused by a DNA poxvirus. It presents as smooth papules and has characteristic cytoplasmic viral inclusions.
- **Bartholin gland abscess** is a polymicrobial infection requiring drainage or excision.

KP00710.indb 219 13/10/22 1:53 PM

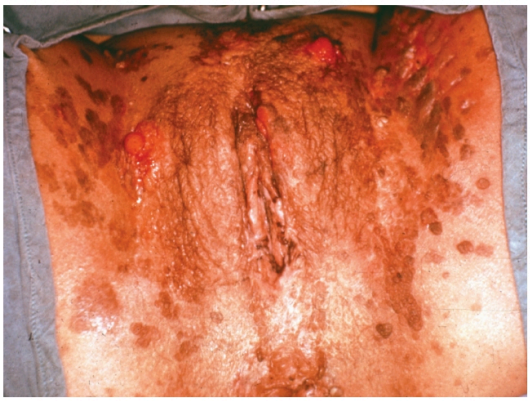


Figure 22-1. Severe Case of Condyloma Acuminata

Tumors

- **Papillary hidradenoma** is a benign tumor of modified apocrine sweat glands of the labia majora or interlabial folds. It occurs along the milk line and may ulcerate, mimicking carcinoma. Papillary hidradenoma is histologically similar to an intraductal papilloma of the breast.
- **Extramammary Paget disease of the vulva** usually involves the labia majora, and it causes an erythematous, crusted rash that is characterized microscopically by intraepidermal malignant cells with pagetoid spread. This form of Paget disease is not usually associated with underlying tumor.
- **Squamous cell carcinoma** is the most common malignancy of the vulva. The most common form occurs in women age >60. The less common form occurs in younger women with HPV serotypes 16 and 18.
- **Melanoma** can occur on the vulva and must be differentiated from lentigo simplex, which is more common.

VAGINA

Tumors

- **Vaginal adenosis and clear cell adenocarcinoma** are rare conditions with increased risk in females exposed to diethylstilbestrol (DES) *in utero*.
- **Embryonal rhabdomyosarcoma** (sarcoma botryoides) affects infants and young children (age <5), in whom it can cause a polypoid, "grapelike," soft tissue mass that protrudes from the vagina. Microscopically, the mass is characterized by polypoid epithelial growth with an underlying immature (cambium) proliferation of spindle-shaped tumor cells with rare cross-striations. Tumor cells are positive for desmin.
- **Vaginal squamous cell carcinoma** is usually related to HPV infection; extension from a cervical cancer is more common. Treatment is radiotherapy.

CLINICAL CORRELATE

DES was used in high-risk pregnancies from 1940–1970, after which time vaginal adenosis and clear cell carcinoma were discovered in the female offspring. Vaginal adenosis is a benign condition that is presumed to be a precursor of clear cell carcinoma.

KP00710.indb 220 13/10/22 1:53 PM

- **Rhabdomyoma** is a benign skeletal muscle tumor that can involve the vagina. It occurs in middle-aged women.

Developmental Disorders

- **Gartner duct cyst** is a cyst of the lateral wall of the vagina that is due to persistence of a mesonephric (Wolffian) duct remnant. Urinary tract abnormalities may exist.
- **Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome** is congenital absence of the upper part of the vagina and uterus. Patients present with primary amenorrhea.

Infections

Vaginitis/vaginosis. All of the following conditions require vaginal swab for definitive diagnosis; molecular diagnostic tests may be indicated in certain situations.

- **Vulvovaginal candidiasis** can occur spontaneously or from antibiotic therapy; it is not usually sexually transmitted. Symptoms include discharge and pruritis. Yeast cells and pseudohyphae are seen on microscopy. Antimycotics are therapeutic.
- **Bacterial vaginosis (BV)** is implicated in preterm labor and pelvic inflammatory disease. Some patients are asymptomatic. BV is a sexually transmitted bacterial infection of polymicrobial origin (although it used to be attributed only to *Gardnerella vaginalis*); recurrence rate is high after treatment with antibiotics. "Clue cells" are squamous cells coated with coccobacilli that may be seen microscopically in swab material.
- ***Trichomonas vaginalis*** is a sexually transmitted motile protozoan. Most infected people are asymptomatic. It can also cause cervicitis, but "strawberry cervix" is not a consistent diagnostic feature. Antibiotics are therapeutic.

CERVIX

Infections

Pelvic inflammatory disease (PID) is an ascending infection (sexually transmitted disease) from the cervix to the endometrium, fallopian tubes, and pelvic cavity. The infecting organisms are most frequently nongonococcal organisms, including *Chlamydia*, *Mycoplasma hominis* and endogenous flora. Broad-spectrum antibiotics are therapeutic.

The distribution of disease includes the endometrium (endometritis), fallopian tubes (salpingitis), and pelvic cavity (peritonitis and pelvic abscesses). **Fitz-Hugh–Curtis syndrome** (perihepatitis) can occur, characterized by "violin-string" adhesions between the fallopian tube and liver capsule. Symptoms include the following:

- Vaginal discharge (cervicitis)
- Vaginal bleeding and midline abdominal pain (endometritis)
- Bilateral lower abdominal and pelvic pain (salpingitis)

KP00710.indb 221 13/10/22 1:53 PM

CLINICAL CORRELATE

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

- Abdominal tenderness and peritoneal signs (peritonitis)
- Pleuritic right upper quadrant pain (perihepatitis)

Complications of PID include tuboovarian abscess, tubal scarring (increasing risk of infertility and ectopic tubal pregnancies), and intestinal obstruction secondary to fibrous adhesions.

Human papillomavirus (HPV) can cause transient infection in the cervix. Persistent HPV infection can cause squamous intraepithelial lesions and cancer.

Acute and chronic cervicitis are common and usually nonspecific inflammatory conditions.

- Acute cervicitis is often caused by *C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis*, *Candida*, and herpes simplex type 2.
- A specific, severe form of chronic cervicitis (**follicular cervicitis**) can be caused by *C. trachomatis*; it can result in neonatal conjunctivitis and pneumonia in infants delivered vaginally through an infected cervix.

Cervical Neoplasia

Table 22-1. Malignant Tumors of the Lower Female Genital Tract in the U.S.

Order of Incidence	Order of Greatest Mortality
1. Endometrial cancer	1. Ovarian cancer
2. Ovarian cancer	2. Endometrial cancer
3. Cervical cancer	3. Cervical cancer

Cervical carcinoma is most commonly squamous cell carcinoma but can also be adenocarcinoma or small cell neuroendocrine carcinoma. Peak incidence is at ages 35–44. Risk factors include the following:

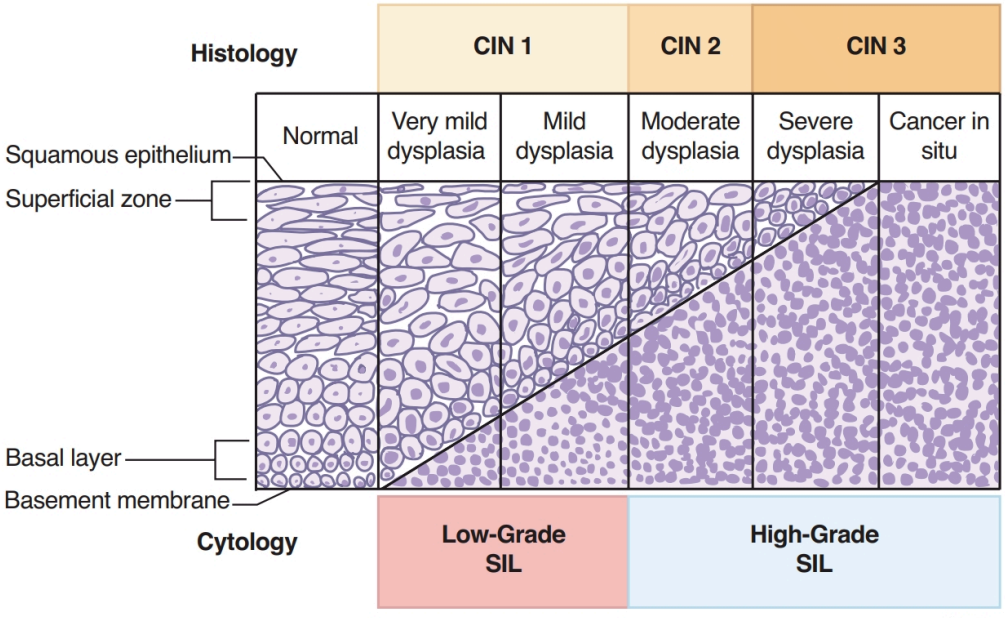
- Early age of first intercourse
- Multiple sexual partners
- Multiple pregnancies
- Oral contraceptive use
- Smoking
- STDs (including human papilloma virus)
- Immunosuppression

Human papilloma virus infection is the most important risk factor, with high-risk types being 16, 18, 31, and 33, and having viral oncoproteins E6 (binds to p53) and E7 (binds to Rb). The precursor lesion is **cervical intraepithelial neoplasia (CIN)**, which is increasing in incidence. CIN occurs commonly at the squamocolumnar junction (transformation zone). Cervical intraepithelial lesions show a progression of histologic changes:

- Low-grade SIL (squamous intraepithelial lesion)
- High-grade SIL

KP00710.indb 222 13/10/22 1:53 PM

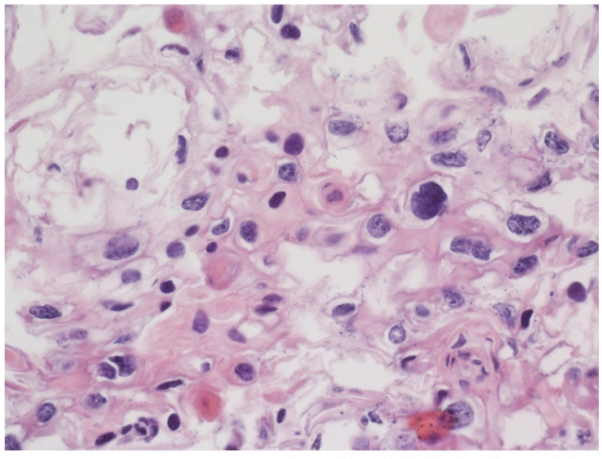
- Carcinoma in situ
- Superficially invasive squamous cell carcinoma
- Invasive squamous cell carcinoma



© Kaplan

Figure 22-2. Progression of Cervical Intraepithelial Lesions

Squamous cell carcinoma of the cervix may be asymptomatic or may present with postcoital vaginal bleeding, dyspareunia, and/or malodorous discharge. To establish the diagnosis, the Papanicolaou (**Pap**) test is useful for early detection, and colposcopy with biopsy for microscopic evaluation.



© Gregg Barré, MD Used with permission.

Figure 22-3. Cervix Biopsy Showing Squamous Cells with Nuclear Hyperchromasia and Perinuclear Vacuoles, Characteristic of HPV Cytopathic Effect

KP00710.indb 223 13/10/22 1:53 PM

Endocervical polyp is a common benign polyp that can be covered with columnar or stratified squamous epithelium.

UTERUS

Nonneoplastic Conditions

Endometritis is inflammation of the endometrial lining in the uterus. It can be acute or chronic.

- **Acute endometritis** is an ascending infection from the cervix; it is associated with pregnancy and abortion.
- **Chronic endometritis** is associated with PID and intrauterine devices; plasma cells are seen in the endometrium.

Endometriosis is the presence of endometrial glands and stroma outside the uterus. It most commonly affects women of reproductive age. Common sites of involvement are the ovaries, ovarian and uterine ligaments, pouch of Douglas, serosa of bowel and urinary bladder, and peritoneal cavity. It can present with chronic pelvic pain, dysmenorrhea and dyspareunia, rectal pain and constipation, abnormal uterine bleeding, or infertility.

Grossly, endometriosis causes red-brown serosal nodules (an *endometrioma* is an ovarian "chocolate" [hemolyzed blood] cyst).

Adenomyosis is an invagination of the deeper layers of the endometrium into the myometrium that causes menorrhagia and dysmenorrhea.

Anovulation can cause abnormal uterine bleeding, especially in women near menarche and menopause. Biopsy shows glandular and stromal breakdown in a background of proliferative phase endometrium.

Endometrial Hyperplasia and Adenocarcinoma

Endometrial hyperplasia refers to a histological proliferation of endometrial glands with 2 important histopathologic categories:

- **Benign endometrial hyperplasia** shows uniform remodeling of glands with cyst formation.
- **Endometrial intraepithelial neoplasia** shows crowded architecture and cytologic alteration on biopsy.
  - Patients are at high risk for endometrial adenocarcinoma.
  - Treatment options include total hysterectomy or progestin therapy with biopsy surveillance.

Endometrial adenocarcinoma is the most common malignant tumor of the lower female genital tract. It most commonly affects postmenopausal women who present with abnormal uterine bleeding. Risk factors are mostly related to estrogen:

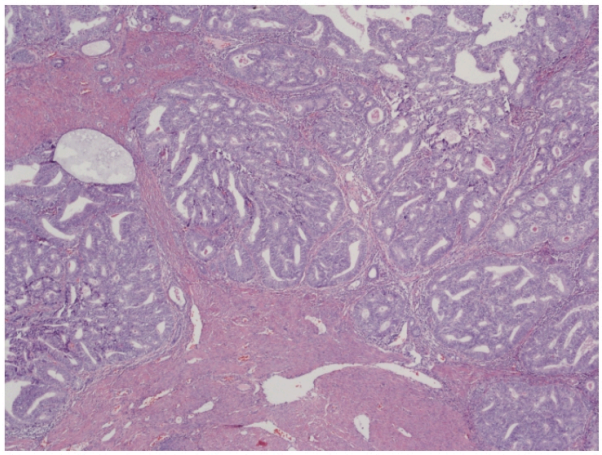
- Early menarche and late menopause
- Nulliparity
- Hypertension and diabetes

KP00710.indb 224 13/10/22 1:53 PM

- Obesity
- Chronic anovulation
- Estrogen-producing ovarian tumors (granulosa cell tumors)
- ERT and tamoxifen
- Endometrial hyperplasia (complex atypical hyperplasia)
- Lynch syndrome (colorectal, endometrial, and ovarian cancers)

Endometrial adenocarcinoma typically forms a tan polypoid endometrial mass; invasion of myometrium is prognostically important.

- Endometrioid adenocarcinoma (most common histological type): associated with *PTEN* mutations
- Serous tumors: associated with *TP53* mutations



© Gregg Barré, MD Used with permission.

Figure 22-4. Endometrial Carcinoma Invading the Myometrium

Other Tumors

Leiomyoma (fibroid), the most common tumor of the female genital tract, is a benign, smooth muscle tumor of the myometrium. Leiomyomas have a high incidence in African Americans, though they are common across all populations. Their growth is estrogen-dependent.

Leiomyomas may present with menorrhagia, abdominal mass, pelvic/back pain, suprapubic discomfort, or infertility and spontaneous abortion.

Grossly, leiomyomas form well-circumscribed, rubbery, white-tan masses with a whorled, trabeculated appearance on cut section. Leiomyomas are commonly multiple and may have subserosal, intramural, and submucosal location. The malignant variant is leiomyosarcoma.

Less common types of uterine malignancy include **leiomyosarcoma**, a malignant, smooth muscle tumor, and **carcinosarcoma**, which contains both malignant stromal cells and endometrial adenocarcinoma.

KP00710.indb 225 13/10/22 1:53 PM

OVARY

Polycystic Ovary Syndrome (PCOS)

Polycystic ovary syndrome (Stein-Leventhal syndrome) is an endocrine disorder of unknown etiology showing signs of androgen excess (clinical or biochemical), oligoovulation and/or anovulation, and polycystic ovaries.

Accurate diagnosis requires exclusion of other endocrine disorders that might affect reproduction. Patients are usually young women of reproductive age who present with oligomenorrhea or secondary amenorrhea, hirsutism, infertility, or obesity. Treatment is lifestyle change and hormone therapy.

Lab studies show elevated luteinizing hormone (LH), low follicle-stimulating hormone (FSH), and elevated testosterone. Gross examination is notable for bilaterally enlarged ovaries with multiple cysts; microscopic examination shows multiple cystic follicles.

Ovarian Tumors

Epithelial ovarian tumors are the most common form of ovarian tumor. Risk factors include nulliparity, family history, and germline mutations.

Previously, epithelial tumors were characterized by histology into the categories cystadenoma (benign), borderline, and cystadenocarcinoma. Now, **serous tumors** are classified as **low grade** and **high grade** for prognostic significance.

- Low-grade serous tumors are associated with *KRAS*, *BRAF*, or *ERB2* mutations.
- Most high-grade serous tumors have *TP53* mutations.

The most common malignant ovarian tumor is **serous cystadenocarcinoma**. Hereditary risk factors include *BRCA1* (breast and ovarian cancers) and Lynch syndrome.

- Well-differentiated serous tumors show psammoma bodies and a lining similar to that of the fallopian tube.

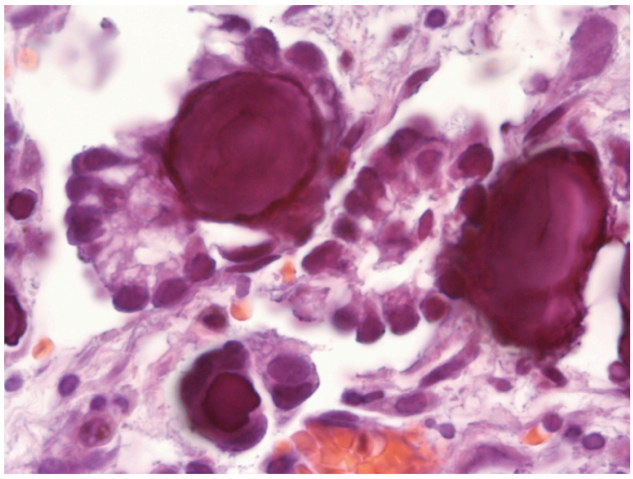
Mucinous tumors commonly have goblet cells like intestinal mucosal cells.

CA 125 can be used to follow treatment.

NOTE

- The Pap test has reduced the incidence of cervical cancer in the United States.
- There is no screening test for ovarian cancer.

KP00710.indb 226 13/10/22 1:53 PM



© Gregg Barré MD Used with permission.

Figure 22-5. Psammoma Bodies (Concentric Calcifications) in a Serous Tumor

Ovarian Germ Cell Tumors

- **Teratoma** (dermoid cyst)
  - Vast majority (>95%) of ovarian (but not testicular) teratomas are benign; commonly occurs in early reproductive years
  - Include elements from all 3 germ cell layers: ectoderm (skin, hair, adnexa, neural tissue), mesoderm (bone, cartilage), and endoderm (thyroid, bronchial tissue)
  - Complications include torsion, rupture, and malignant transformation
  - Can contain hair, teeth, and sebaceous material
  - The term *struma ovarii* is used when there is a preponderance of thyroid tissue
  - Immature teratoma is characterized by histologically immature tissue
- **Dysgerminoma**
  - Malignant; commonly occurs in children and young adults
  - Risk factors include Turner syndrome and disorders of sexual development
  - Gross and microscopic features are similar to seminomas
  - Are radiosensitive; prognosis is good

Ovarian Sex Cord–Stromal Tumors

- **Ovarian fibroma**
  - Most common stromal tumor; forms a firm, white mass
  - **Meigs syndrome** refers to the combination of fibroma, ascites, and pleural effusion.

KP00710.indb 227 13/10/22 1:53 PM

- **Granulosa cell tumor**
  - Potentially malignant, **estrogen-producing** tumor
  - Presentation depends on age:
    - Prepuberal patients with juvenile granulosa cell tumor present with precocious puberty
    - Reproductive age patients present with irregular menses
    - Postmenopausal patients present with vaginal bleeding
  - Complications include endometrial hyperplasia and cancer
  - Tumor forms a yellow-white mass that microscopically shows polygonal tumor cells and formation of follicle-like structures (Call-Exner bodies)
- **Sertoli-Leydig cell tumor** (androblastoma) is an **androgen-producing tumor** that presents with virilization, usually in young women.

Primary sites for **metastatic tumor** to the ovary include breast cancer, colon cancer, endometrial cancer, and gastric "signet-ring cell" cancer (Krukenberg tumor).

Table 22-2. Origins of Common Ovarian Neoplasms

	Surface Epithelial Cells	Germ Cell	Sex Cord–Stroma	Metastasis to Ovaries
Age group affected	20+ years	0–25+ years	All ages	Variable
Types	• Serous tumor • Mucinous tumor • Endometrioid tumor • Clear cell tumor • Brenner tumor	• Teratoma • Dysgerminoma • Endodermal sinus tumor • Choriocarcinoma	• Fibroma • Granulosa–theca cell tumor • Sertoli-Leydig cell tumor	
Overall frequency	65–70%	15–20%	5–10%	5%
Percentage of malignant ovarian tumors	90%	3–5%	2–3%	5%

PLACENTA

Gestational Trophoblastic Disease

Hydatidiform mole (molar pregnancy) is a tumor of placental trophoblastic tissue. Incidence in the United States is 1 per 1,000 pregnancies, with an even higher incidence in Asia. Women ages <15 and >40 are at increased risk.

- **Complete mole** results from fertilization of an ovum that *lost* all of its chromosomal material, so that 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

KP00710.indb 228 13/10/22 1:53 PM

- **Partial mole** results from fertilization of an ovum (that has not lost its chromosomal material) by 2 sperms, one 23,X and one 23,Y.
  - Results in a triploid cell 69, XXY (23,X [maternal] + 23,X [one sperm] + 23,Y [the other sperm])
  - The embryo may develop for a few weeks
- **Invasive mole** is a mole that invades the myometrium of the uterine wall.

Patients with hydatidiform mole typically present with the following:

- Excessive uterine enlargement ("size greater than dates")
- Vaginal bleeding
- Passage of edematous, grape-like soft tissue
- Elevated beta-human chorionic gonadotropin (β-hCG)

Microscopically, molar tissue will show edematous chorionic villi, trophoblast proliferation, and fetal tissue (only in partial mole). Diagnosis is by U/S. Treatment is endometrial curettage and following of β-hCG levels.

Table 22-3. Partial Mole Versus 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	2%	10%
Choriocarcinoma	Rare	2%

Choriocarcinoma is a malignant germ cell tumor derived from the trophoblast that forms a necrotic and hemorrhagic mass. Almost 50% arise from complete moles. The most common presentation is a rising or plateaued titer of hCG after a molar pregnancy, abortion, or ectopic pregnancy.

Microscopically, choriocarcinoma shows proliferation of cytotrophoblasts, intermediate trophoblasts, and syncytiotrophoblasts. Hematogenous spread can occur, with seeding of tumor to lungs, brain, liver, etc. Treatment is chemotherapy.

Placental site trophoblastic tumor is a tumor of intermediate trophoblast; it usually presents <2 years after pregnancy with bleeding and an enlarged uterus. Treatment is surgical; it does not respond well to chemotherapy.

KP00710.indb 229 13/10/22 1:53 PM

Ectopic Pregnancy

In **ectopic pregnancy**, the fetus implants outside the normal location, most often in the fallopian tube, and less often in the ovaries or abdominal cavity. The fetus almost never survives. The mother is at risk for potentially fatal intra-abdominal hemorrhage. Risk factors include scarring of fallopian tubes from PID, endometriosis, and decreased tubal motility.

Placental Abnormalies

Enlarged placenta is common with maternal diabetes mellitus, Rh hemolytic disease, and congenital syphilis.

Succenturiate lobes are accessory lobes of the placenta that may cause hemorrhage if torn away from the main part of the placenta during delivery.

Placental abruption is partial premature separation of the placenta away from the endometrium, with resulting hemorrhage and clot formation. Risk factors include hypertension, cigarette use, cocaine, and older maternal age.

Placenta previa describes when the placenta overlies the cervical os. Vaginal delivery can cause the placenta to tear, with potentially fatal maternal or fetal hemorrhage.

In **placenta accreta**, the placenta implants directly in the myometrium rather than in endometrium. Hysterectomy is required after delivery to remove the rest of the placenta.

Twin Placentation

- **Fraternal twins** always have 2 amnions and 2 chorions; placental discs are usually separate, but can grow together to appear to be a single placental disc.
- **Identical twins** have a variable pattern in the number of membranes and discs due to variations in the specific point in embryonic development at which the twins separated. Twin-twin transfusion syndrome can occur if (a) there is only one placental disc and (b) one twin's placental vessels connect to the other twin's placental vessels.
- **Conjoined twins** are always identical twins with one amnion, one chorion, and one disc, though there are rare reports of diamniotic placentation.

Preeclampsia

Preeclampsia is a condition of new onset hypertension and either proteinuria or end-organ dysfunction after 20 weeks gestation in a previously normotensive woman. It is linked to abnormal uteroplacental blood flow.

- The term **eclampsia** is used when the patient has seizures not attributable to other causes.
- **HELLP syndrome** is a rare complication of preeclampsia characterized by hemolysis, elevated liver enzymes, and low platelets.

KP00710.indb 230 13/10/22 1:53 PM

Breast Pathology 23

LEARNING OBJECTIVES

- ❑ Explain information related to mastitis
- ❑ Demonstrate understanding of fibrocystic changes
- ❑ Solve problems concerning benign and malignant neoplasms
- ❑ Answer questions about gynecomastia

INFLAMMATORY CONDITIONS

Mastitis

Mastitis is an infection of the breast tissue.

Acute mastitis causes an area of erythema and firmness in the breast, commonly during lactation. The most common infecting organism is *S. aureus*. The breast is often biopsied to differentiate the condition from inflammatory carcinoma, another painful breast condition. Microscopically there is acute and chronic inflammation with abscess formation in some cases.

Fat Necrosis

Fat necrosis is often related to trauma or prior surgery, and it may produce a palpable mass or a discrete lesion with calcifications on mammography. Microscopic changes include fat necrosis, chronic inflammation, hemosiderin deposits and fibrosis with calcification.

FIBROCYSTIC CHANGES

Fibrocystic changes (formerly called *fibrocystic disease*) are a group of very common, benign changes that can be classified as **proliferative** (having an increase in the glandular elements or epithelial cells) or **nonproliferative**. Because they carry varying degrees of risk for breast cancer, it is important to identify each type histologically.

Fibrocystic changes primarily affect women in their reproductive years. The changes most often involve the upper outer quadrant and may produce a palpable mass or nodularity.

- **Fibrosis** may mimic a tumor on clinical exam and U/S.
- **Cysts** can usually be diagnosed by U/S.
- **Apocrine metaplasia** is often seen in cyst walls.

KP00710.indb 231 13/10/22 1:53 PM

- **Microcalcifications** occur in benign and malignant processes.
- **Ductal hyperplasia** is classified as usual or atypical on the basis of cytology and microlumen architecture; **atypical ductal hyperplasia** is differentiated from ductal carcinoma in situ (DCIS) on the basis of microscopic extent.
- **Atypical lobular hyperplasia** is differentiated from lobular carcinoma in situ (LCIS) histologically on the basis of the percentage of acini involved.
- **Sclerosing adenosis** is distinguished from carcinoma histologically by the preservation of the myoepithelial layer.

Table 23-1. Nonproliferative Versus Proliferative Fibrocystic Changes

Nonproliferative	Proliferative Changes
Fibrosis Cysts (blue-domed) Apocrine metaplasia Microcalcifications	Ductal hyperplasia ± atypia Sclerosing adenosis Atypical lobular hyperplasia

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 ductal hyperplasia, papillomas
4–5×	Atypical ductal or lobular hyperplasia

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

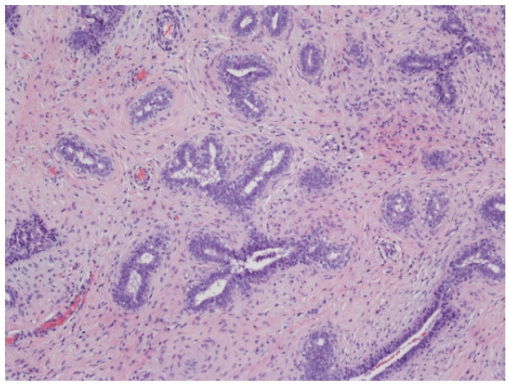
Fibrocystic Change	Breast Cancer
Often bilateral	Often unilateral
May have multiple nodules	Usually single
Menstrual variation	No menstrual variation
May regress during pregnancy	Does not regress during pregnancy

BENIGN NEOPLASMS

Stromal Tumors

Fibroadenoma is the most common benign breast tumor in women age <35. It causes a palpable, round, movable, rubbery mass, which on cross-section shows small, cleft-like spaces. Microscopically, the mass shows proliferation of benign stroma, ducts, and lobules.

KP00710.indb 232 13/10/22 1:53 PM



© Gregg Barré, MD Used with permission.

Figure 23-1. Fibroadenoma

Phyllodes tumor (cystosarcoma phyllodes) usually involves an older patient population (age 50s) and can be benign or malignant. Local recurrence is common but the incidence of metastasis is low. Microscopically, the mass shows increased stromal cellularity, clefts lined by epithelium, stromal overgrowth, and irregular margins.

Ductal Tumors

Intraductal papilloma commonly presents as a bloody nipple discharge. Microscopically, papilloma causes benign papillary growth within lactiferous ducts or sinuses; the myoepithelial layer is preserved.

MALIGNANT NEOPLASMS

Breast Carcinoma

Carcinoma of the breast is the most common cancer in women and affects 1 in 9 women in the United States. It is also the second most common cause of cancer death. The incidence is increasing and is higher in the United States than in Japan.

Risk factors. Incidence of breast carcinoma increases with:

- Age
- Unusually long/intense exposure to estrogens (long length of reproductive life, nulliparity, obesity, exogenous estrogens)
- Presence of proliferative fibrocystic changes, especially **atypical hyperplasia**
- First-degree relative with breast cancer

Hereditary influences are thought to be involved in 5–10% of breast cancers, with important genes as follows:

- ***BRCA1*** (error-free repair of DNA double-strand breaks) chromosome 17q21
- ***BRCA2*** (error-free repair of DNA double-strand breaks) chromosome 13q12.3
- ***TP53*** germline mutation (Li-Fraumeni syndrome)

KP00710.indb 233 13/10/22 1:53 PM

NOTE

The World Health Organization has recently changed the term "invasive ductal carcinoma" to "**invasive breast carcinoma of no special type**."

NOTE

As per current practice guidelines, all primary invasive breast cancers are evaluated for ER/PR status and HER2 expression.

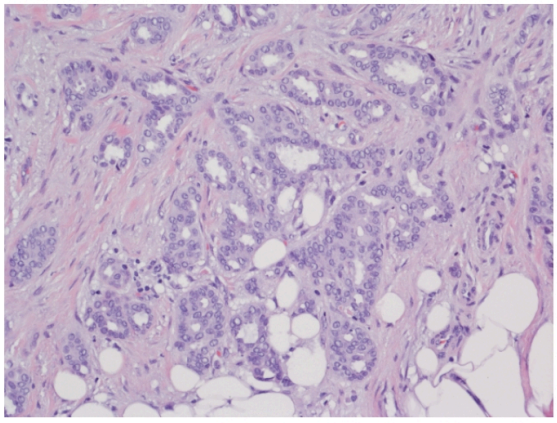
Carcinoma in situ and risk of invasive carcinoma. About 35% of women with untreated DCIS will develop invasive cancer, usually in the same quadrant of the breast. About 35% of women with LCIS will develop invasive lobular or ductal carcinoma, in either breast.

Breast cancer is most common in the upper outer quadrant. Gross examination of a breast cancer typically shows a stellate, white-tan, gritty mass. Clinically, it can cause:

- Mammographic calcifications or architectural distortion
- Palpable solitary painless mass
- Nipple retraction or skin dimpling
- Fixation of breast tissue to the chest wall

Histologic variants of breast cancer are as follows:

- **Preinvasive lesions** include ductal carcinoma in situ **(DCIS)** and lobular carcinoma in situ **(LCIS)**. Preservation of the myoepithelial cell layer distinguishes them from their invasive counterparts.
- **Invasive (infiltrating) ductal carcinoma** is the most common form (>80% of cases). Microscopically, it shows tumor cells forming ducts within a desmoplastic stroma. About 70% of cases are ER/PR positive and 30% overexpress HER2.



© Gregg Barré, MD Used with permission.

Figure 23-2. Invasive Ductal Carcinoma

- **Invasive (infiltrating) lobular carcinoma** (5–10% of cases) is characterized by small, bland tumor cells forming a single-file pattern.
- Multifocal and bilateral disease occurs commonly.
  - About 50% are ER/PR-positive; these tumors do not overexpress HER2.
- **Mucinous (colloid) carcinoma** is characterized microscopically by clusters of bland tumor cells floating within pools of mucin. It has a better prognosis.
  - Hormone receptors are positive; these tumors do not overexpress HER2.

KP00710.indb 234 13/10/22 1:53 PM

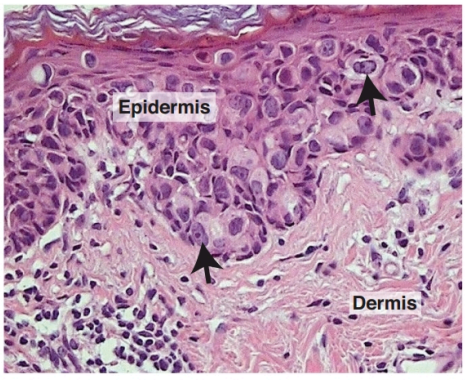
- **Tubular carcinoma** rarely metastasizes and has an excellent prognosis.
  - Hormone receptors are positive; these tumors do not overexpress HER2.
- **Medullary carcinoma** is characterized microscopically by pleomorphic tumor cells forming syncytial groups surrounded by a dense lymphocytic host response. It has a better prognosis.
  - Hormone receptors are negative; the tumors do not overexpress HER2.
- **Inflammatory carcinoma** is related to tumor invasion into the dermal lymphatics with resulting lymphatic edema; it presents with red, warm, edematous skin. The prognosis is poor.
  - The term *peau d'orange* is used when the thickened skin resembles an orange peel. This sign is caused by the accentuation of the attachments of the suspensory ligaments of Cooper to the dermis.



© Richard P. Usatine, MD Used with permission.

Figure 23-3. Advanced Breast Cancer with Peau d'Orange Skin Involvement

Mammary Paget disease (Paget disease of the nipple) is commonly associated with an underlying invasive or in situ ductal carcinoma. It may present with ulceration, oozing, crusting, and fissuring of the nipple and areola. Microscopic examination shows intraepidermal spread of tumor cells (Paget cells), with the cells occurring singly or in groups within the epidermis; there is often a clear halo surrounding the nucleus.



© Giovannini, D'Atri, et al. *World Journal of Surgical Oncology*. 2006. Used with permission.

Figure 23-4. Paget Disease of the Nipple

Note the intraepidermal tumor cells (arrows) with prominent nucleoli and dermal lymphocytic infiltrate.

KP00710.indb 235 13/10/22 1:53 PM

The prognosis of breast cancer depends on the following:

- Axillary lymph node status as determined by sentinel node biopsy (SNB) or axillary dissection. In most cases, SNB is recommended to evaluate clinically tumor-free regional nodes.
- Size of tumor
- Histological type and grade of tumor
- ER/PR receptor status is used to select patients for endocrine forms of therapy.
- Overexpression of HER2/neu is associated with more aggressive behavior than other types of breast cancer; patients may respond to therapy with trastuzumab.

Treatment of breast cancer depends on the stage and other tests.

- Urokinase plasminogen activator (uPA) and plasminogen activator inhibitor (PAI-1) as measured by ELISA are used to guide treatment decisions with node-negative breast cancer, along with multiparameter gene expression analysis.
- Cancer antigen 15-3 (CA 15-3), cancer antigen 27.29 (CA 27.29), and carcinoembryonic antigen (CEA) are used to monitor patients with metastatic disease undergoing therapy.

Metastatic Cancers

Although the majority of cancers in the breast are primaries, **cancer from other organs can spread to the breast**. Lung cancer may spread by contiguity or via the lymphatics.

GYNECOMASTIA

Gynecomastia is a unilateral or bilateral benign breast enlargement in a male.

Causes

Causes of gynecomastia include conditions altering the androgen-estrogen balance:

- Physiologic (newborn infants, pubescent adolescents, and elderly)
- Pathologic (cirrhosis, Klinefelter syndrome, pituitary tumors such as prolactinomas)
- Side effect of drugs (spironolactone and ketoconazole)

Histologic Features

Microscopically, gynecomastia is characterized by:

- Ductal epithelial hyperplasia
- Ductal elongation and branching
- Proliferation of periductal fibroblasts
- Increase in vascularity in the involved tissue

KP00710.indb 236 13/10/22 1:53 PM

Male Pathology 24

LEARNING OBJECTIVES

- ❑ Explain information related to the pathology of the penis and testes
- ❑ Solve problems concerning testicular cancer
- ❑ Solve problems concerning prostate disease

PENIS

Congenital Disorders

Epispadias is a urethral opening on the dorsal surface of the penis, while **hypospadias** is a urethral opening on the ventral surface. Both disorders have an increased risk of urinary tract infection and infertility.

NOTE

Both epispadias and hypospadias may be associated with undescended testes.

Acquired Conditions

Balanitis/balanoposthitis is inflammation of the glans penis, and the glans and foreskin, respectively. Causes include poor hygiene and lack of circumcision.

Peyronie disease is penile fibromatosis resulting in curvature of the penis during erection.

HPV-Associated Conditions

Condyloma acuminatum is a warty, cauliflower-like growth, with the causative agents most frequently being HPV serotypes 6 and 11.

Squamous cell carcinoma (SCC) is uncommon in the United States, and is often related to infection with HPV serotypes 16 and 18. There is an increased risk in uncircumcised males (multicentric carcinoma in situ). Precursor lesions include Bowen disease, bowenoid papulosis, and erythroplasia of Queyrat (a red plaque with carcinoma in situ histology).

Erectile Disorders

Priapism is a persistent painful erection that can be caused by sickle cell anemia (causes blood sludging in penis), trauma, and drugs (e.g., trazodone).

Erectile dysfunction (ED). Causes of impotence include psychological factors, decreased testosterone, vascular insufficiency (most common cause age >50), neurologic disease (multiple sclerosis, diabetic neuropathy, radical prostatectomy), some medications (leuprolide, methyldopa, finasteride, psychotropic medications), hypothyroidism, prolactinoma, and penile disorders.

KP00710.indb 237 13/10/22 1:53 PM

TESTES

Nonneoplastic Conditions

Varicocele is a dilated pampiniform venous plexus and internal spermatic vein, usually on the left side. It may cause infertility. Clinically, it resembles a "bag of worms" superior to the testicle.

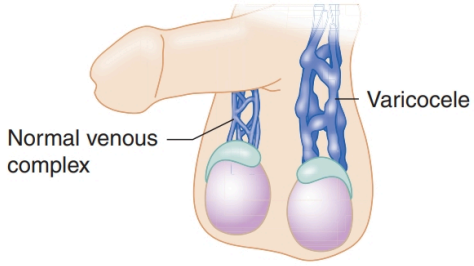


Figure 24-1. Varicocele

Hydrocele refers to fluid within the tunica vaginalis.

Spermatocele is an epididymal cyst containing sperm. On physical examination it transilluminates.

Epididymitis presents with fever and gradual onset of scrotal pain.

- Acute epididymitis that affects men age <35 is often caused by *N. gonorrhoeae* or *C. trachomatis*.
- Acute epididymitis that affects men age >35 is often caused by *E. coli* or *Pseudomonas*.
- Chronic epididymitis can be caused by TB.

Orchitis presents with sudden onset of testicular pain and fever. It is frequently viral, particularly due to the mumps virus.

Testicular torsion is twisting of the spermatic cord; may be associated with physical activity or trauma; and is a clinical emergency that can cause painful hemorrhagic infarction leading to gangrene.

Cryptorchidism is a failure of one or both testes to descend; the undescended testes are most commonly found in the inguinal canal. The undescended testes have an increased risk for developing seminoma.

Male infertility

- Decreased sperm count due to **primary testicular dysfunction** can be caused by Leydig cell dysfunction or seminiferous tubule dysfunction.
- Decreased sperm count due to **secondary hypogonadism** can be caused by pituitary and hypothalamic dysfunction.
- Inability of sperm to exit the body in sufficient numbers may be caused by **obstruction of the vas deferens or disordered ejaculation**.

KP00710.indb 238 13/10/22 1:53 PM

TESTICULAR CANCER

Testicular cancer typically presents with a firm, painless testicular mass; nonseminomatous tumors may present with widespread metastasis. Caucasians have a higher incidence than African Americans.

Risk factors include:

- Cryptorchidism (3–5× increased risk)
- Testicular dysgenesis (testicular feminization and Klinefelter syndrome)
- Positive family history

Diagnostic Studies

Clinically, U/S typically shows a hypoechoic intratesticular mass. Serum tumor marker studies can be helpful in confirming the diagnosis. Treatment is radical orchiectomy and possible chemotherapy/radiotherapy. Staging includes examination of the surgically resected specimen, including a lymph node dissection, along with imaging studies and lab tests.

Serum markers are used to monitor disease.

- AFP is produced by yolk sac tumors.
- β-hCG is produced by choriocarcinoma and any tumor with syncytiotrophoblastic giant cells.
- LDH is used to measure tumor burden.

Histologic Types of Testicular Tumors

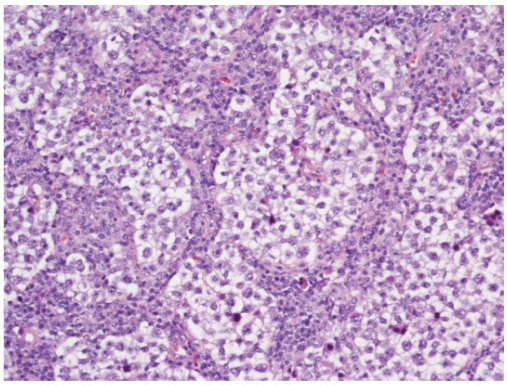
Germ cell tumors are usually hyperdiploid.

- **Seminoma** is the most common germ cell tumor in adults, with mean age 40. It is characteristically sensitive to both chemotherapy and radiation, and has an excellent prognosis (early stage seminoma has 95% cure rate). A variant is spermatocytic seminoma, a disease of older men, also with an excellent prognosis. On gross examination the tumor has a pale tan, bulging cut surface. Microscopic exam shows sheets of monotonous cells (with clear cytoplasm and round nuclei) separated by fibrous septae. Lymphocytes, granulomas, and giant cells may be seen.

CLINICAL CORRELATE

The most common regional metastatic lymph nodes for testicular cancer are the **paraaortic lymph nodes**, with lymphatic drainage following the gonadal vessels to the retroperitoneum.

KP00710.indb 239 13/10/22 1:53 PM



© Gregg Barré, MD Used with permission.

Figure 24-2. Seminoma

- **Embryonal carcinoma** is more aggressive than seminoma and affects adults ages 20–40. It causes bulky masses with hemorrhage and necrosis. Microscopy shows large primitive cells.
- **Choriocarcinoma** is a highly malignant tumor that often has widespread metastasis at the time of diagnosis; hematogenous spread to lungs and liver is particularly common. The often small tumor has extensive hemorrhage and necrosis. Microscopically, syncytiotrophoblasts and cytotrophoblasts are seen.
- **Yolk sac tumor (endodermal sinus tumor)** is the most common germ cell tumor in children; in pediatric cases, the prognosis is good. In adults, the prognosis may depend on the other histologic types that are admixed. Microscopically, yolk sac tumors show numerous patterns. Schiller-Duval bodies are glomeruloid structures.
- **Teratoma** often causes cystic masses which may contain cartilage and bone. Microscopically, mature teratoma usually contains ectodermal, endodermal, and mesodermal tissue in a haphazard arrangement. Immature elements contain embryonic tissue. Prepubertal cases are benign regardless of immature elements; teratomas in adults have malignant potential.



Figure 24-3. Teratoma of Testes, Producing Hair and Teeth

KP00710.indb 240 13/10/22 1:53 PM

- **Mixed germ cell tumors.** As many as 60% of germ cell tumors contain >1 component. When both teratoma and embryonal carcinoma are present, the name *teratocarcinoma* is used.

Sex cord–stromal tumors include Leydig cell and Sertoli cell tumors.

- **Leydig cell tumors** cause painless testicular masses, and have a bimodal distribution (prepubertal and age >50). They may produce androgens and estrogens.
  - In adults, the hormonal secretion can produce gynecomastia; in children, it can produce precocious puberty.
  - Benign tumors (90%) have an excellent prognosis; malignant tumors (10%) can be refractory to chemotherapy and radiation therapy.
  - Tumor cells have abundant pink cytoplasm.
- **Sertoli cell tumors** are rare and usually benign. Microscopically, they show tubule formation.

Other tumors:

- **Testicular lymphoma** is the most common testicular tumor in men >age 60. It is most commonly non-Hodgkin lymphoma, diffuse large cell type.
- **Scrotal squamous cell carcinoma** is associated with exposure to soot (chimney sweeps).

PROSTATE

Benign Prostatic Hyperplasia

Benign prostatic hyperplasia (BPH) (also called nodular hyperplasia; glandular and stromal hyperplasia) is extremely common. Androgens (dihydrotestosterone) play an important role in the pathogenesis, and the lesion is not premalignant. The incidence increases with age (age 60 is 70%; age 70 is 80%). BPH typically presents with the following:

- Decreased caliber and force of stream
- Trouble starting (hesitancy)/stopping the stream
- Postvoid dribbling
- Urinary retention
- Incontinence
- Urgency/frequency
- Nocturia/dysuria
- Possible elevation in prostate-specific antigen (PSA) but usually <10 ng/mL

Complications include urinary tract infection, urinary bladder trabeculation and diverticula formation, and hydronephrosis and renal failure (rare). Treatment varies, with available modalities including transurethral resection of prostate (TURP); the 5-alpha reductase inhibitor, finasteride (Proscar); and the selective alpaha-1 receptor blockers, terazosin and prazosin.

BRIDGE TO ANATOMY

- Prostatic hyperplasia → transitional/periurethral zone
- Prostatic carcinoma → peripheral zone

KP00710.indb 241 13/10/22 1:53 PM

Grossly, BPH causes an enlarged prostate with well-demarcated nodules in the transition and central (periurethral) zones, which often results in slit-like compression of the prostatic urethra. Microscopically, the lesion shows glandular and stromal hyperplasia resulting in the characteristic prostate enlargement.

Prostate Cancer

Prostate adenocarcinoma is the most common cancer in men in the United States and the second most common cause of cancer death in men. The incidence increases with age, and the highest rate is in African Americans.

- Often clinically silent but may present with lower back pain secondary to metastasis
- Advanced localized disease may present with urinary tract obstruction or UTI (rare)
- Tumor can be detected with digital rectal exam (induration), serum PSA level, and transrectal U/S and biopsy
- Metastases most commonly involve obturator and pelvic lymph nodes
- Osteoblastic bone metastasis to lumbar spine can occur, and can be associated with elevated alkaline phosphatase

Treatment of local disease is prostatectomy and/or external beam radiation. Metastatic disease is treated with orchiectomy, estrogens, or LHRH agonists and anti-androgens. The disease course can be monitored with PSA levels.

Pathologically, an ill-defined, firm, yellow mass commonly arises in the posterior aspect of the peripheral zone. Microscopically, adenocarcinoma is graded with the **Gleason system**, which scores glandular differentiation. *TMPRSS2-ETS* fusion genes are present in nearly 50% of all prostatic carcinomas.

Prostatitis

- **Acute prostatitis** is usually caused by intraprostatic reflux of urinary tract pathogens.
- **Chronic prostatitis** may develop following recurrent acute prostatitis, and bacterial pathogens may not be detectable. Chronic nonbacterial prostatitis (**chronic pelvic pain syndrome**) is more common than bacterial prostatitis.
- Clinical findings can include fever (acute prostatitis), pain (lower back, perineal, or suprapubic), painful prostate on rectal exam, and dysuria (with possible hematuria).

KP00710.indb 242 13/10/22 1:53 PM

Endocrine Pathology 25

LEARNING OBJECTIVES

- ❑ Demonstrate understanding of disease of the thyroid, parathyroid, adrenal, pituitary, and pineal gland
- ❑ Describe the relationship between the hypothalamus and pituitary gland
- ❑ Solve problems concerning multiple endocrine neoplasia syndromes
- ❑ Explain information related to diabetes mellitus

THYROID GLAND

Goiter

Multinodular goiter (nontoxic goiter) refers to an enlarged thyroid gland with multiple colloid nodules. Females are affected more often than males. It is frequently asymptomatic, and the patient is typically euthyroid, with normal T4, T3, and TSH. **Plummer syndrome** is the development of hyperthyroidism (toxic multinodular goiter) late in the course. **Endemic goiter** is due to dietary deficiency of iodine; it is uncommon in the United States.

Microscopically, the tissue shows nodules of varying sizes composed of colloid follicles. Calcification, hemorrhage, cystic degeneration, and fibrosis can also be present.

Hyperthyroidism and Hypothyroidism

The term ***hyperthyroidism*** is used when the mean metabolic rate of all cells is increased due to increased T4 or T3. Clinical features include tachycardia and palpitations; nervousness and diaphoresis; heat intolerance; weakness and tremors; diarrhea; and weight loss despite a good appetite.

- Lab studies:
  - In primary hyperthyroidism, TSH is decreased.
  - In secondary and tertiary hyperthyroidism, TSH is elevated.
  - Free T4 is elevated.
- **Graves disease** is an autoimmune disease characterized by production of IgG autoantibodies to the TSH receptor. Females are affected more frequently than males, with peak age 20–40. Clinical features include hyperthyroidism, diffuse goiter, ophthalmopathy (exophthalmus), and dermopathy (pretibial myxedema). Microscopically, the thyroid has hyperplastic follicles with scalloped colloid.

CLINICAL CORRELATE

TSH is the most sensitive test in thyroid disease. If it is normal, the patient is euthyroid.

NOTE

The original name for the autoantibodies of Graves disease was long-acting thyroid stimulator (LATS). The current name is **thyroid-stimulating immunoglobulin (TSI).**

KP00710.indb 243 13/10/22 1:53 PM

- **Other causes of hyperthyroidism** include toxic multinodular goiter, toxic adenoma (functioning adenoma producing thyroid hormone), and Hashimoto and subacute thyroiditis (transient hyperthyroidism).

The term ***hypothyroidism*** is used when the mean metabolic rate of all cells is decreased due to decreased T4 or T3. Clinical features include fatigue and lethargy; sensitivity to cold temperatures; decreased cardiac output; myxedema (accumulation of proteoglycans and water); facial and periorbital edema; peripheral edema of the hands and feet; deep voice; macroglossia; constipation; and anovulatory cycles.

- Lab studies:
  - In primary hypothyroidism, TSH is elevated.
  - In secondary and tertiary hypothyroidism, TSH is decreased.
  - Free T4 is decreased.

Iatrogenic hypothyroidism is the most common cause of hypothyroidism in the United States, and is secondary to thyroidectomy or radioactive iodine treatment. Treatment is thyroid hormone replacement.

Congenital hypothyroidism (cretinism) in endemic regions is due to iodine deficiency during intrauterine and neonatal life, and in nonendemic regions is due to thyroid dysgenesis. Patients present with failure to thrive, stunted bone growth and dwarfism, spasticity and motor incoordination, and mental retardation. Goiter is seen in endemic cretinism.

Thyroiditis

Hashimoto thyroiditis is a chronic autoimmune disease characterized by immune destruction of the thyroid gland and hypothyroidism. It is the most common noniatrogenic/nonidiopathic cause of hypothyroidism in the United States; it most commonly causes painless goiter in females more than males, with peak age 40–65.

Hashimoto thyroiditis is the most common cause of hypothyroidism (due to destruction of thyroid tissue), though the initial inflammation may cause transient hyperthyroidism (hashitoxicosis). Hashimoto may be associated with other autoimmune diseases (SLE, rheumatoid arthritis, Sjögren syndrome, etc.), and it has an increased risk of non-Hodgkin B-cell lymphoma. Grossly, Hashimoto produces a pale, enlarged thyroid gland; microscopically, it shows lymphocytic inflammation with germinal centers and epithelial "Hürthle cell" changes.

Subacute thyroiditis (also called de Quervain thyroiditis and granulomatous thyroiditis) is the second most common form of thyroiditis; it affects females more than males, with peak age 30–50. Patients may complain of odynophagia (pain on swallowing).

- Typically preceded by a viral illness
- Produces a tender, firm, enlarged thyroid gland
- May be accompanied by transient hyperthyroidism

Microscopy shows granulomatous thyroiditis. The disease typically follows a self-limited course.

KP00710.indb 244 13/10/22 1:53 PM

Riedel thyroiditis is a rare disease of unknown etiology, characterized by destruction of the thyroid gland by dense fibrosis and fibrosis of surrounding structures (trachea and esophagus). It affects females more than males, and most patients are middle-aged.

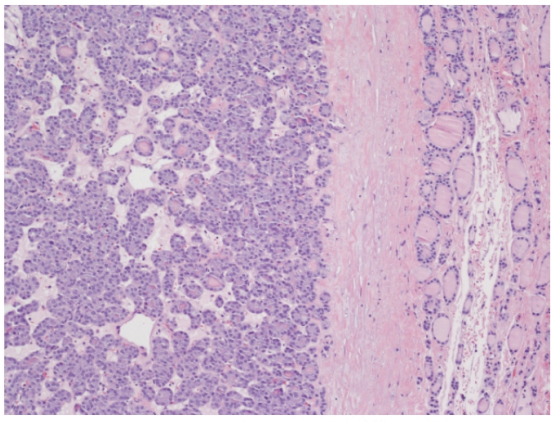
- Causes an irregular, hard thyroid that is adherent to adjacent structures
- May clinically mimic carcinoma and present with stridor, dyspnea, or dysphagia

Microscopic exam shows dense fibrous replacement of the thyroid gland with chronic inflammation. Reidel thyroiditis is associated with retroperitoneal and mediastinal fibrosis.

Thyroid Neoplasia

Thyroglossal duct cyst presents as a midline neck mass in a young patient. Its epithelium varies with location (squamous/respiratory). It may become infected and painful. Treatment is surgical.

Adenomas: follicular adenoma is the most common. Clinically, adenomas are usually painless, solitary, encapsulated nodules that appear "cold" on thyroid scans. They may be functional and cause hyperthyroidism (toxic adenoma).



© Gregg Barré, MD Used with permission.

Figure 25-1. Follicular Adenoma *(left)*, Separated from Normal Thyroid Parenchyma *(right)*, by the Capsule *(center)*

Papillary carcinoma accounts for 80% of malignant thyroid tumors. It affects females more than males, with peak age 20–50. Radiation exposure is a risk factor. Resection is curative in most cases. Radiotherapy with iodine 131 is effective for metastases. The prognosis is excellent, with 20-year survival 90% due to slow growth and metastasis to regional cervical lymph nodes. There are chromosomal rearrangements of the *RET* oncogene.

Microscopically, the tumor typically exhibits a papillary pattern. Occasional psammoma bodies may be seen. Characteristic nuclear features include clear "Orphan Annie eye" nuclei, nuclear grooves, and intranuclear cytoplasmic inclusions. Lymphatic spread to cervical nodes is common.

KP00710.indb 245 13/10/22 1:53 PM

Follicular carcinoma accounts for 15% of malignant thyroid tumors. It affects females more than males, with peak age 40–60. Hematogenous metastasis to the bones or lungs is common. These cancers are microscopically distinguished from follicular adenoma by the presence of capsular invasion.

Medullary carcinoma accounts for 5% of malignant thyroid tumors. It arises from C cells (parafollicular cells) and secretes calcitonin. Microscopic exam shows nests of polygonal cells in an amyloid stroma. A minority of cases (25%) is associated with MEN 2 and MEN 3 syndromes, and those cases tend to be multicentric. Activating *RET* mutations are present in familial and sporadic types.

Anaplastic carcinoma affects females more than males, with peak age >60. It can present with a firm, enlarging, and bulky mass, or with dyspnea and dysphagia. The tumor has a tendency for early widespread metastasis and invasion of the trachea and esophagus. Microscopically, the tumor is composed of undifferentiated, anaplastic, and pleomorphic cells. This very aggressive tumor is often rapidly fatal.

PARATHYROID GLANDS

Hyperparathyroidism

Primary hyperparathyroidism can be caused by the following:

- Adenomas (80%); may be associated with MEN 1
- Parathyroid hyperplasia (15%)
  - Characterized by diffuse enlargement of all 4 glands; the enlarged glands are usually composed of chief cells
  - Parathyroid carcinoma is very rare
- Hyperparathyroidism can also occur as a paraneoplastic syndrome of lung and renal cell carcinomas.

The excess production of parathyroid hormone (PTH) leads to hypercalcemia, with lab studies showing elevated serum calcium and PTH.

NOTE

Osteitis fibrosa cystica (von Recklinghausen disease) is seen when excessive parathyroid hormone (hyperparathyroidism) causes osteoclast activation and generalized bone resorption (causing possible bone pain, deformities, and fractures). It is common in primary hyperparathyroidism.

- Excess parathyroid hormone may be produced by parathyroid adenoma or parathyroid hyperplasia
- "Brown tumors" are masses produced by cystic enlargement of bones with areas of fibrosis and organized hemorrhage

Hypoparathyroidism

Primary hyperparathyroidism is often asymptomatic, but may cause kidney stones, osteoporosis and osteitis fibrosa cystica, metastatic calcifications, or neurologic changes.

Secondary hyperparathyroidism is caused by any disease that results in hypocalcemia, leading to increased secretion of PTH by the parathyroid glands; it can result from chronic renal failure, vitamin D deficiency, or malabsorption.

Hypoparathyroidism can result from the surgical removal of glands during thyroidectomy, DiGeorge syndrome, or a hereditary autoimmune syndrome caused by mutations in the autoimmune regulator gene *AIRE*. Patients present with muscle spasm and tingling of toes and lips. The hypocalcemia may also cause psychiatric disturbances and cardiac conduction defects (ECG: prolonged QT interval).

Treatment of hypoparathyroidism is vitamin D and calcium.

KP00710.indb 246 13/10/22 1:53 PM

PITUITARY GLAND, HYPOTHALAMUS, AND PINEAL GLAND

Pituitary Glands

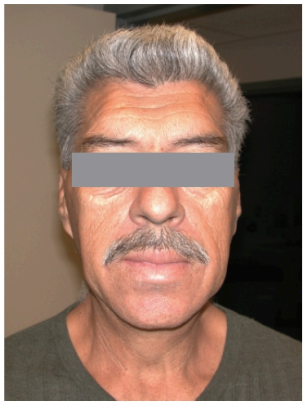
Pituitary adenomas are categorized as follows:

- Microadenoma if <1 cm
- Macroadenoma if >1 cm

Macroadenomas cause visual field defects.

GNAS1 mutations are common. Pathologically, adenomas are monomorphic compared with normal pituitary.

- **Prolactinoma** is the most common type of pituitary adenoma. Lactotroph cells secrete prolactin, which results in hyperprolactinemia. Clinical features include galactorrhea, amenorrhea, and infertility, or decreased libido and impotence.
- **Nonfunctional adenoma** may produce hypopituitarism.
- **Growth-hormone–producing adenoma** is characterized by elevated GH and elevated somatomedin C (insulin-like growth factor 1 [IGF-1]). It causes gigantism in children and acromegaly in adults.



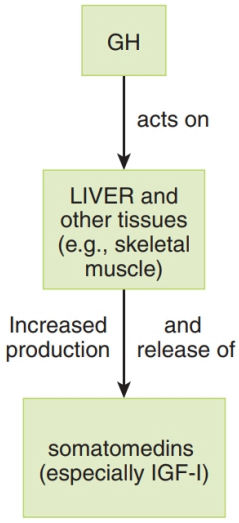
© Richard P. Usatine, MD
Used with permission.

Figure 25-2. Coarse Facial Features and Protruding Jaw Seen with Acromegaly

Sheehan syndrome is ischemic necrosis of the pituitary secondary to hypotension from postpartum hemorrhage resulting in panhypopituitarism.

Posterior pituitary syndromes include the following:

- **Diabetes insipidus**
  - Central diabetes insipidus is caused by ADH deficiency, which results in hypotonic polyuria, polydipsia, hypernatremia, and dehydration. Causes include head trauma and tumors.
  - Nephrogenic diabetes insipidus is caused by a lack of renal response to ADH.



CLINICAL CORRELATE

Primary pituitary disease that ablates >75% of the pituitary may lead to panhypopituitarism, which is characterized by abnormalities of the thyroid, adrenal gland, and reproductive organs. Common causes are:

- Pituitary adenomas
- Sheehan syndrome
- Craniopharyngiomas

CLINICAL CORRELATE

The most common cause of ectopic ADH secretion is cancer (especially small cell lung cancer, though any lung lesion can lead to this manifestation). For this reason, SIADH may be a marker for occult malignancy. Drugs that may also lead to SIADH include chlorpropamide, carbamazepine, cyclophosphamide, tricyclic antidepressants, and SSRIs.

KP00710.indb 247 13/10/22 1:53 PM

- **Syndrome of inappropriate ADH secretion (SIADH)** is caused by excessive production of antidiuretic hormone (ADH), resulting in oliguria, water retention, hyponatremia, and cerebral edema. Causes include paraneoplastic syndrome and head trauma.

Craniopharyngioma is a benign pituitary tumor derived from Rathke pouch remnants that are usually located above the sella turcica, but can extend downward to destroy the pituitary. It is the most common cause of hypopituitarism in children.

Hypothalamus

Hypothalamic disorders can cause a variety of problems:

- **Hypopituitarism** (including dwarfism) can be due to a lack of releasing hormones from the hypothalamus.
- **Central diabetes insipidus** is due to lack of ADH synthesis.
- **Precocious puberty** is usually due to a midline hamartoma in boys.
- The hypothalamus can also be affected in **hydrocephalus**.
- **Visual field changes** can complicate hypothalamic disorders.
- Masses can affect the hypothalamus, i.e., pituitary adenoma, craniopharyngioma, midline hamartoma, and Langerhans histiocytosis.
- Inflammatory processes can affect the hypothalamus, i.e., sarcoidosis and meningitis.

Pineal Gland

Pineal diseases include dystrophic calcification (a useful landmark for radiologists) and rarely tumors, with most being germ cell tumors.

ADRENAL GLAND

Hyperadrenalism

Cushing syndrome is characterized by increased levels of glucocorticoids. It is investigated with lab and imaging studies (*see* Physiology Lecture Notes). The most common cause is exogenous glucocorticoid administration.

Endogenous causes include:

- Cushing disease (hypersecretion of ACTH, usually due to a pituitary microadenoma)
- Secretion of ACTH from nonpituitary tumors (e.g., small cell lung cancer)
- ACTH-independent Cushing syndrome due to adrenal neoplasia

Clinical manifestations include hypertension, weight gain (truncal obesity, "buffalo hump" and moon facies), cutaneous striae, hirsutism and mental disturbances.

NOTE

Administration of **dexamethasone** (a cortisol analog) will typically suppress pituitary ACTH production, resulting in suppression of adrenal cortisol production and a decrease in urinary free cortisol.

KP00710.indb 248 13/10/22 1:53 PM

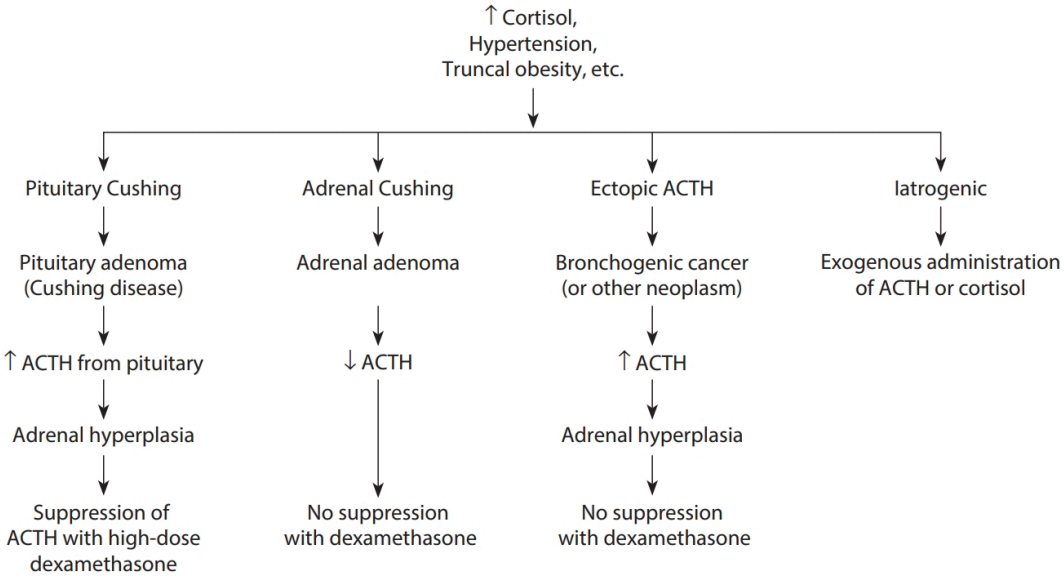


Figure 25-3. Cushing Syndrome and Its Effects

Hyperaldosteronism may cause hypertension and hypokalemia.

- **Primary** (decreased plasma renin)
  - Adrenocortical neoplasm: adenoma (Conn syndrome)
    - Circumscribed yellow nodule with vacuolated cells
    - Carcinoma: poorly demarcated lesion with cystic change and pleomorphic cells
  - Bilateral nodular hyperplasia of the adrenal
- **Secondary** (increased plasma renin) (e.g., renal artery stenosis)

Adrenogenital syndromes are adrenal disorders characterized by excess production of androgens and virilization. They are caused either by adrenocortical adenoma/carcinoma, which produces androgens, or by congenital adrenal hyperplasia, a cluster of autosomal recessive enzyme defects (most common is 21-hydroxylase deficiency).

Adrenal Insufficiency

Waterhouse-Friderichsen syndrome (acute adrenal insufficiency) is a potentially fatal, bilateral hemorrhagic infarction of the adrenal glands associated with sepsis, often due to an *N. meningitidis* infection in children. It is clinically characterized by disseminated intravascular coagulation (DIC), acute respiratory distress syndrome, hypotension and shock, and acute adrenal insufficiency. Treatment is antibiotics and steroid replacement.

Addison disease (chronic adrenocortical insufficiency) is caused by destruction of the adrenal cortex, leading to a deficiency of glucocorticoids, mineralocorticoids, and androgens. The most common cause is autoimmune adrenalitis, though adrenal involvement by TB or metastatic cancer are other possible causes. Patients present with gradual onset of weakness, skin hyperpigmentation, hypotension, hypoglycemia, poor response to stress, and loss of libido. Treatment is 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.

KP00710.indb 249 13/10/22 1:53 PM

Secondary adrenocortical insufficiency may be caused by disorders of the hypothalamus or pituitary (cancer or infection, for example). Since ACTH levels are low, hyperpigmentation does not occur.

Pheochromocytoma

Pheochromocytoma ("dark/dusky-colored tumor") is an uncommon benign tumor of the adrenal medulla, which produces catecholamines (norepinephrine and epinephrine). It can present with sustained or episodic hypertension and associated severe headache, tachycardia, palpitations, diaphoresis, and anxiety. Note the **rule of 10s**:

- 10% occur in **children**
- 10% are **bilateral**
- 10% are **malignant**
- 10% are **familial (MEN 2A and 2B)**
- 10% occur **outside the adrenal gland**

Urinary vanillylmandelic acid (VMA) and catecholamines are elevated. Microscopically, the tumor shows nests of cells (Zellballen) with abundant cytoplasm. Treatment is control of the patient's BP and surgical removal of the tumor.

ENDOCRINE DISORDERS IMPACTING MULTIPLE ORGANS

Multiple Endocrine Neoplasia Syndromes

Multiple endocrine neoplasia (MEN) syndromes are autosomal dominant conditions with incomplete penetrance that are characterized by hyperplasia and tumors of endocrine glands occurring at a young age.

- **MEN 1** (Werner syndrome) features tumors of the pituitary gland, parathyroids, and pancreas.
- Associated with peptic ulcers and Zollinger-Ellison syndrome
  - Affected gene is *MEN1*, a tumor suppressor gene which encodes a nuclear protein called menin
- **MEN 2A** (Sipple syndrome) features medullary carcinoma of the thyroid, pheochromocytoma, and parathyroid hyperplasia or adenoma.
  - Mutation of *RET* proto-oncogene
- **MEN 2B** features medullary carcinoma of the thyroid, pheochromocytoma, and mucocutaneous neuromas.
- Mutation of *RET* proto-oncogene

Diabetes Mellitus

Diabetes mellitus (DM) is a chronic systemic disease characterized by insulin deficiency or peripheral resistance, resulting in hyperglycemia and nonenzymatic glycosylation of proteins. Diagnosis is established by demonstrating **either** of the following:

KP00710.indb 250 13/10/22 1:53 PM

- Fasting glucose >126 mg/dL on at least 2 separate occasions
- Positive glucose tolerance test

A glycated hemoglobin (HbA1c) assay is used for certain patient populations. The diagnostic cutoff is 6.5%.

Type 1 diabetes (10% of cases) affects young people age <20.

- Risk factors include Northern European ancestry and specific HLA types (DR3, DR4, and DQ)
- Thought to be caused by autoimmune reaction triggered by an infection (coxsackie B virus) in a genetically susceptible individual
- Pathogenesis involves a lack of insulin due to autoimmune destruction of β cells (type IV hypersensitivity reaction)
- Symptoms include 3P's (polydipsia, polyuria, polyphagia); dehydration/electrolyte imbalance; metabolic ketoacidosis; coma/possible death
- Microscopic evaluation shows lymphocytic inflammation involving the islets of Langerhans (insulitis), leading to loss of β cells and fibrosis of the islets
- Treatment is insulin; patients are absolutely dependent on insulin to prevent ketoacidosis and coma

Type 2 diabetes (90% of cases) affects obese individuals of all ages. Approximately 10 million people in the United States are affected (half are undiagnosed), and incidence increases with age.

- Risk factors include obesity, increasing age, and genetic predisposition
- Pathogenesis involves reduced insulin secretion ("*peripheral insulin resistance*" describes reduced tissue sensitivity to insulin due to decreased numbers of insulin receptors on cell membranes)
- Symptoms may include 3P's (polydipsia, polyuria, polyphagia) or hyperosmolar nonketotic diabetic coma, but patients are commonly asymptomatic
- Microscopic evaluation shows nonspecific pancreas changes, focal atrophy, and amyloid deposition in islets (hyalinization)
- Treatment is diet/weight loss, oral antidiabetic drugs, and insulin as needed (more common in long-standing cases)

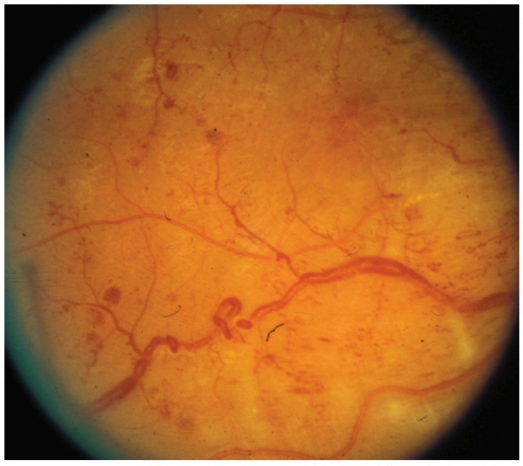
Vascular pathology. Diabetes is a major risk factor for atherosclerosis and its complications, including myocardial infarction (most common cause of death), stroke (CVA), and peripheral vascular disease. The vascular disease can lead to atrophy of skin and loss of hair of the lower extremities, claudication, nonhealing ulcers, and gangrene of lower extremities.

Diabetic nephropathy includes glomerular lesions, arteriolosclerosis, and pyelonephritis (*see* Renal chapter).

Diabetic retinopathy. Nonproliferative retinopathy is characterized by microaneurysms, retinal hemorrhages, and retinal exudates. Proliferative retinopathy is characterized by neovascularization and fibrosis. Diabetics also have an increased incidence of cataracts and glaucoma.

KP00710.indb 251 13/10/22 1:53 PM

Diabetic neuropathy can cause peripheral neuropathy, neurogenic bladder, and sexual impotence.



© Richard P. Usatine, MD / Paul D. Comeau, MD
Used with permission.

Figure 25-4. Diabetic Retinopathy with Hemorrhages, Venous Beading, and Looping of Vessels

KP00710.indb 252 13/10/22 1:53 PM

Bone Pathology 26

LEARNING OBJECTIVES

- ❑ Describe normal bone
- ❑ Explain information related to hereditary bone disorders
- ❑ Answer questions about Paget disease
- ❑ Differentiate osteoporosis, osteomalacia, and rickets
- ❑ Solve problems concerning osteomyelitis, benign tumors of bone, and malignant tumors of bone

NORMAL BONE

Components

Normal bone is composed of organic matrix and inorganic matrix.

- The **organic matrix** includes cells, type I collagen (90% of bone protein), osteocalcin, glycoproteins, and proteoglycans.
- The **inorganic matrix** includes calcium hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$, magnesium, potassium, chloride, sodium, and fluoride.

There are 3 cell types.

- **Osteoblasts** are responsible for the production of osteoid (unmineralized bone); they contain high amounts of alkaline phosphatase, have receptors for parathyroid hormone (PTH), and modulate osteoclast function.
- **Osteocytes** are responsible for bone maintenance; they are osteoblasts that have become incorporated in the matrix.
- **Osteoclasts** are responsible for bone resorption; they contain high amounts of acid phosphatase and collagenase, and resorb bone within Howship's lacunae.

Bone Physiology

Bone remodeling occurs throughout life and is necessary to maintain healthy bones. **Bone resorption** by osteoclasts is tightly balanced with bone formation by osteoblasts.

Important **hormones** involved in bone physiology include PTH, calcitonin, vitamin D, estrogen, thyroid hormone, cortisol, and GH.

KP00710.indb 253 13/10/22 1:53 PM

Formation of bones is as follows:

- **Intramembranous bone** occurs as direct bone formation without a "cartilage model." Intramembranous bones include flat bones such as the cranium, clavicle, vertebrae, wrist, and ankle bones. Intramembranous growth is also involved in appositional bone growth.
- **Endochondral bone** is indirect bone formation from a "cartilage model" at the epiphyseal growth plates; this type of bone formation occurs in long bones such as the femur, humerus, tibia, fibula, etc.

GENETIC SKELETAL DISORDERS

Achondroplasia

Achondroplasia is the most common form of inherited dwarfism. It is caused by an autosomal dominant mutation in fibroblast growth factor receptor 3 (*FGFR3*). Activation of *FGFR3* inhibits cartilage synthesis at the epiphyseal growth plate, resulting in decreased endochondral bone formation and premature ossification of the growth plates.

- Long bones are short and thick, leading to dwarfism with short extremities.
- Cranial and vertebral bones are spared, leading to relatively large head and trunk.
- Intelligence, life span, and reproductive ability are normal.

Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) ("brittle bone disease") is a hereditary defect leading to abnormal synthesis of type I collagen.

- Patients have generalized osteopenia (brittle bones), resulting in recurrent fractures and skeletal deformity
- Abnormally thin sclera with blue hue is common
- Laxity of joint ligaments leads to hypermobility
- Involvement of inner and middle ear bones produces deafness
- Occasional dentinogenesis imperfecta, characterized by small, fragile, and discolored teeth due to a deficiency of dentin
- Dermis may be abnormally thin, and skin is susceptible to easy bruising
- **Treatment** is supportive

NOTE

McCune-Albright syndrome presents with café au lait spots, precocious puberty (and other endocrine abnormalities), and polyostotic fibrous dysplasia.

Fibrous Dysplasia

Fibrous dysplasia presents with painful swelling, deformity, or pathologic fracture of involved bone (typically ribs, femur, or cranial bones), usually in children and young adults. *GNAS* gene mutations cause osteoblasts to produce fibrous tissue (microscopically, irregularly scattered trabeculae) rather than bone.

KP00710.indb 254 13/10/22 1:53 PM

Osteopetrosis

Osteopetrosis (or marble bone disease) is a hereditary defect leading to decreased osteoclast function, with resulting decreased resorption and thick sclerotic bones. X-ray shows symmetrical generalized osteosclerosis. Long bones may have broadened metaphyses, causing an "Erlenmeyer flask"-shaped deformity. Treatment is hematopoietic stem cell transplantation.

- **Autosomal recessive** type (**malignant**):
  - Affects infants and children (causes multiple fractures and early death due to anemia, infection, and hemorrhage)
- **Autosomal dominant** type (**benign**):
  - Affects adults (causes fractures, mild anemia, and cranial nerve impingement)

Pathology shows increased bone density and thickening of bone cortex. Myelophthisic anemia may result from marrow crowding. Cranial nerve compression due to narrowing of cranial foramina may result in blindness, deafness, and facial nerve palsies. Hydrocephalus may develop due to obstruction of CSF.

METABOLIC DISORDERS OF BONE

Paget Disease

Paget disease (osteitis deformans) is a 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. There is an association with paramyxovirus and mutations of *SQSTM1*.

- Seen in those age >40
- Common in those of European ancestry
- Common sites of involvement include the skull, pelvis, femur, and vertebrae
- Majority of cases are polyostotic and mild

Paget disease develops in 3 stages:

- **Osteolytic stage** (osteoclastic activity predominates)
- **Mixed osteolytic-osteoblastic stage**
- **Osteosclerotic stage** (osteoblastic activity predominates in this "burnout stage")

Paget disease can cause bone pain and deformity, fractures, and warmth of the overlying skin due to bone hypervascularity. X-rays show bone enlargement with lytic and sclerotic areas. Lab studies show highly elevated serum alkaline phosphatase and increased levels of urinary hydroxyproline. Complications include arteriovenous shunts within marrow, which may result in high-output cardiac failure and an increased incidence of osteosarcoma and other sarcomas.

Microscopically, there is a haphazard arrangement of cement lines, creating a "mosaic pattern" of lamellar bone. Involved bones are thick but weak and fracture easily. Skull involvement leads to increased head size and foraminal narrowing that can impinge on cranial nerves, often leading to deafness. Involvement of facial bones may produce a lion-like facies.

KP00710.indb 255 13/10/22 1:53 PM

NOTE

In osteoporosis, bone is formed normally but in decreased amounts.

Osteoporosis

Osteoporosis is decreased bone mass (osteopenia), resulting in thin, fragile bones susceptible to fracture. It is the most common bone disorder in the United States. It most commonly occurs in postmenopausal Caucasian women and the elderly.

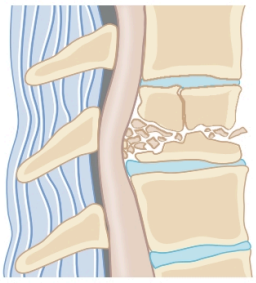


Figure 26-1. Marked Thinning of Bony Trabeculae in Osteoporosis

Primary causes of osteoporosis include the following:

- Estrogen deficiency (postmenopausal, Turner syndrome)
- Genetic factors (low density of original bone)
- Lack of exercise
- Old age
- Nutritional factors

Secondary causes include immobilization, endocrinopathies (e.g., Cushing disease, thyrotoxicosis), malnutrition (e.g., deficiencies of calcium, vitamins C and D, protein), corticosteroids, smoking/alcohol consumption, genetic disease (e.g., Gaucher disease).



Compression Fracture

- Patients may experience bone pain and fractures; weight-bearing bones are predisposed to fractures.
- Common fracture sites include vertebrae (compression fracture); femoral neck (hip fracture); and distal radius (Colles fracture).
- Kyphosis and loss of height may result.
- X-rays show generalized radiolucency of bone (osteopenia).

Dual-energy x-ray absorptiometry (DEXA) can measure bone mineral density to predict fracture risk. Lab studies may show normal serum calcium, phosphorus, and alkaline phosphatase, but the diagnosis is not based on labs. Microscopically, the bone has thinned cortical and trabecular bone.

Treatment can include estrogen replacement therapy (controversial; not recommended currently); weight-bearing exercise; calcium and vitamin D; bisphosphonate (alendronate); and calcitonin.

KP00710.indb 256 13/10/22 1:53 PM

Osteomalacia and Rickets

Osteomalacia and rickets are both characterized by decreased mineralization of newly formed bone. They are usually caused by deficiency or abnormal metabolism of vitamin D. Specific causes include dietary deficiency of vitamin D, intestinal malabsorption, lack of sunlight, and renal and liver disease. Treatment is vitamin D and calcium supplementation.

- **Osteomalacia** (adults) is due to impaired mineralization of the osteoid matrix resulting in thin, fragile bones susceptible to fracture. The patient may present clinically with bone pain or fractures (vertebrae, hips, and wrist). X-rays show transverse lucencies called Looser zones. Lab studies show low serum calcium, low serum phosphorus, and high alkaline phosphatase.
- **Rickets** (children) occurs in children prior to closure of the epiphyses. Both remodeled bone and bone formed at the epiphyseal growth plate are undermineralized. Enchondral bone formation is affected, leading to skeletal deformities. Skull deformities include craniotabes (softening, seen in early infancy) and frontal bossing (hardening, later in childhood). The "rachitic rosary" is a deformity of the chest wall as a result of an overgrowth of cartilage at the costochondral junction. Pectus carinatum, lumbar lordosis, bowing of the legs, and fractures also occur.

NOTE

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

CLINICAL CORRELATE

Lab findings help to distinguish osteomalacia from osteoporosis.

Osteitis Fibrosis Cystica

Osteitis fibrosa cystica (or von Recklinghausen disease of bone) is seen when excessive parathyroid hormone (hyperparathyroidism) causes osteoclast activation and generalized bone resorption, resulting in possible bone pain, bone deformities, and fractures.

- Seen commonly in primary hyperparathyroidism
- Excess parathyroid hormone may be produced by parathyroid adenoma or parathyroid hyperplasia
- Can be resolved if hyperparathyroidism is treated

Microscopic exam shows excess bone resorption with increased number of osteoclasts, fibrous replacement of marrow, and cystic spaces in trabecular bone (dissecting osteitis). "Brown tumors" are brown bone masses produced by cystic enlargement of bones with areas of fibrosis and organized hemorrhage.

INFLAMMATORY BONE DISEASE

Pyogenic Osteomyelitis

Pyogenic osteomyelitis is bone inflammation due to bacterial infection. The most common route of infection is **hematogenous spread** (leading to seeding of bone after bacteremia); this type of spread often affects the metaphysis. Other routes of spread include direct inoculation (e.g., trauma) and spread from an adjacent site of infection (e.g., prosthetic joint).

The most common infecting organism is *S. aureus*; other important pathogens include *E. coli*, streptococci, gonococci, *H. influenzae*, *Salmonella* (common in sickle cell disease), and *Pseudomonas* (common in IV drug abusers and diabetics).

KP00710.indb 257 13/10/22 1:53 PM

Clinically, osteomyelitis is characterized by fever and leukocytosis; and localized pain, erythema, and swelling. X-ray studies may be normal for up to 2 weeks, and then initially show periosteal elevation followed by a possible lytic focus with surrounding sclerosis. MRI and nuclear medicine studies are more sensitive and specific.

Microscopic examination shows suppurative inflammation. Vascular insufficiency can lead to ischemic necrosis of bone; a sequestrum is an area of necrotic bone, while an involucrum is the new bone formation that surrounds the sequestrum. The diagnosis is established with blood cultures or with bone biopsy and culture.

Patients are treated with antibiotics and some may require surgical drainage. Complications include fracture, intraosseous (Brodie) abscess, secondary amyloidosis, sinus tract formation, squamous cell carcinoma of the skin at the site of a persistent draining sinus tract, and, rarely, osteogenic sarcoma.



Source: commons.wikimedia.org

Figure 26-2. Tibial Radiolucencies Representing Osteomyelitis.

Tuberculous osteomyelitis is seen in 1% of cases of TB. It presents with pain or tenderness, fever, night sweats, and weight loss. Biopsy shows caseating granulomas with extensive destruction of the bones. Common sites of involvement include thoracic and lumbar vertebrae ("Pott disease"). Complications include vertebral compression fracture, psoas abscesses, and secondary amyloidosis.

Osgood-Schlatter Disease

Osgood-Schlatter disease is a common cause of knee pain in adolescents. It develops when stress from the quadriceps during rapid growth causes inflammation of the proximal tibial apophysis at the insertion of the patellar tendon. Permanent changes to the knees (knobby knees) may develop. The lesion is not usually biopsied.

KP00710.indb 258 13/10/22 1:53 PM

MISCELLANEOUS BONE DISORDERS

Avascular Necrosis

Avascular necrosis (or aseptic necrosis and osteonecrosis) is the term used for ischemic necrosis of bone and bone marrow. Causes include trauma and/or fracture (**most common**); idiopathic; (25% of cases); steroid use; sickle cell anemia; Gaucher disease; and caisson disease (seen in divers).

Avascular necrosis can be complicated by osteoarthritis and fractures.

Hypertrophic Osteoarthropathy

Hypertrophic Osteoarthropathy, presents with painful swelling of wrists, fingers, ankles, knees, or elbows.

- Seen in the setting of bronchogenic carcinoma (a paraneoplastic syndrome), chronic lung diseases, cyanotic congenital heart disease, and inflammatory bowel disease
- Can regress if underlying disease is treated

Pathologically, the ends of long bones show periosteal new bone formation, which can produce digital clubbing and often arthritis of adjacent joints.

BONE NEOPLASIA

Benign Tumors of Bone

Osteoma is a benign neoplasm that frequently involves the skull and facial bones. Osteoma can be associated with Gardner syndrome. Malignant transformation doesn't occur.

Osteoid osteoma is a benign, painful growth of the diaphysis of a long bone, often the tibia or femur. Males are affected more than females, with peak age 5–25. Pain tends to be worse at night and relieved by aspirin. X-rays show central radiolucency surrounded by a sclerotic rim. Microscopically, osteoblasts line randomly connected trabeculae.

Osteoblastoma is similar to an osteoid osteoma but larger (>2 cm) and often involves vertebrae.

Osteochondroma (exostosis) is a benign bony metaphyseal growth capped with cartilage, which originates from epiphyseal growth plate. It typically presents in adolescent males who have firm, solitary growths at the ends of long bones. It may be asymptomatic, cause pain, produce deformity, or undergo malignant transformation (rare). *Osteochondromatosis* (multiple hereditary exostoses) produces multiple, often symmetric, osteochondromas. Excision is usually curative.

KP00710.indb 259 13/10/22 1:53 PM



Figure 26-3. Osteochondroma Seen on Bony Protuberance on Distal Ulna

Enchondroma is a benign cartilaginous growth within the medullary cavity of bone, usually involving the hands and feet. It is typically solitary, asymptomatic, and requires no treatment. Multiple enchondromas (*enchondromatosis*) can occur as part of both Ollier disease (multiple and unilateral) and Maffucci syndrome (with hemangiomas), and carry a risk of malignant transformation.

Giant cell tumor of bone ("osteoclastoma") is a benign neoplasm containing multinucleated giant cells admixed with stromal cells. It is uncommon but occurs more often in females than in males, with peak age 20–50. Clinically, the tumor produces a bulky mass with pain and fractures. X-rays show an expanding lytic lesion surrounded by a thin rim of bone, with a possible "soap bubble" appearance. Treatment is surgery (curettage or *en bloc* resection). Osteoclastoma is locally aggressive with a high rate of recurrence (40–60%). In spite of being considered benign, approximately 2% will metastasize to the lungs.

Grossly, the tumor causes a red-brown mass with cystic degeneration that often involves the epiphyses of long bones, usually around the knee (distal femur and proximal tibia). Microscopically, multiple osteoclast-like giant cells are distributed within a background of mononuclear stromal cells.

Malignant Tumors of Bone

Osteosarcoma (osteogenic sarcoma) is the most common primary malignant tumor of bone. It occurs more frequently in males than in females, with most cases in teenage years (ages 10–25). Patients with familial retinoblastoma have a high risk.

Osteosarcoma presents with localized pain and swelling. The classic x-ray findings are Codman triangle (periosteal elevation), "sun burst" pattern, and bone destruction. Treatment is surgery and chemotherapy. The prognosis is poor, but is improved with aggressive management such as resection of single pulmonary metastases (hematogenous metastasis to the lungs is

KP00710.indb 260 13/10/22 1:53 PM

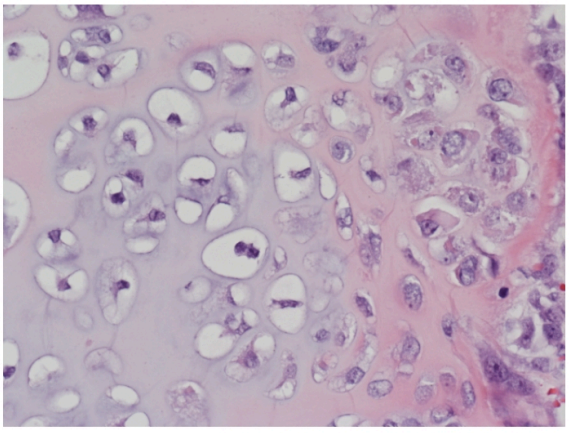
common). **Secondary osteosarcoma** is seen in the elderly; these highly aggressive tumors are associated with Paget disease, irradiation, and chronic osteomyelitis.



Figure 26-4. Osteosarcoma Seen in Fuzzy Calcifications Adjacent to Distal Femur

Grossly, osteosarcoma often involves the metaphyses of long bones, usually around the knee (distal femur and proximal tibia). It produces a large, firm, white-tan mass with necrosis and hemorrhage. Microscopically, anaplastic cells producing osteoid and bone are seen.

Chondrosarcoma is a malignant tumor of chondroblasts which may arise *de novo* or secondary to a preexisting enchondroma, exostosis, or Paget disease. Males are affected more frequently than females, with peak ages 30–60. It presents with enlarging mass with pain and swelling, and it typically involves the pelvic bones, spine, and shoulder girdle. Microscopically, there is cartilaginous matrix production. Radiographs show osteolytic destruction and "popcorn" calcification. The 5-year survival is predicted by histologic differentiation.



© Gregg Barré, MD Used with permission.

Figure 26-5. Chondrosarcoma

KP00710.indb 261 13/10/22 1:53 PM

Ewing sarcoma is a malignant neoplasm of undifferentiated cells arising within the marrow cavity. Males are affected slightly more often than females, with most cases in teenage years (ages 5–20). The classic translocation for Ewing sarcoma is t(11;22), which produces the EWS-FLI1 fusion protein.

Clinically, patients present with pain, swelling, and tenderness. X-ray studies show concentric "onion-skin" layering of new periosteal bone with soft tissue extension. Treatment is chemotherapy, surgery, and/or radiation; the 5-year survival rate is 75%.

Grossly, Ewing sarcoma often affects the diaphyses of long bones, with the most common sites being the femur, pelvis, and tibia. The tumor characteristically produces a white-tan mass with necrosis and hemorrhage. Microscopically, Ewing sarcoma is characterized by sheets of undifferentiated small, round, blue cells resembling lymphocytes, which may form Homer Wright pseudorosettes. The tumor cells erode through the cortex and periosteum and invade surrounding tissues.

Metastasis to bone is much more common than primary bone tumor. Common primary sites include prostate (often osteoblastic), breast, lung, thyroid, and kidney.

KP00710.indb 262 13/10/22 1:53 PM

Joint Pathology 27

LEARNING OBJECTIVES

- ❑ Solve problems concerning osteoarthritis, rheumatoid arthritis, and seronegative spondyloarthropathies
- ❑ Describe arthritis related to crystal deposition, infectious arthritis, and neuropathic arthropathy (Charcot joint)

ARTHRITIS

Osteoarthritis

Osteoarthritis (OA) (degenerative joint disease) is joint degeneration with loss of articular cartilage, with no to minimal inflammation. It is the most common form of arthritis. Risk increases with age; OA affects at least 1 joint in 80% of people age >70.

Clinically, there is an insidious onset of joint stiffness; deep, aching joint pain, which worsens with repetitive motion; decreased range of motion; crepitus; and joint effusions and swelling. Osteophytes may cause nerve compression. X-ray studies show narrowing of the joint space due to loss of cartilage; osteosclerosis and bone cysts; and osteophytes (osteophytic lipping).

The pathogenesis involves both biomechanical factors (aging or wear and tear of articular cartilage) and biochemical factors (chondrocyte injury and abnormal collagen activity). Predisposing factors include obesity, previous joint injury, ochronosis, diabetes, and hemarthrosis.

OA affects weight-bearing joints (knees, hips, and spine), often with asymmetrical involvement.

- There is degeneration and loss of articular cartilage with eburnation (exposed bone becomes polished) and subchondral bone sclerosis.
- The changes may include subchondral bone cysts, loose bodies (joint mice), which are free-floating fragments of cartilage and bone, and osteophytes (bone spurs), which are reactive bony outgrowths.
- **Heberden nodes** are osteophytes at the distal interphalangeal (DIP) joints, while **Bouchard nodes** are osteophytes at the proximal interphalangeal (PIP) joints.

Osteoarthritis vs RA

Osteoarthritis	RA
"Wear and tear"	Systemic autoimmune disease (+) Rheumatoid factor (+) Rheumatoid nodules
Degeneration of articular cartilage	Synovial proliferation
Knees and hands (DIP) in women; hips in men	Hands (PIP) and feet
Asymmetrical	Symmetrical and migratory

KP00710.indb 263 13/10/22 1:53 PM



© commons.wikimedia.org.

Figure 27-1. Heberden (Distal Interphalangeal Joint) and Bouchard (Proximal Interphalangeal Joint) Nodes in Patient with Osteoarthritis

Rheumatoid Arthritis

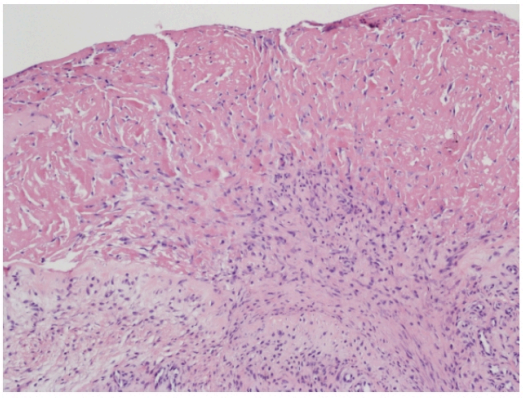
Rheumatoid arthritis (RA) is a systemic, chronic, inflammatory disease characterized by progressive arthritis, production of rheumatoid factor, and extra-articular manifestations. It affects females 4× more than men, with highest incidence at ages 20–50. Some cases have a genetic predisposition (HLA-DR4 and -DR1).

RA is thought to be caused by an autoimmune reaction triggered by an infectious agent in a genetically susceptible individual.

RA most commonly affects the hand, wrist, knee, and ankle joints, and the involvement tends to be symmetrical. There is often morning stiffness, which improves with activity.

- There is typically fusiform swelling, redness, and warmth of the proximal interphalangeal (PIP) joint.
- X-ray studies show juxta-articular osteoporosis and bone erosions; joint effusion may also be present.
- RA causes a diffuse proliferative synovitis, pannus formation (proliferation of the synovium and granulation tissue over the articular cartilage of the joint), fibrous and bony ankylosis (joint fusion), and joint deformities. Joint deformities can include:
  - Radial deviation of the wrist and ulnar deviation of the fingers
  - Swan neck deformity (hyperextension of PIP joint and flexion of DIP joint)
  - Boutonniere deformity (flexion of PIP and extension of DIP joints)
- Baker cysts (synovial cysts in the popliteal fossa) may be present.

KP00710.indb 264 13/10/22 1:53 PM



© Gregg Barré, MD Used with permission.

Figure 27-2. Pannus Formation (Rheumatoid Arthritis)

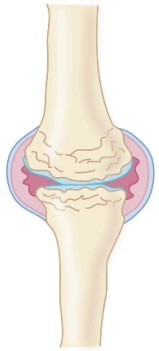
Lab studies show elevated sedimentation rate and hypergammaglobulinemia. Rheumatoid factor (RF) is an autoantibody (usually IgM) against the Fc fragment of IgG; it is present in 80% of cases. RF may circulate and form immune complexes, and titer of RF correlates with the severity of the arthritis and prognosis.

- Extra-articular manifestations may be prominent. Systemic symptoms include low-grade fever, malaise, fatigue, lymphadenopathy, and weakness. Arteries may show acute necrotizing vasculitis due to circulating antigen-antibody complexes.
- **Rheumatoid nodules**, subcutaneous skin nodules, are present in 25% of cases. They are usually found on extensor surfaces of the forearms and elbows, but can also be found in the heart valves, lung, pleura, pericardium, and spleen. They are composed of central fibrinoid necrosis surrounded by epithelioid macrophages, lymphocytes, and granulation tissue.
- **Sjögren syndrome** may be present in 15%. In **Felty syndrome**, RA accompanies splenomegaly and neutropenia. In **Caplan syndrome**, RA is associated with pneumoconiosis.
- Secondary amyloidosis may also complicate RA.



© Richard P. Usatine, MD Used with permission.

Figure 27-3. Ulnar Deviation at the Metacarpophalangeal Joints in Advanced Rheumatoid Arthritis



Rheumatoid Arthritis

27_Preclinical_Pathology_Ch27.indd 265 10/6/22 9:03 PM

CLINICAL CORRELATE

Complete fusion of the spine can occur in ankylosing spondylitis and can cause complete rigidity of the spine. The resulting condition is known as **bamboo spine**, which can be seen on x-ray.

Seronegative Spondyloarthropathies

Seronegative spondyloarthropathies are a group of disorders characterized by the following:

- Rheumatoid factor seronegativity
- Involvement of the sacroiliac joints
- Association with **HLA-B27**

Ankylosing spondylitis occurs predominantly in young men with HLA-B27 (90% of cases); usually involves the sacroiliac joints and spine; and may be associated with inflammatory bowel disease.



Figure 27-4. Ankylosing Spondylitis Can Cause Fusion of Vertebrae, Leading to a "Bamboo Spine"

Reactive arthritis is characterized by a classic triad of conjunctivitis, urethritis, and arthritis. The arthritis affects the ankles and knees. It affects males more than females, with onset age 20s–30s. Onset often follows a venereal disease or bacillary dysentery.

Enteropathic arthritis occurs in 10–20% of patients with inflammatory bowel disease.

Psoriatic arthritis affects 5–10% of patients with psoriasis; is often a mild and slowly progressive arthritis, with pathology similar to RA.

BRIDGE TO BIOCHEMISTRY

Uric acid is the end product of purine metabolism.

Arthritis Related to Crystal Deposition

In **gout**, hyperuricemia and the deposition of monosodium urate crystals in joints will result in recurrent bouts of acute arthritis. The hyperuricemia can be caused by overproduction or underexcretion of uric acid.

KP00710.indb 266 13/10/22 1:53 PM

- **Primary gout** (90%) is idiopathic, affects males more than females, and is typically seen in older men.
- **Secondary gout** (10%) is seen with excessive cell breakdown (chemotherapy), decreased renal excretion (drugs), and Lesch-Nyhan syndrome.

Gout affects the great toe (podagra, characterized by an exquisitely painful, inflamed big toe), ankle, heel, and wrist.

Joint aspiration shows birefringent, needle-shaped uric acid crystals and numerous neutrophils. **Tophi** are deposits of crystals surrounded by inflammation. Skin ulceration and destruction of adjacent joints may occur. Complications include joint destruction and deformity, uric acid renal calculi, and renal failure. Treatment is NSAIDs, colchicine, probenecid, and allopurinol.



© Richard P. Usatine, MD Used with permission.

Figure 27-5. Gout

Pseudogout (chondrocalcinosis) is deposition of calcium pyrophosphate crystals in joints, leading to inflammation. Affected patients are usually age >50. The knee joint is most commonly involved. Aspiration of the joint demonstrates positively birefringent (weak), rhomboid-shaped crystals. Pseudogout is associated with many metabolic diseases (e.g., diabetes, hypothyroidism, ochronosis), and it may mimic OA or RA.

Infectious Arthritis

Suppurative arthritis may result from seeding of the joint during bacteremia. Other routes include spread from an adjacent site of infection and direct inoculation. Infecting organisms include gonococci, *Staphylococcus, Streptococcus*, *H. influenzae*, and gram-negative bacilli.

Suppurative arthritis causes a tender, painful, swollen, and erythematous joint. Large joints (knee, hip, shoulder) are most often infected, and the arthritis is usually monoarticular. Joint aspiration shows cloudy synovial fluid that clots readily and has a high neutrophil count. Gram stain and culture are positive in 50–70% of cases. Treatment is rapid intervention with antibiotics to prevent permanent joint damage.

NOTE

Lesch-Nyhan Syndrome

- X-linked recessive
- Deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HPRT)
- Cognitive impairment
- Dystonia
- Self-mutilating behaviors
- Hyperuricemia

NOTE

In the presence of pseudogout age <50, suspect one of these metabolic abnormalities (4H):

- Hemochromatosis
- Hyperparathyroidism
- Hypophosphatemia
- Hypomagnesemia

KP00710.indb 267 13/10/22 1:53 PM

BRIDGE TO MICROBIOLOGY

Arthropod-borne diseases transmitted by ticks include:

- Rocky Mountain spotted fever
- *Ehrlichia*
- Babesiosis
- Tularemia
- Lyme disease

Lyme disease is caused by the spirochete *Borrelia burgdorferi*. The disease is arthropod-borne, spread by deer ticks (*Ixodes scapularis* [Eastern United States] and *Ixodes pacificus* [Western United States]). Symptoms are skin rash (erythema chronicum migrans), and migratory arthritis involving the knees, shoulders, and elbows. The histology of the arthritic joint is similar to RA. Lyme disease can also have CNS and cardiac involvement. Serologic tests may remain negative until infection has been present for several weeks.



© Richard P. Usatine, MD Used with permission.

Figure 27-6. Large Targetoid Lesion of Erythema Chronicum Migrans Considered Pathognomonic of Lyme Disease

OTHER JOINT CONDITIONS

Neuropathic Arthropathy (Charcot Joint)

Charcot joint refers to joint damage secondary to impaired joint innervation (neuropathy), leading to an inability to sense pain. The damage also leads to destruction of joint surfaces, debris in joints, deformity, and dislocations.

Different **underlying neurologic diseases** tend to affect different joints.

- Diabetes mellitus (most common cause) tends to damage the tarsometatarsal joint in the midfoot.
- Syringomyelia (cavity in spinal cord) tends to damage the shoulder, elbow, and wrist joints.
- Tabes dorsalis (neurosyphilis) tends to damage the hip, knee, and ankle joints.

Ganglion Cyst

A **ganglion** is a small cyst that occurs most commonly on the wrist or hand; it can also occur on the foot. It contains viscous fluid and lacks a true lining. Recurrence after drainage or excision is not uncommon.

KP00710.indb 268 13/10/22 1:53 PM

Soft Tissue and Peripheral Nerve Pathology

28

LEARNING OBJECTIVES

- ❑ Demonstrate understanding of inflammatory myopathies and neuropathies
- ❑ Describe the mechanism of action of myasthenic syndromes
- ❑ Explain information related to muscular dystrophy
- ❑ Solve problems concerning soft tissue and peripheral nerve tumors

SKELETAL MUSCLE

Types of Skeletal Muscle

Type I (red) skeletal muscle is used in postural weight bearing. It produces a slow twitch as a result of aerobic metabolism of fatty acids.

Type II (white) skeletal muscle is used for purposeful movement. It produces a fast twitch as a result of anaerobic glycolysis of glycogen.

NOTE

Skeletal muscle fiber type is determined by innervation.

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

KP00710.indb 269 13/10/22 1:53 PM

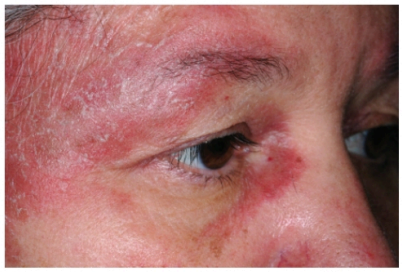
CLINICAL CORRELATE

Anti-tRNA synthetase antibodies such as the anti-Jo-1 antibody are known to be highly specific for inflammatory myopathies.

Inflammatory Myopathies

Polymyositis is an autoimmune disease seen in adults. It presents with bilateral proximal muscle weakness. Microscopic exam demonstrates endomysial lymphocytic inflammation (mostly cytotoxic T8) and skeletal muscle fiber degeneration and regeneration. Patients respond to immunosuppression.

Dermatomyositis is a connective tissue disorder involving inflammation of skeletal muscle and skin. It can affect both children and adults. It presents with bilateral proximal muscle weakness, skin rash of the upper eyelids, and periorbital edema. Microscopic exam demonstrates perimysial and vascular lymphocytic inflammation, perifascicular fiber atrophy, and skeletal muscle fiber degeneration and regeneration. Adult patients are at increased risk of lung, colon, breast, and gynecologic cancers.



© Richard P. Usatine, MD
Used with permission.

Figure 28-1. Periorbital Heliotrope Rash of Dermatomyositis

Inclusion body myositis affects adults age >50, causing slowly progressive, asymmetrical, distal muscle weakness. Light microscopy demonstrates autophagic vacuoles and inclusion bodies in addition to inflammation and necrosis. The disease is refractory to immunosuppressive therapy.

Myasthenic Syndromes

Myasthenia gravis is an autoimmune disease characterized by autoantibodies against the acetylcholine (ACh) receptor of the neuromuscular junction, resulting in muscular weakness predominantly affecting the facial muscles. Females are affected more frequently than males.

- Extraocular muscle weakness may lead to ptosis and diplopia; the weakness worsens with repeated contractions.
- Respiratory muscle involvement may lead to death.
- There is an association with thymic hyperplasia and thymomas.

Treatment is anticholinesterase agents, steroids, and thymectomy.

KP00710.indb 270 13/10/22 1:53 PM

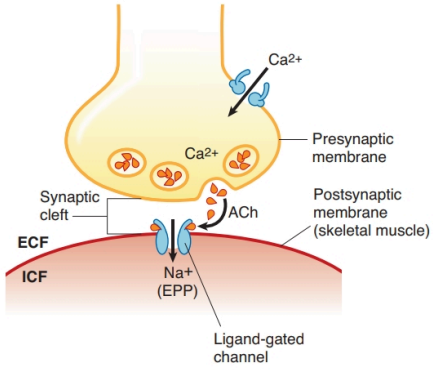


Figure 28-2. Neuromuscular Transmission

Lambert-Eaton myasthenic syndrome is caused by autoantibodies directed against the presynaptic calcium channels of the neuromuscular junction. Patients report dry mouth and proximal muscle weakness. It frequently arises as a paraneoplastic syndrome of small cell lung cancer. Treatment is immunotherapy and cancer treatment in cases arising as a paraneoplastic syndrome.

SKELETAL MUSCLE

Muscular Dystrophy

Duchenne muscular dystrophy is a recessive X-linked form of muscular dystrophy leading to rapid progression of muscle degeneration. It is the most common and severe form of muscular dystrophy. The affected gene is the dystrophin gene on the X chromosome (Xp21); dystrophin protein is an important muscle structural protein, and mutation results in a virtual absence of the dystrophin protein.

Affected boys are normal at birth but have onset of symptoms by age 5. Clinical features include:

- Progressive muscular weakness
- Calf pseudohypertrophy
- Proximal weakness of shoulder and pelvic girdles
- Possible heart failure and arrhythmias
- Respiratory insufficiency and pulmonary infections as a result of decreased mucociliary clearance

Lab studies show elevated serum creatine kinase. Muscle biopsy shows muscle fibers of various sizes; necrosis, degeneration, and regeneration of fibers; fibrosis; and fatty infiltration. Immunostains show decreased dystrophin protein. Diagnosis can also be confirmed with genetic testing.

KP00710.indb 271 13/10/22 1:53 PM

Becker muscular dystrophy is a recessive X-linked inherited disorder leading to slowly progressive muscle weakness of the legs and pelvis.

- Less severe than Duchenne
- Not as common as Duchenne
- Has a later onset than Duchenne, with variable progression
- Mutation produces an altered dystrophin protein
- Cardiac involvement is rare, and patients can have relatively normal lifespan

Note the characteristic pattern of rising from the floor using a sequence of hand pushes

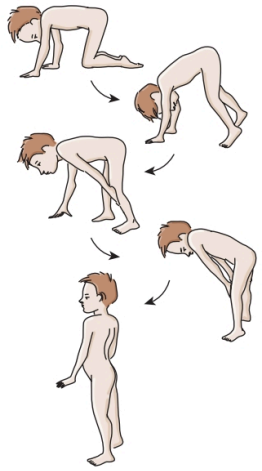


Figure 28-3. Gower Sign in Duchenne Muscular Dystrophy

PERIPHERAL NERVE DISORDERS

Diabetic Peripheral Neuropathy

Peripheral neuropathy is the most common type of neuropathy in diabetes mellitus. Patients develop symptoms of pain and numbness, first in the lower extremities, and later in the upper extremities. Loss of sensory input can impair ambulation; ulceration can lead to amputation. Clinical testing includes skin biopsy and neurologic tests.

Inflammatory Neuropathy

Guillain-Barré syndrome is an autoimmune disease leading to the destruction of Schwann cells and peripheral nerve demyelination. Clinically, it is preceded by a viral illness. Muscular weakness occurs with an ascending paralysis, accompanied by loss of deep tendon reflexes. Diagnosis can be established with nerve conduction studies; lumbar puncture shows elevated protein.

Microscopic examination demonstrates inflammation and demyelination of peripheral nerves and spinal nerve roots, resulting in muscular weakness. Guillain-Barré syndrome is fatal in 5% of cases because of respiratory paralysis. Treatment is plasmapheresis and immunoglobulin therapy.

KP00710.indb 272 13/10/22 1:53 PM

SOFT TISSUE TUMORS

Fibromatosis

Fibromatosis is a non-neoplastic proliferative connective tissue disorder that can histologically resemble a sarcoma. Fibrous tissue infiltrates muscle or other tissue, and may cause a mass lesion. The cut surface is trabeculated. Microscopically, bundles of fibroblasts and collagen are seen.

- **Superficial fibromatoses** arise from fascia or aponeuroses (palmar **most common**). Penile fibromatosis is known as Peyronie's disease.
- **Deep fibromatoses** (desmoids) occur in extraabdominal sites (children) and abdominal wall and extraabdominal sites (adults). Abdominal desmoids often occur in women within a year of pregnancy. They may also follow surgery or trauma. Intraabdominal fibromatosis is commonly associated with Gardner syndrome (*see* Gastrointestinal Tract Pathology, chapter 16).

Soft Tissue Tumors

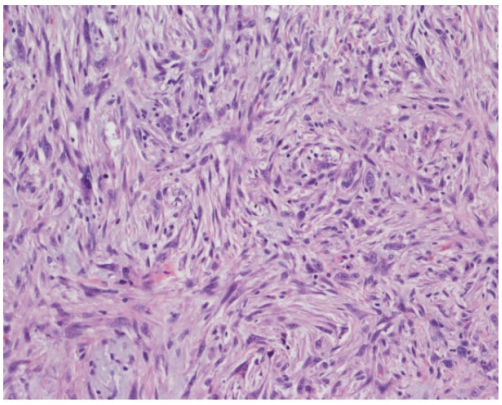
Lipoma is a benign adipose tissue tumor that most often arises in subcutaneous tissue of trunk, neck, or proximal extremities. It is the most common benign soft tissue tumor. The tumor is usually more of a cosmetic problem than a medical one. Microscopically, it is composed of mature fat cells but can contain other mesenchymal elements.

Liposarcoma is a malignant adipose tissue tumor that most often arises in the thigh or retroperitoneum. It is the most common adult sarcoma. It is distinguished from lipoma by the presence of **lipoblasts**. Grossly, it tends to be larger than lipoma, and the cut surface shows fibrous bands. Microscopically, well-differentiated liposarcoma consists of mature fat with varying numbers of hyperchromatic spindle cells and multivacuolated lipoblasts. Metastases are rare but retroperitoneal tumors tend to recur.

Dermatofibroma is a benign dermal spindle cell proliferation that most often arises in the extremities. A small, red nodule is seen, which is tender and mobile on examination.

Fibrosarcoma is a malignant fibrous tumor, commonly seen on the thigh and upper limb. It may arise spontaneously or after therapeutic/accidental irradiation. Microscopically, there are uniform spindle cells with a "herringbone" pattern. Metastases are hematogenous, often to the lung.

KP00710.indb 273 13/10/22 1:53 PM



© Gregg Barré, MD Used with permission.

Figure 28-4. Fibrosarcoma

Undifferentiated pleomorphic sarcoma (previously known as malignant fibrous histiocytoma) is a large multilobulated tumor seen in the extremities and retroperitoneum of older adults. Microscopically, they may have a storiform (cartwheel-like) pattern. They recur and metastasize.

Rhabdomyoma (*See* Female Genital and Cardiac Pathology, chapters 22 and 13.)

Embryonal rhabdomyosarcoma (*See* Female Genital chapter.)

Leiomyoma is a benign smooth muscle tumor most often seen in the uterus (*see* Female Genital chapter) and gastrointestinal tract. Less often it is seen in skin, and only rarely in deep soft tissue.

Leiomyosarcoma of soft tissue is less common than its counterpart in the gastrointestinal tract and uterus (*see* Female Genital chapter). In soft tissue, it usually arises in the retroperitoneum of older women.

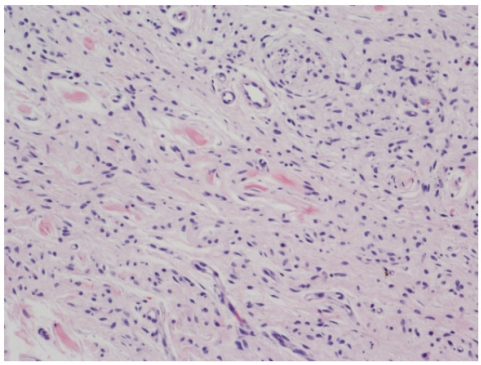
Grossly, the tumor is fleshy and white with hemorrhage and necrosis. Microscopically, the tumor nuclei are blunt ended ("cigar-shaped"). Longitudinal striations can be seen with Masson trichrome staining. The tumor is highly aggressive in the retroperitoneum, where complete resection may not be possible.

Synovial sarcoma occurs in young adults. The knee is a common location. The gross appearance is variable but calcification is common. Microscopically, tumors may be biphasic (epithelial and spindle cells) or monophasic (spindle cell or epithelial).

Peripheral Nerve Sheath Tumors

- **Schwannoma** is an encapsulated nerve sheath tumor with alternating Antoni A and B areas (*see* Central Nervous System, chapter 20). There is an association with NF2.
- **Neurofibroma** is nonencapsulated and may have a solitary, diffuse, or plexiform pattern. Microscopically, neoplastic cells are interspersed among wavy, loose or dense collagen bundles. There is an association with NF1 (*see* Genetic Disorders, chapter 6).

KP00710.indb 274 13/10/22 1:53 PM



© Gregg Barré, MD Used with permission.

Figure 28-5. Neurofibroma

- **Malignant peripheral nerve sheath tumor** may arise from neurofibromas or *de novo* in a peripheral nerve. It typically occurs in young adults in major nerve trunks (sciatic nerve, brachial plexus, and sacral plexus). Microscopically, it resembles fibrosarcoma. Recurrence and distant metastases are common.

KP00710.indb 275 13/10/22 1:53 PM

Index

A

Acanthocytes, 87
Acanthosis nigricans, 72–73, 82
Achalasia, 155
Achondroplasia, 254
Achrocordons, 78
Acid fast stain, 3*t*
Acquired coagulopathies, 32
Acquired immunodeficiency syndrome (AIDS), 58–61, 59*f,* 60*f,* 60*t,* 61*f*
Acquired megacolon, 160
Acral lengitinous melanoma, 77
Acromegaly, 247, 247*f*
Actinic keratosis, 83
Acute aseptic (viral) meningitis, 184
Acute hemorrhagic gastritis, 157
Acute inflammation, 15–20
  stomach, 157
Acute intermittent porphyria, 199
Acute lymphoblastic leukemia (ALL), 216
Acute myelogenous leukemia (AML), 213–214
Acute nonspecific lymphadenitis, 207, 207*f*
Acute pancreatitis, 167–168
Acute poststreptoccocal glomerulonephritis (APSGN), 140
Acute purulent (bacterial) meningitis, 184
Acute pyelonephritis, 145
Acute rejection, 61
Acute respiratory distress syndrome (ARDS), 127
Acute tubular injury (ATI), 146
Adamantinoma, 203
Addison's disease, 76, 249–250
Ademona, pituitary, 247
Adenocarcinoma
  ampulla of Vater, 173
  colonic, 165
  endometrial, 224–225
  esophagus, 156
  gastric, 159
  lung cancer, 131–132
  pancreatic, 169, 169*f*
  prostate, 242
  urinary bladder, 153
Adenomas, thyroid, 245, 245*f*
Adenomyosis, 224
Adenosine deaminase, 56
Adhesion molecules, 16–17, 16*f,* 16*t*
Adrenal gland disorders, 248–250, 249*f*
Adrenal insufficiency, 249–250
Adrenocorticotropic hormone (ACTH), hyperadrenalism, 248–249, 249*f*
Adrenogenital syndromes, 249
Adult T-cell leukemia/lymphoma (ATLL), 211
African Americans, glucose-6-phosphate dehyrogenase deficiency, 93
AIDS-defining diseases, 60–61, 61*f,* 85, 103
Alanini aminotransferase (ALT), 9, 14
Albinism, 44, 76
Alcoholic brain disorders, 200
Alcoholic liver disease, 180
Alkaline phosphatase, biliary tract obstruction, 9
Alkaptonuria (ochronosis), 44
Allele-specific oligonucleotide (ASO) probe, 44*f*
α-1-antitrypsin deficiency, 181
α-Thalassemia, 90
Alport syndrome, 142
Altitude, compensatory hyperplasia and, 12
Alzheimer disease, 64, 197–198, 197*t*
Amebic liver abscess, 179
Ames test, 67
Amphibole asbestos, 129
Ampull of Vater, adenocarcinoma, 173
Amylase, pancreatitis, 9
Amyloidosis, 63–64
Amyloid structure, 63
Amyotrophic lateral sclerosis (ALS), 199, 199*f*
Anaerogic glycolysis, 9
Anal intraepithelial neoplasia (AIN), 166
Anal skin tags, 166
Anaphylactic reaction, 36, 53
Anaplastic astrocytoma, 201
Anaplastic carcinoma, 246
Anasarca, 27
Ancillary studies, 2
Anemias
  of chronic disease (AOCD), 90
  classification, 88*f*
  diminished erythropoiesis, 89
  macrocytic, 95–96
  microcytic, 89–91, 90*t*
  normocytic, 91–94
  overview, 88–89
Anemic infarcts, 35
Anencephaly, 193
Aneurysms, 100–101, 100*f*
Angelman syndrome, 51
Angina pectoris, 105–106
Angiodysplasia, 163
Angiogenesis, cancer and, 69
Angiomyolipoma, 149
Angiosarcoma
  cutaneous, 85
  liver, 183
  vascular, 103
Anitschkow cells, 110
Ankylosing spondylitis, 266, 266*f*
Annular pancreas, 167
Anovulation, 224
Antibody-dependent cell-mediated cytotoxicity (ADCC), 53
Antibody-mediated (type II) hypersensitivity, 53
Antimitochondrial autoantibodies (AMA), 177
Antioxidants, cellular injury, 7
Antiphospholipid antibody syndrome, 111
Antiplatelet antibodies, 31
Anti-Ro (SS-A) antibodies, 55
Anti-tRNA synthetase antibodies, 270
Antral type chronic gastritis, 158
Anus, pathology, 166
Aortic dissecting aneurysm, 100*f,* 101
Aplastic anemia, 94–95
Apocrine metaplasia, breast, 231, 232*t*
Apoptosis, 9*f*
  non-inflammatory response, 11–12
  regulation, 11–12, 69
Appendicitis, 163
Arachidonic acid, 19
Architectural disorders, 77
Arnold-Chiari malformation, 194, 194*f*
Arrhythmogenic right ventricular cardiomyopathy, 116
Arteiorvenous (AV) fistulas, 101
Arterial transposition, 112, 112*t,* 113*f*
Arteriosclerosis, 98–99
Arthritis, 263–268
Asbestosis, 129–130, 130*f*
Ascending cholangitis, 172
Aschoff body, 110
Aspartate aminotransferase (AST), 9, 14
Aspiration, lung infection, 121
Aspirin, hemostasis and, 28
Asteroid bodies, 123
Asthma, 124–125, 125*f*
Astrocytoma, 201
Atelectasis, 120
Atherosclerosis, 98–99
  aneurysms and, 100*f,* 101
Atopic asthma, 125

KP00710.indb 277 13/10/22 1:53 PM

Atopic dermatitis, 82
ATP, cellular injury and, 7, 9
Atrial septal defect (ASD), 114, 114*f*
Atrophy, 12, 13*f*
Atypical lobular hyperplasia, 232
Atypical pneumonia, 121
Auerbach plexus, 160
Auer rods, 213
Autoantibodies, systemic lupus erythematosus, 55
Autoimmune diseases, 55–56
  bullous pemphigoid, 79, 80*f*
  hemolytic anemia, 94
  pancreatitis, 168
Autosomal disorders, 39–41
  dominant disorders, 46–49, 138, 255
  recessive disorders, 43–46, 43*t*, 44*f*, 138, 255
Avascular necrosis, 259

B

Bacillus Calmette-Guerin vaccine, 121
Backward congestive heart failure, 108
Bacterial meningitis, 184
Bacterial pneumonia, 120
Bacterial vaginosis (BV), 221
Baker cysts, rheumatoid arthritis, 264
Balanitis/balanoposthitis, 237
Bamboo spine, 266, 266*f*
Barrett esophagus, 13, 156
Barthonlin gland abscess, 219
Basal cell carcinoma, skin, 84, 84*f*
Basophilic stippling, 87
Basophils
  chronic inflammation, 20, 20*f*
  leukocytosis, 206
B-cell neoplasms, 208–211
B-chronic lymphocytic leukemia, 208
Bcl-2,apoptosis regulation, 11, 69
Becker muscular dystrophy, 272
Beckwith-Wiedemann syndrome (BWS), 151
Benign hyperphenylalaninemia, 44
Benign nephrosclerosis, 148
Benign prostatic hyperplasia (BPH), 241–242
Berger disease, 141–142
Bernard-Soulier syndrome, 29
Berry aneurysm, 100*f*, 101, 190, 191*f*
Berylliosis, 130
β-Thalassemia, 90–91
Bicuspid aortic valve defect, 109
Bilateral agenesis, 137
Bilateral hilar lymphadenopathy, 123
Bile duct cancer, 173, 173*f*
Biliary tract
  cancer, 173, 173*f*
  obstruction, 9, 176
Bilirubin, 14
Bilirubinemia, 174–175, 174*t*
Biochemical pathways, cellular injury, 7
2,3-Bisphosphoglycerate (2,3 BPG), 94
Bite cells, 87
Black lung disease, 129
Bladder pathology, 152–153, 153*f*
Blast cells, acute leukemias, 216
Bleeding disorders, 31–33, 32*t*, 33*f*
Blood clot, thrombosis *vs.*, 34, 34*t*
Bone
  components, 253
  inflammatory disease, 257–258, 258*f*
  metabolic disorders, 255–257
  miscellaneous disorders, 259
  neoplasia, 259–262
  osteomalacia and rickets, 257
  osteoporosis, 256, 256*f*
  physiology, 253–254
Bouchard nodes, 263
Bradykinin, 18–19, 19*f*
Brain injury, 24, 191–193, 192*f*
  developmental abnormalities, 193–194, 194*f*, 194*t*
BRCA1/2 genes, breast carcinoma, 233
Breast
  benign neoplasms, 232–233, 233*f*
  cancer, 231, 232*t*
  fibrocystic changes, 231–232, 232*t*
  gynecomastia, 236
  inflammation, 231
Bronchial carcinoids, 133
Bronchiectasis, 125–126, 126*f*
Bronchitis, chronic, 124
Bronchopneumonia, 120–121
Bronchopulmonary sequestration, 119
Brown tumors, hyperparathyroidism, 246
Bruton X-linked agammaglobulinemia, 50, 56
Budd-Chiari syndrome, 181–182
Bulla(e)(skin lesion), 79
Bullous pemphigoid, 79, 80*f*
Burkholderia cepacia complex, 43
Burkitt lymphoma, 210, 210*f*
Burr cells, 87

C

Calcium influx, cellular injury, 7, 14
Calcium oxalate stones, 146
Calories, intake, 6
Cancer
  biliary tract, 173, 173*f*
  biology, 68–70
  breast, 231, 232*t*
  diagnosis, 70–72
  epidemiology of, 65
  geographic factors, 66
  grading and staging, 72
  hallmarks, 69
  invasiveness, 70
  laryngeal, 134
  lungs, 72–73, 131–132
  in men, 66
  metastasis, 70
  paraneoplastic syndromes, 72–73
  prostate, 242–243
  skin, 77–78, 83–84
  testicular, 239–241, 240*f*
  in women, 66
Capillary permeability, pulmonary edema, 131
Caplan syndrome, 129
Carcinogenesis, defined, 65
Carcinogens, distribution of, 66–67
Carcinoid heart disease, 109
Carcinoid syndrome, 166
Carcinoid tumors
  colon cancer, 165–166
  lung cancer, 133
Carcinoma
  breast, 233–236, 234*f*, 236*f*
  defined, 65
  endometrial, 224–225, 225*f*
  esophageal, 156
  gastric, 159
  hepatocellular, 183
  metastatic, 133
  pancreatic, 169
  renal cell, 149–150, 149*f*, 151*f*
  thyroid, 246
  transitional cell, 152–153
Carcinoma in situ (CIS)
  breast, 234
  urinary bladder, 153
Carcinosarcoma, uterine, 225
Cardiogenic shock, 36
Carney triad, 133
Carpal tunne syndrome, 63
Caseous necrosis, 10
Caspases, apoptosis, 11
Catalase, 7
CD4+ cell count, AIDS and, 58–59
Celiac sprue, 160, 160*f*
Cell death, 10–12, 11*f*
Cell-mediated (type IV) hypersensitivity, 54, 54*f*
Cell membrane permeability, 7
Cellular injury, 5–14
  adaptive responses, 12–13, 13*f*
  causes, 5–6
  irreversible, 9, 9*f*
  mechanisms, 7, 8*f*
  pathologic accumulations, 13–14
  responses, 6–7, 7*f*
  reversible, 9
Central necrosis, 21
Central nervous system
  infection, 184–188
  trauma, 191–193
  tumors, 200–204, 200*t*, 201*f*–203*f*
Central pontine myelinolysis (CPM), 195, 200
Centrilobular emphysema, 124
Cerebellar malformations, 194
Cerebellar tonsillar herniation, 193, 193*f*
Cerebral abscess, 187
Cerebral amyloid angiopathy, 198
Cerebral infarction, 189–190, 190*t*

KP00710.indb 278 13/10/22 1:53 PM

Cerebrovascular disease, 189–191, 190*t*, 191*f*
Cervical intraepithelial neoplasia (CIN), 222, 223*f*
Cervicitis, acute and chronic, 222
Cervix, infections, 221–222
CFTR gene, 43
Chagas disease, 160
Charcot joint, 268
Charcot-Leyden crystals, 125
Charcot's triad, 172
Chediak-Higashi syndrome, 17, 76
Chemical injury, 5
Chemotaxis, 17
Children, cancer in, 66
Cholecystitis, acute and chronic, 172, 172*f*
Cholelithiasis, 171
Cholestasis, 174
Cholesterolosis, 172
Cholesterol stones, 171
Choncrosarcoma, 261–262, 261*f*
Choriocarcinoma
  gestational trophoblastic disease, 229
  testicular, 240
Christmas disease, 32
Chromophobe renal cell carcinoma, 150
Chromosomal deletion disorders, 41
Chronic blood loss, anemia and, 89, 91
Chronic bronchitis, 124
Chronic gastritis, 157
Chronic glomerulonephritis, 144–145
Chronic inflammation, 20–22
  cancer and, 67
Chronic interstitial lung disease, 128
Chronic ischemic heart disease, 108
Chronic kidney disease, 147
Chronic lymphocytic leukemia (CLL), 208
Chronic myelogenous leukemia (CML), 214–215, 214*f*
Chronic nonspecific lymphadenitis, 208
Chronic obstructive pulmonary disease (COPD), 123–127
Chronic pancreatitis, 168
Chronic passive congestion, 182
Chronic pelvic pain syndrome, prostatis, 242
Chronic peptic ulcer, 158
Chronic pyelonephritis, 145
Chronic rejection, 61
Chronic traumatic encephalopathy, 193
Circulatory pathology
  bleeding disorders, 31–33, 32*t*, 33*f*
  coagulation, 28–33
  edema, 27–28
  embolism, 34–35, 34*t*
  infarction, 35–36, 36*f*
  shock, 36–37
  thrombosis, 34, 34*t*
Cirrhosis, 174, 177
  alcoholic, 180, 180*f*
  primary biliary, 176–177
Clear cell adenocarcinoma, vaginal, 220
Clear cell renal cell carcinoma, 150
Clinical significance, defined, 1
Cloacal exstrophy, 52
Clotting disorders, 28–30
Coagulation cascade, 29–30, 30*f*
Coagulation factors, 29
Coagulative dysfunction, 28–33
Coagulative necrosis, 10
Coal worker's pneumoconiosis, 129
Coarctation of the aorta, 115, 115*f*
Collagen vascular disease, 128
Colloid osmotic pressure, edema and, 27
Colon
  disorders, 163–166, 165*t*
  diverticula, 164
  flexure of, 163
  polyps, 164
Common variable immunodeficiency, 56
Compensation, in shock, 37
Complement cascade, 19
  antibody-mediated (type II) hypersensitivity, 53
Complement system disorders, 57
Compression atelectasis, 120
Compression fracture, 256, 256*f*
Concussion, 191
Condyloma acuminatum, 166, 237
Congenital disorders, 5
  brain, 193–194, 194*f*, 194*t*
  cerebellar malformations, 194
  esophagus, 155–156
  heart disease, 111–115, 112*t*, 113*f*–115*f*
  hypothyroidism, 244
  kidney, 137–138
  lung malformations, 119
  pancreas, 167
  penis, 237
  skeletal, 254–255
  stomach, 156–157
  ureteral disorders, 152
  urinary bladder, 152
Congenital nevi, 77
Congestive heart failure (CHF), 108
Congo red stain, 3*t*
Contact dermatitis, 82
Contraction (scar) atelectasis, 120
Contusion, cerebral, 191
Cooley anemia, 91
Coronary artery thrombosis, 106
Cor pulmonale, 108
Cortical adenoma, 149
Courvoisier law, 173
CPK-MB, myocardial injury, 9
Cranial cavity
  trauma, 191–193, 192*f*
  tumors, 202
Craniopharyngioma, 203, 247, 248
Creatine kinase (CK-MB), 14
Crescentic glomerulonephritis, 141
CREST syndrome, 56
  Raynaud phenomena, 98
Creutzfeldt-Jakob disease, 188, 188*t*
Cri du chat syndrome, 41
Crigler-Najar syndrome, 176
Crohn's disease (CD), 161–162, 161*f*, 162*t*
  perianal, 166
Crush artifacts, small cell lung cancer, 133*f*
Cryptococcus neoformans, 60*f*
Cryptogenic organizing pneumonia, 128
Cryptorchidism, 238
Crystal deposition, arthritis and, 266–267
Curschmann spirals, 125
Cushing syndrome, 73, 248–249, 249*f*
Cutaneous angiosarcoma, 85
Cutaneous lupus erythematosus, 82
Cyclooxygenase pathway, 19
Cystic fibrosis, 43, 44*f*, 125
Cystic kidney disease, 138–139
Cystine stones, 146
Cystitis, 152
Cystitis cystica et glandularis, 152
Cystocele, 152
Cytogenetics, 2
  disorders, 39–42
Cytokines, 19
Cytology, cancer diagnosis, 71
Cytomegalovirus, 177
Cytopathic/cytoproliferative inflammation, 22

D

Dandy-Walker malformation, 194
Decompensation, 37
Deep vein thrombosus (DVT), 34–35
Degenerative calcific aortic valve stenosis, 109
Degranulation, 17
Demyelinating disorders, 195
Dendritic cell diseases, 213
Denys-Drash syndrome (DDS), 151
Dermatitis
  herpetiformis, 79, 80*f*
  variants, 82
Dermatofibroma, 273
Dermatomyositis, 270, 270*f*
DES, vaginal adenosis and, 220
Developmental polycystic kidney disease, 139
Dexamethasone, ACTH production, 248
Diabetes insipidus, 247–248
Diabetes mellitus, 250–252
  secondary glomerulonephritis, 144, 144*f*
Diabetic nephropathy, 251
Diabetic retinopathy, 251, 252*f*
Diaphragmatic hernia, 156–157
Diet, iron deficiency in, 89
Diffuse axonal injury, 192
Diffuse cortical necrosis, 149
Diffuse large B-cell lymphoma (DLBCL), 209, 209*f*
DiGeorge syndrome, 56
Dilated cardiomyopathy, 115–116

KP00710.indb 279 13/10/22 1:53 PM

Disorders of sexual development (DSD), 52
Disseminated intravascular coagulation (DIC), 33, 33*f*, 92
Distal acinar emphysema, 124
Diverticula, 163–164
  urinary bladder, 152
DNA
  cellular injury and, 7
  repair, 69
DNA oncogenic viruses, 67
Dohle bodies, 205
Down syndrome, 39, 40*f*, 50
Dressler syndrome, 108
Drug-induced asthma, 125
Drug-induced tubular interstitial nephritis, 145
Dry skin, 82
Dual-energy x-ray absorptiometry (DEXA), osteoporosis, 256, 256*f*
Dubin-Johnson syndrome, 176
Duchenne muscular dystrophy, 271, 272*f*
Ductal carcinoma in situ (DCIS), breast, 234
Ductal hyperplasia, 232
Ductal sex determination, 52
Ductal tumors, breast, 233
Duodenal peptic ulcer, 158, 158*f*
Dysgerminoma, ovarian, 227
Dysplastic nevus, 77
Dystrophic calcification, 14

E

Echinocytes, 87
Eclampsia, 230
Ectopic kidney, 137
Ectopic pancreatic tissue, 167
Ectopic pregnancy, 230
Eczema, 82
Edema
  causes, 27
  fluid composition, 28
  types, 27–28
Edwards syndrome, 40, 40*f*
Effusion, 27
  pleural, 134
Ehlers-Danlos syndrome (EDS), 47
Eisenmenger complex, 113–114
Ejaculatory disorders, 238
Elliptocytes, 87
Embolism, 34–35
  cerebral, 189–190
Embryonal carcinoma, 240
Embryonal (primitive) tumors, 202
Embryonal rhabdomyosarcoma, 220
Emigration (diapedesis), 17
Emphysema, 124, 124*t*
Encephalitis, 185–186
Enchondroma, 260
Endemic goiter, 243
Endocarditis, 109–111
Endocervical polyps, 224
Endochondral bone, 254
Endocrine disorders, multiple organs, 250–251
Endogenous pigments, cellular injury, 14
Endometriosis, 224
Endometritis, 224
Endothelial permeability
  bleeding disorders, 31
  edema and, 27
Engulfment, 17
Entamoeba histolytica, 179
Enteropathic arthritis, 266
Environmental enteropathy, 161
Eosinophilic granulomatosis with polyangiitis, 98
Eosinophilic pneumonia, 129
Eosinophils
  chronic inflammation, 20, 20*f*
  leukocytosis, 205–206
  leukopenia, 206
Ephelides (freckles), 76
Epidermal growth factor receptor (EGFR), 133
Epidermoid cyst, 78
Epididymitis, 238
Epidural hematoma, 192, 192*f*
Epispadias, 237
Epithelial ovarian tumors, 226
Epithelioid cells, 21
Epndymoma, 202
Epstein-Barr virus (EBV), 177
  AIDS and, 60–61
Erectile disorders, 237
Erlotinib (Tarceva), 133
Erythema multiforme, 80
Erythema nodosum, 81
Erythematous diseases, 80–81
Erythroid hyperplasis, 91
Esophageal carcinoma, 156
Esophageal obstruction, 132
Esophageal varices, 102, 156
Esophageal webs, 155
Esophagitis, 156
Esophagus, congenital/mechanical disorders, 155–156
Essential thrombocytopenia, 215
Etiology, 1
Ewing sarcoma, 262
Exogenous pigments, cellular injury, 14
Exstrophy of the bladder, 152
Extracellular glycosaminoglycans, 27
Extracellular matrix (ECM) tissue repair, 23
Extravascular (EV) hemolysis, 92
Extrinsic coagulation pathway, 29, 30*f*
Exudate, 28
Exudative inflammation, 22
Exudative pleural effusion, 134

F

Familial adenomatous polyposis (FAP), 164
Familial hypercholesterolemia, 46–47
Familial Mediterranean fever, 63
Familial retinoblastoma, 69
Fas ligand, apoptosis, 11
Fatal familial insomnia, 188, 188*t*
Fat necrosis
  breast, 231
  cell death, 10
Fatty change (statosis), 180
Fatty liver disease, 181
Ferritin, 89
Ferruginous bodies, 129
Fetal alcohol syndrome, 194
Fever, chemical mediators, 19
Fibrillary (diffuse) astrocytoma, 201
Fibrillin gene (FBN1), 47
Fibrin degradation products (FDP), 30
Fibrinoid necrosis, 10
Fibrin-platelet thrombi, 31
Fibroadenoma, breast, 232, 233*f*
Fibroblast growth factor receptor 3 (FGFR3), achondroplasia, 254
Fibrocystic breast changes, 231–232, 232*t*
Fibromatosis, 273
Fibromuscular dysplasia, renal artery stenosis, 148, 148*f*
Fibrosarcoma, 273, 274*f*
Fibrous dysplasia, 254
Fite stain, 3*t*
Fitz-Hugh-Curtiss syndrome, 221–222
Focal nodular hyperplasia, 182
Focal segmental glomerulosclerosis, 143
Folate deficiency, megaloblastic anemia, 95–96
Follicular carcinoma, 246
Follicular lymphomas, 209
45,XX DSD category, 52
45,XY DSD category, 52
Forward congestive heart failure, 108
Fragile X syndrome, 50
Frameshift mutations, 42
Freckles, 76
Free erythrocyte protoporphyrin (FEP), 89
Friction rub, 108
Friedreich ataxia, 199
Fundic type chronic gastritis, 157
Fungal meningitis, 185

G

Gallbladder
  cancer, 173, 173*f*
  inflammation, 171–172
  stones, 171
Gallstones, 171
Gamma-glutamyltransferase (GGT), 9
Ganglion cyst, 268
Gangrenous necrosis, 10, 11*f*
Gardner syndrome, 164
Gartner duct cyst, 221
Gastric lymphoma, 159
Gastric neoplasia, 159
Gastric peptic ulcer, 158, 158*f*

KP00710.indb 280 13/10/22 1:53 PM

Gastric stress ulcers, 157, 158
Gastrinoma (G-cell tumor), 168
Gastritis, acute and chronic, 157–158, 157*f*
Gastroesophageal reflux disease (GERD), 156
Gastrointestinal stromal tumor (GIST), 166
Gaucher disease, 46
Genetic instability
  cancer and, 66, 132
  colon cancer, 165
Genomic imprinting, 51, 51*f*
Germ cell tumors
  central nervous system, 204
  ovaries, 227
  testicular cancer, 239–240, 240*f*
Germinal matrix hemorrhage, 194
Germline mutations, 69
Gerstmann-Straussler disease, 188, 188*t*
Gestational trophoblastic disease, 228–229
Ghon complex, 122
Giant cell arteritis, 97
Giant cell tumor of bone, 260
Gilbert syndrome, 176
Glanzmann thrombasthenia, 32
Glioblastoma multiforme, 201–202, 201*f*, 202*f*
Glomerular diseases, 139–144, 139*t*, 140*f*
Glomerulonephritis
  acute, 140–141, 141*f*
  chronic, 144–145
Glomerulopathies
  nephritic syndrome, 140–142
  nephrotic syndrome, 143–144, 144*f*
Glomus tumors, 103
Glucagonoma, 168
Glucose-6-phosphatase deficiency, 45
Glucose-6-phosphate dehydrogenase deficiency (G6PD), 93–94
Glutathione peroxidase, 7
Glycogen storage diseases, 13, 45
Glycosaminoglycan-rich edema, 28
Goiter, 243
Gonadal sex determination, 52
Gout, 266–267, 267*f*
Gower sign, Duchenne muscular dystrophy, 272*f*
Granulomatosis with polyangiitis, 98
Granulomatous inflammation, 21–22, 21*f*, 22*f*
Granulosa cell tumor, 228
Granulovacuolar degeneration, 198
Graves disease, 27, 243–244
Great arteries, transposition of, 112, 112*t*, 113*f*
Gross examination, 1
Growth-hormone-producing adenoma, 247
Guillain-Barre syndrome, 272
Gynecomastia, 236

H

H. influenzae infection, 43
Hageman factor, 18, 19*f*
Hairy cell leukemia, 209
Hamartomas, 133
Hashimoto thyroiditis, 244
Heart disease
  arterial supply, 106*f*
  cardiac tumors, 116–117
  congenital, 111–115, 112*t*, 113*f*–115*f*
  ischemic, 105–108
  myocarditis, 111
  pericardial disease, 117
  primary cardiomyopathies, 115–116
  rheumatic, 110
  valvular, 109–111
Heart muscle, injury and healing, 24
Heberden nodes, 263, 264*f*
Heinz bodies, 87, 93–94
Helicobacter pylori, 157–158, 157*f*
HELLP syndrome, 230
Helmet cells, 92*f*
Hemangioblastoma, 103
Hemangiomas, 85, 102, 102*f*
  liver, 182
Hemarthrosis, 32
Hemartomatous polyps, 164
Hematagenous spread, pyogenic osteomyelitis, 257–258, 258*f*
Hematoxylin and eosin (H&E) stain, 2*t*
Hemochromatosis, 181
Hemodialysis-associated amyloidosis, 63
Hemodynamics
  inflammation, 15
  liver disease, 181–182
Hemoglobin
  composition, 90
  electrophoresis, 92–93
  hemoglobin C, 93
Hemoglobin C disease, 93
Hemoglobin H disease, 90
Hemolytic anemia, 32, 89, 91–95, 92*f*
Hemolytic uremic syndrome (HUS), 31–32
Hemophilia A, 32
Hemophilia B, 32
Hemorrhage, cerebral, 190–191
Hemorrhagic infarct, 35
Hemorrhagic necrosis, temporal lobes, 186
Hemorrhoids, 102, 163, 166
Hemosiderin, 14
Hemostasis, 28–30
Hemothorax, 134
Henoch-Schonlein Purpura, 142
Heparin therapy, 29
Hepatic failure, 174
Hepatitis
  alcoholic, 180
  cellular injury, 9
  transaminases, 9
Hepatitis A, 177–178, 178*t*, 179*t*
Hepatitis B, 177–178, 178*t*, 179*t*
Hepatoblastoma, 183
Hepatocellular adenoma (HCA), 182
Hepatocellular carcinoma (HCC), 183
Hereditary elliptocytosis, 94
Hereditary hemochromatosis, 181
Hereditary nonpolyposis colorectal cancer (HNPCC), 164
Hereditary spherocytosis (HS), 94
Herniation, cerebral, 193, 193*f*
Herpes simplex virus (HSV)
  encephalitis, 187*f*
  vulva, 219
Herpes virus, 177
Hirano bodies, 198
Hirschsprung disease, 160
Histamine, inflammation mediation, 18, 19*f*
Histochemical stain, 2
Histocytes, diseases, 213
Histology, cancer diagnosis, 71
HIV encephalopathy, 186
HMG-CoA reductase, 46
Hodgkin lymphoma, 212–213, 212*f*
Honeycomb fibrosis, 128, 128*f*
Hormones, bone physiology, 253–254
Horner syndrome, 131–132
Horseshoe kidney, 137
Howell-Jolly bodies, 87
Human immunodeficiency virus (HIV), HIV encephalopathy, 185
Human papillomavirus (HPV)
  anal involvement, 166
  cervix, 222, 223*f*
  penis, 237
  vulva, 219
Huntington disease, 50, 196–197
Hyaline change, 13
Hydatidiform mole, 228–229, 229*t*
Hydrocele, 238
Hydrocephalus, 248
Hydrogen peroxide, 7
Hydrops fetalis, 90
Hydrops of gallbladder, 172
Hydrostatic pressure
  edema and, 27
  pulmonary edema, 131
Hydroxyl ions, 7
Hyperacute rejection, 61
Hyperadrenalism, 248–249, 249*f*
Hyperaldosteronism, 249
Hyperbilirubinemias, hereditary, 175–176
Hypercalcemia, PTH-related protein secretion, 73
Hyper IgM syndrome, 57
Hyperparathyroidism, 246
Hyperpigmentation, 76
Hyperplasia, 13, 13*f*
  breast, 232
  endometrial, 224
  polyps, 164
  thymic, 217
Hypersensitivity reactions, 53–54
  pneumonitis, 129

KP00710.indb 281 13/10/22 1:53 PM

Hypertension (HTN), 99–100
malignant, 148
portal, 174
pulmonary hypertension, 131
Hyperthyroidism, 243–244
Hypertrophic cardiomyopathy, 116
Hypertrophic gastropathy, 157
Hypertrophic osteoarthropathy, 72–73, 259
Hypertrophy, 12, 13*f*
scar formation, 24
Hypervitaminosis, 6
Hypoalbunemia, edema and, 27
Hypoparathyroidis, 246
Hypopigmentation, 75–76
Hypopituitarism, 248
Hypoplasia, kidney, 137
Hypospadias, 237
Hypothalamus, 248
Hypothyroidism, 243–244
Hypovolemic shock, 36
Hypoxanthine-guanine phosphoribosyltransferase (HGPRT), 50
Hypoxia, cellular injury, 5, 8*f*

I

Iatrogenic hypothyroidism, 244
Ichthyosis vulgaris, 82
Idiopathic hypertension, 100
Idiopathic pulmonary fibrosis (IPF), 128, 128*f*
IgA nephropathy, 141–142
Immediate (type I) hypersensitivity, 53
Immune complex-mediated (type III) hypersensitivity, 54
Immune deficiency diseases, 56–58, 58*f*
Immune regulation, cancer and loss of, 67
Immune thrombocytopenia purpura (ITP), 31
Immunofluorescence microscopy (IFM), 2
Immunohemolytic anemia, 89
Immunohistochemical (antibody) stains, 1
cancer diagnosis, 71, 71*f*
Immunologic dysfunction, 5
Incarcerated hernia, 160
Infarction, 35–36, 36*f*
cerebral, 189–190, 190*t*
renal, 148
Infectious agents, tissue responses to, 22
Infectious arthritis, 267–268
Infectious mononucleosis, 206
Infective bacterial endocarditis, 109–110
Infertility, male, 238
Inflammation
acute, 15–20
breast, 231
cell death with, 10, 11*f*
chemical mediators, 18–20, 19*f*
chronic, 20–22
gall bladder, 171–172
granulomatous, 21–22, 21*f*, 22*f*
hemodynamic changes, 15
neutrophils, 15–18, 15*f*, 16*f*, 16*t*
pancreas, 167–168
tissue responses, infectious agents, 22
valvular disease, 109–110
Inflammatory bone disease, 257–258, 258*f*
Inflammatory bowel disease (IFB), 161–162, 161*f*, 162*t*, 166
Inflammatory carcinoma, breast, 235, 235*f*
Inflammatory myopathies, 270–271
Inflammatory neuropathy, 272
Inheritance patterns, genetic diseases, 42
Inorganic matrix (bone), 253
Insulinoma (β-cell tumor), 168
Integrins, migration and adhesion, 16, 16*f*, 16*t*
Interacellular targeting, 6
Intermediate filaments, cancer diagnosis, 71*t*
Interstitial inflammation, 22
Interstitial sodium, edema and, 27
Intracellular killing, 17
Intracerebral (intraparenchymal) hemorrhage, 190–191
Intraductal papillary mucinous neoplasms, 169
Intraductal papilloma, 233
Intramembranous bone, 254
Intravascular (IV) hemolysis, 91
Intrinsic coagulation pathway, 29, 30*f*
Intussusception, 159–160
Iron deficiency anemia, 89–90
Irregular emphysema, 124
Irritable bowel syndrome (IBS), 160
Ischemia, 5
glocal cerebral, 189
Ischemic bowel disease, 163
Ischemic heart disease, 105–108

J

Jaundice, 174–177

K

Kallikrein, 18, 19*f*
Kaposi sarcoma, 60, 61*f*, 85, 103
Kartagener syndrome, 125
Karyolysis, 9, 9*f*, 11
Karyorrhexis, 9, 9*f*, 11
Karyotypic sex determination, 52
Kawasaki disease, 97
Keloid formation, 25, 25*f*
Keratoacanthoma, 83
Kidney
chronic disease, 147
congenital anomalies, 137
cystic disease, 138–139
diabetic nephropathy, 251
tumors, 149–151
vascular disorders, 147–149, 148*f*
Kinin system, 18, 19*f*
Klinefelter syndrome, 41
Knudson's "two-hit hypothesis," 69
Korsakoff psychosis, 200
Kuru disease, 188, 188*t*

L

Labile cells, tissue repair, 23
Lactate dehyrogenase, myocardial injury, 9
Lambert-Eaton myasthenic syndrome, 72, 271
Langerhans histiocytosis, 213
Large cell carcinoma, 133
Large intestine, mechanical disorders, 159–160
Laryngeal cancer, 134
Leber hereditary optic neuropathy, 51
Left heart
failure, 108
valvular disease, 109
Left-to-right shunt, congenital heart disease, 113–114
Leiomyoma, 225, 274
Leiomyosarcoma, 225, 274
Lengito maligna melanoma, 77
Lesch-Nyhan syndrome, 50, 267
Leukemias
acute lymphoblastic, 216
acute myelogenous, 213–214
adult T-cell leukemia/lymphoma (ATLL), 211
chronic lymphocytic, 208–209
chronic myelogenous, 214–215, 214*f*
defined, 65
hairy cell, 209
Leukocyte adhesion deficiency type 1, 17
Leukocyte count, 205–208
Leukocytosis, 205–206
Leukopenia, 206
Lewy body dementia, 198
Leydig cell tumors, 241
Libman-Sacks endocarditis, 111
Lichen sclerosis, 219
Lichen simplex chronicus, 219
Li-Fraumeni syndrome, 69, 233
Lipase, pancreatitis, 9, 14
Lipids, cellular injury accumulation, 13
Lipoblasts, 273
Lipofuscin, 14
Lipoma, 273
Liposarcoma, 273
Lipoxygenase pathway, 19
Liquefaction necrosis, 10
Liver
injury, 24
pathology, 174–183
tumors, 182–183
Lobar pneumonia, 120
Lobular carcinoma in situ (LCIS), breast, 234–235, 234*f*
Long-acting thyroid stimulator (LATS), 243
Low density lipoprotein receptor gene (LDLR) mutation, 46
Lung cancer, 130–133
small cell, 72–73
squamous cell, 73

KP00710.indb 282 13/10/22 1:53 PM

Lungs
abscess, 121
atelectasis, 120
bronchiectasis, 125–126, 126*f*
cancer, 72–73, 131–132
congenital malformations, 119
infiltrative restrictive disease, 127–130
injury and healing, 24
obstructive pulmonary disease, 123–127
obstructive *vs.* restrictive disease, 126*t*, 127*t*
occupation-associated disease, 129–130
pulmonary infections, 120–122
pulmonary tumors, 131–133
sarcoidosis, 122–123, 123*f*
vascular disorders, 131
Lung transplantation, cystic fibrosis, 43
Lyme disease, 268, 268*f*
Lymphadenopathy, 207–208
Lymphatic obstruction, edema and, 27
Lymphedema, 28
Lymph node
anatomy, 207*f*
breast cancer and, 236
testicular cancer, 239–241
Lymphoblastic lymphoma, 216
Lymphocyte-depleted lymphoma, 212
Lymphocyte-predominant lymphoma, 212
Lymphocyte-rich Hodgkin lymphoma, 212
Lymphocytes
chronic inflammation, 20–21
leukopenia, 206
Lymphocytosis, 206
Lymphomas
central nervous system, 204
defined, 65
diffuse large B-cell, 209, 209*f*
follicular, 209
gastric, 159
Hodgkin, 212–213, 212*f*
lymphoblastic, 216
lymphoplasmacytic, 211
Mantle cell, 210
marginal zone, 210
small lymphocytic lymphoma, 208
small noncleaved (Burkitt), 210, 210*f*
testicular, 241
Lyon's hypothesis of X-inactivation, 42
Lysosomal storage diseases, 45*t*, 46
Lysosomal α-1,4-glucosidase (acid maltase), 45
Lysosome, cell injury and disruption of, 9

M

M. avium complex (MAC), 122
Macrocytic anemias, 95–96
Macrophages, chronic inflammation, 20
Macule (skin lesion), 79
Malabsorption
iron deficiency, 89
syndromes, 160–161
Vitamin B12, 95
Malakoplakia, urinary bladder, 153
Malar rash, 83
Malignant melanoma, 77–78, 78*f*
Mallory-Weiss tears, 156
Mantle cell lymphoma, 210
Marfan syndrome, 47, 47*f*
Marginal zone lymphoma (MALToma), 210
Mast cell diseases, 216
Mastitis, 231
Mastocytosis, 216
Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome, 221
McArdle syndrome, 45
McCune-Albright syndrome, 254
Mean corpuscular hemoglobin concentration (MCHC), 88
Mean corpuscular hemoglobin (MCH), 88
Mean corpuscular volume (MCV), 88
Meckel diverticulum, 163
Mediterranean glucose-6-phosphate dehydrogenase deficiency, 93
Medullary carcinoma, 246, 250
Medullary cystic disease, 139
Megaloblastic anemias, 95–96
Meissner plexus, 160
Melanin, 14
Melanocytic nevus, 77
Melanoma, of vulva, 220
Melanosis coli, 163
Melasma, 76
Membranoproliferative glomerulonephritis (MPGN), 142
Membranous glomerulonephritis, 143
Men, cancer in, 66
Mendelian inheritance disorders, 42–50
Menetrier disease, 157
Meninges, tumors of, 203, 203*f*
Meningioma, 203, 203*f*
Meningitis, 184–185, 185*t*
Meningocele, 193, 194*f*
Meningoencephalitis, 185
Meningomyelocele, 193, 194*f*
Menkes disease, 50
Mesothelioma, malignant, 130, 130*f*
Metabolic disorders, 199
bone, 255–257
Metabolic liver disease, 180–181
Metaplasia, 13, 13*f*
Metastasis, 70
bone, 262
breast cancer, 236
central nervous system, 204
liver, 183
lung cancer, 133
Metastatis calcification, 14
MHC class II deficiency, 57
Microaneurysms, 100*f*, 101
Microcalcifications, breast, 232
Microcytic anemias, 89–91, 90*t*
Microdeletions, 41
Microscopic examination, 1
Microscopic infarction, 106
Mikulicz syndrome, 56
Minimal change disease, 143
Mitochondrial DNA disorders, 51
Mitochondrial dysfunction, cell injury, 7, 9
Mitral valve prolapse, 109
Mixed cellularity lymphoma, 212
Mixed connective tissue disease, 56
Mixed germ cell tumors, testes, 241
Molecular diagnostic techniques, 2
Molluscum contagiousm, 219
Monckeberg Medical Calcific Sclerosis, 98
Monocytes, leukocytosis, 205–206
Mosaicism, 39
Motility disorders, 160
Mucinous neoplasms, 169
breast carcinoma, 234
ovaries, 226
Mucopolysaccharidosis (MPS), 46
Mucous plugs, 125
Multicystic encephalopathy, 194
Multifactorial inheritance, 51
Multinodular goiter, 243
Multinucleated giant cells, 21
Multiple endocrine neoplasia (MEN) syndromes, 250
Multiple melanoma, 210–211
Multiple sclerosis (MS), 195
Murphy's sign, gallstones, 171
Muscle glycogen phosphorylase, 45
Muscular dystrophy, 271–272, 272*f*
Myasthenia gravis, 270
Myasthenic syndromes, 270–271
Mycobacteria
nontuberculous, 122
tuberculosis, 121–122
Mycobacterial meningitis, 185
Mycosis fungoides, 211–212
Mycotic aneurysms, 100*f*, 101
Myelin figures, 9
Myelocele, 193, 194*f*
Myelodysplastic syndromes (MDS), 214
Myelofibrosis (MF) with myeloid metaplasia, 215
Myeloid neoplasms, 213–215
Myeloma, multiple, 210–211
Myeloproliferative neoplasms (MPN), 214–215, 215*f*
Myocardial ischemia/infarction, 8*f*, 9, 106–108, 107*t*
Myocarditis, 111
Myoclonic epilepsy with ragged red fibers (MERRF), 51
Myxoma, 116–117

N

Na^+K^+ ATPase pump, cellular injury and, 9
Natural selection, cancer and, 66
Necrosis, 9*f*
central, 21
types, 10
Necrotizing inflammation, 22

KP00710.indb 283 13/10/22 1:53 PM

Neoplasia
benign *vs.* malignant, 70*t*
bone, 259–262
breast, 232–236, 233*f*–235*f*
causes, 66–67
cervical, 222–224, 222*t*, 223*f*
gastric, 159
intestinal, 165–166, 165*t*
lymphadenopathy, 208
lymphoid, 208
mature B-cell neoplasms, 208–211
myeloid, 213–215
natural killer cells, 211–212
ovarian, 228*t*
pancreatic, 168–169
peripheral T-cell, 211–212
thyroid, 245–246, 245*f*
vascular neoplasms, 102–103
Nephritic syndrome, 139–142, 139*t*
Nephronophthisis-medullary cystic disease complex, 139
Nephrotic syndrome, 139–140, 139*t*
glomerulopathies, 143–144, 144*f*
Neural tube defects, 193–194, 194*f*, 194*t*
Neuritic plaques, 198
Neuroendocrine tumors
lung, 74
pancreatic, 168
Neuroepithelial tissue, tumors of, 201
Neurofibrillary tangles, 198
Neurofibroma, 71*f*, 274, 275*f*
Neurofibromatosis, 48–49, 48*f*
Neurogenic shock, 36
Neuropathic arthropathy, 268
Neurosecretory granules, 133
Neutrophils
casts, 145
inflammation, 15–18, 15*f*, 16*f*, 16*t*
leukocytosis, 205–206
leukopenia, 206
migration and adhesion, 16, 16*f*
Nevi (nevus), 77
flammeus nuchae, 102
Newborn, jauncide of, 175
Niemann-Pick disease, 46
Nitroblue tetrazolium reduction, 18, 18*f*
Nodular melanoma, 77
Nodular sclerosis, 213
Nodule (skin lesion), 79
Nonalcoholic fatty liver disease, 181
Nonatopic asthma, 125
Noncaseating granulomas, sarcoidosis, 123, 123*f*
Non-Hodgkin lymphoma, Sjögren syndrome and, 56
Noninfective endocarditis, 111
Non-inflammatory response, apoptosis, 11
Non-Mendelian inheritance disorders, 50–51
Nonproliferative fibrocystic changes, 231, 232*t*
Nonspecific interstitial pneumonia, 128
Normocytic anemias, 91–95
Notch signaling pathway, angiogenesis, 69
Nuclear damage, cell injury, 9
Nutrition
cellular injury and, 5
iron deficiency in, 89

O

Obesity, 5
Obstruction/resorption atelectasis, 120
Occupational asthma, 125
Occupation-associated lung disease, 129–130
Oculocutaneous albinism, 76
Oligodendroglioma, 202
Oligohydramnios, 137
Oncocytomas, 149
Oncogenes
clinical importance, 68*t*
growth activation, 68
Oncogenic viruses, 67
Oncotic pressure, pulmonary edema, 131
Opportunistic infection, AIDS patients, 59–60, 60*t*
Orchitis, 238
Organ failure, shock, 37
Organic matrix (bone), 253
"Orphan Annie eye" test, 245
Osgood-Schlatter disease, 258
Osler-Weber-Rendu syndrome, 163
Osteitis fibrosa cystica, 246, 257
Osteoarthritis (OA), 263–264, 263*t*
Osteoblastoma, 259
Osteoblasts, 253
Osteochondroma, 259, 260*f*
Osteoclasts, 253
Osteocytes, 253
Osteogenesis imperfecta, 254
Osteoid osteoma, 259
Osteoma, 259
Osteomalacia, 257
Osteomyelitis
pyogenic, 257–258, 258*f*
tuberculous, 258
Osteopetrosis, 255
Osteoporosis, 256, 256*f*
Osteosarcoma, 260–261, 261*f*
Ovarian fibroma, 227
Ovarian sex cord/stromal tumors, 227–228
Ovaries, germ cell tumors, 227
Ovary
disorders of, 226–228
tumors of, 226
"Overriding aorta," 112
Ovotesticular disorder, 52
Oxygen-dependent killing, 17–18, 18*f*

P

P. aeruginosa infection, 43
Paget disease
of bone, 255
of breast, 235–236, 235*f*, 236*f*
of vulva, 220
Pain, chemical mediators, 19
Panacinar emphysema, 124
Pancoast tumor, 131
Pancreas
cancer, 65, 168–169
congenital anomalies, 167
Pancreatic agenesis, 167
Pancreatic divisum, 167
Pancreatic pseudocyst, 167
Pancreatitis, 9
acute, 167–168
chronic, 168
Pannus formation, rheumatoid arthritis, 265, 265*f*
Papenheimer bodies, 87
Papillary carcinoma, thyroid, 245–246
Papillary hidradenoma, 220
Papillary renal cell carcinoma, 150
Papillary renal necrosis, 151
Pap test, 226
Papular skin diseases, 79, 81
Para-aortic lymph nodes, testicular cancer, 239–241
Paraneoplastic acanthosis nigricans, 72, 82
Paraspinal nerves, tumors, 202
Parathyroid glands, 246
Parietal pleural plaques, 130
Parkinson disease (PD), 196
Parkinson syndrome, 196
Paroxysmal nocturnal hemoglobinuria, 94
Partial thromboplastin time (PTT), 29–30
Patau syndrome, 40, 41*f*
Patch (skin lesion), 79
Patchy atelectasis, 120
Patent ductus arteriosus (PDA), 114, 114*f*
Pathogenesis, 1
Pathogens, 5
Pathology
definitions, 1
disease considerations, 1
overview, 1
techniques, 1–3
Pauci-immune crescentic glomerulonephritis, 141
Peau d'orange, breast carcinoma, 235, 235*f*
Pelvic inflammatory disease (PID), 221–222
Pelvic kidney, 137
Pemphigus, 79
Penis
acquired conditions, 237
congenital disorders, 237
Peptic ulcer, 158
Pericardial effusion, 117
Pericarditis, 108, 117
Perinatal brain injury, 194
Periodic acid-Schiff (PAS) stain, 3*t*
Peripheral nerve sheath tumors, 274, 275*f*
Peripheral nervous system
disorders, 272
injury, 24
Peripheral neuropathy, 272
Peripheral T-cell lymphoma, 211–212
Periventricular leukomalacia, 194
Permanent cells, tissue repair, 23

KP00710.indb 284 13/10/22 1:53 PM

Peutz-Jeghers syndrome, 164, 165
Peyronie disease, 237
p53 protein, 11
Phagocyte deficiencies, 57
Phagocytosis, 17
Phemphigus vulgaris, 79, 80*f*
Phenotypic sex determination, 52
Phenylalanine at position 508, 43
Phenylketonuria (PKU), 44
Pheochromocytoma, 250
Photodermatoses, 82
Phototoxic dermatitis, 82
Phyllodes tumor, 233
Physical injury, 5
Pigmentation disorders, 75–76, 76*f*
Pigmented bilirubinate stones, 171
Pilocytic astrocytoma, 201
Pineal gland, 248
Pituitary gland, 247–248
Pityriasis rosea, 80
Placenta, 228–230, 229*t*
  ectopic pregnancy, 230
  gestational trophoblastic disease, 228–229
  twins, 230
Placenta accreta, 230
Placental site trophoblastic tumor, 229
Placenta previa, 230
Plascental abruption, 230
Plasma cells, chronic inflammation, 21
Plasmacytoma, 211
Plasma-membrane blebs, 9
Plasminogen activator inhibitor (PAI-1), breast cancer, 236
Plasmodium falciparum infection, 92
Platelet activation, adhesion and aggregation
  bleeding disorders, 31–33, 32*t*
  coagulation and, 28, 29*f,* 29*t*
Pleomorphic sarcoma, 274
Pleural cavity, disorders, 134–135
Pleural effusion, 134
Plummer syndrome, 243
Plummer-Vinson syndrome, 89
Pneumoconioses, 129
Pneumonia, 120–121
  cryptogenic organizing, 128
  eosinophilic, 129
  nonspecific interstitial, 128
Pneumonitis
  collagen vascular disease, 128
  hypersensitivity-related, 129
  smoking-related, 128
Pneumothorax, 134, 135*f*
Point mutations, 42
Polyarteritis nodosa, 97
Polycystic kidney disease, 138, 138*f*
Polycystic ovary syndrome (PCOS), 226
Polycythemia, 96
Polycythemia vera, 215
Polymerase chain reaction (PCR), 2
Polymorphisms, 51
Polymorphous light eruption, 80
Polymyositis, 270
Pompe disease, 45
Porcelain gallbladder, 173, 173*f*
Pores of Kohn, 120
Porphyria cutanea tarda, 79–80, 80*f*
Portal hypertension, 174
Port wine staine, 102, 102*f*
Postductal coarctation, 115
Postoperative endocarditis, 111
Potter facies, 137–138
Prader-Willi syndrome, 51
Precocious puberty, 248
Preductal coarctation, 115
Preeclampsia, 230
Priapism, 237
Primary amyloidosis, 63
Primary (azurophilic) granules, 15
Primary biliary cirrhosis, 176–177
Primary cardiomyopathies, 115–116
Primary sclerosing cholangitis (PSC), 177
Primary union, 24
Prion infections, 188, 188*t*
Pro-apoptotic protease activating factor (Apaf-1), 11
Progressive multifocal leukoencephalopathy (PML), 187
Prolactinoma, 247
Proliferative fibrocystic changes, 231, 232*t*
Prostaglandin E2, congenital heart defects, 112–113
Prostate
  benign prostatic hyperplasia, 241–242
  cancer, 242
Prostatis, 242
Protease-antiprotease imbalance, 181
Protein electrophoresis, 2
Proteins
  Alzheimer disease, 197–198, 197*t*
  apoptosis regulation, 11
  cellular injury accumulation, 13
  intake, 5
  prion, 188, 188*t*
Protein synthesis, cell injury and, 9
Prothrombin time (PT), 29–30
  liver disease, 177
Proto-oncogenes, 68
Prussian blue stain, 3*f,* 3*t*
Psammoma bodies, ovarie, 226, 227*f*
P-selectin, 17
Pseudodiverticula, 164
Pseudogout, 267
Pseudomembranous colitis, 162
Psoriasis, 81, 81*f*
Psoriatic arthritis, 266
Pulmonary airway malformation, 119
Pulmonary atresia, 109, 112, 112*t*
Pulmonary edema, 27, 131
Pulmonary emboli (PE), 35
Pulmonary hypertension, 131
Pulmonary infarction, 35–36, 36*f*
Pulmonary infections, 120–122
Pyelonephritis, 145
Pyknosis, 9, 9*f,* 11
Pyloric stenosis, 156
Pyogenic granulomas, 85
Pyogenic osteomyelitis, 257–258, 258*f*
Pyruvate kinase deficiency, 94
Pyuria, 145

R

Rabies, 186
Radiation, cancer and, 67
Rapidly progressive glomerulonephritis (RPGN), 141, 141*f*
Rashes, 79–82
Raynaud phenomena, 98
Reactive arthritis, 266
Reactive systemic amyloidosis, 63
Red blood cells (RBCs)
  increased turnover, 175
  indices, 88
  morphology, 87
Red cell distribution width (RDW), 88
Red skeletal muscle, 269–271, 269*t*
Reed-Sternberg cells, 212–213, 212*f*
Reflux esophagitis, 156
Regeneration, tissue repair, 23
Relative polycythemia, 96
Remodeling, bone, 253
Renal artery stenosis, 147–148, 148*f*
Renal cell carcinoma (RCC), 149–150, 149*f,* 151*f*
Renal dysplasia, 139
Renal failure, hemolytic uremic syndrome, 32
Renal pathology
  chronic kidney disease, 147
  congenital kidney anomalies, 137
  cystic disease, 138–139, 138*f*
  glomerular disease, 139–144, 139*t,* 140*f*
  tubular injury, 146
  tubulointerstitial nephritis, 145
  urolithiasis, 146–147, 147*f*
Renal stones, 146–147, 147*f,* 152
Replication, cancer and, 69
Resorption, bone, 253
Respiratory distress syndrome of the newborn, 127–128
Restrictive cardiomyopathy, 116
Reticulin stain, 3*t*
Reticulocytes, 88
Retina, diabetic retinopathy, 251, 252*f*
Retroperitionea fibrosis, 152
Retrovirus, 58*f*
Reye syndrome, 181
Rhabdomyoma, 116–117
  vaginal, 221
Rhabdomyosarcoma, embryonal, 220
Rheumatic fever, 110–111, 110*t*
Rheumatoid arthritis (RA), 263*t,* 264–265, 265*f*
Rickets, 6, 6*f,* 257
Riedel thyroiditis, 245
Right heart
  failure, 108
  valvular disease, 109

KP00710.indb 285 13/10/22 1:53 PM

Right-to-left shunt, congenital heart disease, 112, 112*t*, 113*f*
Ring sideroblasts, 87
RNA oncogenic viruses, 67
Robertsonian translocation, 39
Rotor syndrome, 176
Rouleaux erythrocytes, 87
Rule of 10s, pheochromocytoma, 250

S

S. aureus infection, 43
Sanctuary sites, acute leukemias, 216
Sarcoidosis, 122–123, 123*f*
Sarcoma, defined, 65
Scar formation, 24–25
Schaumann bodies, 123
Schistocytes, 87, 92*f*
Schistosoma haematobium, squamous cell carcinoma, 153, 153*f*
Schwannoma, 202, 274
Scleroderma, 56
Sclerosing adenosis, 232
Scrapie, 188, 188*t*
Secondary adrenocortical insufficiency, 250
Secondary glomerulonephritis, 144, 144*f*
Secondary granules, 16
Secondary hemochromatosis, 181
Secondary hypertension, 100
Secondary polycythemia, 13, 96
Secondary union, 24
Selectins, migration and adhesion, 16, 16*f*, 16*t*
Selective IgA deficiency, 57
Sellar region, tumors of, 203
Seminoma, 239, 240*f*
Senile cardiac/systemic amyloidosis, 64
Senile cerebral amyloidosis. *See* Alzheimer disease
Septate hyphae, 60*f*
Septic shock, 36
Seronegative spondyloarthropathies, 266
Serotonin, inflammation mediation, 18, 19*f*
Serous neoplasms, 169
  ovarian, 226
Serpentine asbestos, 129
Sertoli cell tumors, 241
Sertoli-Leydig cell tumor, 228
Serum enzymes, cellular injury, 14
Serum tumor markers, 72
Severe combined immunodeficiency (SCID), 56
Sex chromosome disorders, 41–42, 42*f*
Sex cord-stromal tumors, 241
Sex determination, 52
Sezary syndrome, 212
Sheehan syndrome, 247
Shock, 36–37
Sickle cell disease, 92
  renal infarction, 148
Sickle cells, 87
Sideroblastic anemia, 91
Signet Ring Cell carcinoma, 70*f*
Silicosis, 130
Sipple syndrome, 250
Sjögren syndrome (sicca syndrome), 55–56, 265
Skeletal disorders
  genetic, 254–255
  muscular dystrophy, 271–272, 272*f*
Skeletal muscle, anatomy, 269–271, 269*t*
Skin
  anal skin tags, 166
  anatomy, 75*f*
  benign growths, 78
  benign melanocytic lesions, 76–77
  dry skin, 82
  lesions, 79
  malignant melanoma, 77–78
  nonmelanoma cancer, 83–84
  pigmentation disorders, 75–76, 76*f*
  rashes or dry skin, 79–82
  systemic disease and changes to, 82–83
  vascular tumors, 85
Small cell lung cancer, 72–73, 133, 133*f*
Small intestine
  malabsorption syndromes, 160–161, 160*f*
  mechanical obstruction, 159–160
  motility disorders, 160
Small lymphocytic lymphoma, 208
Smoking-related pneumonitis, 128
Soft tissue tumors, 273
Solar lentigines (actinic lentigines), 77
Somatostatinoma, 168
Spermatocele, 238
Spherocytes, 87
Spider telangiectasias, 102
Spina bifida occulta, 193, 194*f*
Spinal cord injuries, 193
Spleen, diseases of, 217
Splenomegaly, 217
Squamous cell carcinoma
  anus, 166
  bladder, 153, 153*f*
  cervix, 223, 223*f*
  esophagus, 156
  lung cancer, 73, 132, 132*f*
  penis, 237
  scrotal, 241
  skin, 83, 83*f*
  vaginal, 220
  of vulva, 220
Stable cells, tissue repair, 23
Stein-Leventhal syndrome, 226
Stewart-Trevers syndrome, 85
Stomach, congenital disorders, 156–157
Stroke, 189
Stromal tumors
  breast, 232–233, 233*f*
  testes, 241
Struvite stones, 146–147, 147*f*
Subacute sclerosing panencephalitis, 187
Subacute thyroiditis, 244
Subarachnoid hemorrhage, 190
Subdural hematoma, 192, 192*f*
Subendocardial infarction, 106
Subfalcine (cingulate gyrus) herniation, 193
Succenturiate lobes, 230
Sudden cardiac death, 108
Superficial spreading melanoma, 77
Superior vena cava syndrome, 132
Superoxide dismutase, 7
Suppurative arthritis, 267
Swan neck deformity, rheumatoid arthritis, 264
Sweat test, cystic fibrosis diagnosis, 43
Syndrome of inappropriate ADH secretion (SIADH), 73, 247–248
Syndromic albinism, 76
Synovial sarcoma, 274
Syphilis, vulvar infection, 219
Syphilitic aneurysms, 101
Syringomyelia, 194, 194*f*
Systemic diseases, 58
Systemic lupus erythematosus (SLE), 55, 55*f*, 83
  secondary glomerulonephritis, 144

T

Takayasu arteritis, 97
Target cells, 87
Tartrate-resistant acid phosphatase (TRAP) stain, hairy cell leukemia, 209
Tay-Sachss disease, 45
T-chronic lymphocytic leukemia, 209
Teardrop cells, 87
Tension pneumothorax, 134
Teratoma
  ovarian, 227
  testicular, 240, 240*f*
Testes
  cancer, 239–241, 240*f*
  nonneoplastic conditions, 238
Testicular feminization, 50
Testicular torsion, 238
Tetralogy of Fallot, 112, 112*t*, 113*f*
Thalassemia syndromes, 90–91
Thrombin time (TT), 29–30
Thromboangiitis obliterans, 97
Thrombocytopenia, 32
  essential, 215
Thromboemboli, 34–35
Thrombosis, 34, 34*t*
Thrombotic occlusion, 189–190
Thrombotic thrombocytopenic purpura (TTP), 31
Thymomas, 217
Thymus, diseases of, 217
Thyroglossal duct, 245
Thyroid, papillary carcinoma, 245–246
Thyroid gland
  goiter, 243
  hyperthyroidism/hypothyroidism, 243–244
Thyroiditis, 244–245
Thyroid neoplasia, 245–246, 245*f*

KP00710.indb 286 13/10/22 1:53 PM

Thyroid-stimulating immunoglobulin (TSI), 243
Tissue injury, shock, 37
Tissue repair
  overview, 23
  regeneration, 23
  scar formation, 24
TNM cancer staging, 72
  colorectal cancer, 165
Tophi(gout), 267, 267*f*
Toxic CNS disorders, 200
Toxic megacolon, 160
Toxoplasmosis, 187
TP53 germline mutation, breast carcinoma, 233
Tracheoesophageal fistula, 155, 155*f*
Tram-tracking, MPGN diagnosis, 142
Transient ischemic attack (TIA), 189
Transitional cell carcinoma, 152
Transitional cell carcinoma (TCC), 152–153
Transmission electron microscopy (TEM), 2
Transmural myocardial infarction, 106
Transplant immunology, 61
Transporter of thyroxine and retinol (TTR), 64
Transtentorial (uncal) herniation, 193, 193*f*
Transudate, 28
Trauma, central nervous system, 191–193, 192*f*
Trichomas vaginalis, 221
Trichrome stain, 3*t*
Tricuspid atresia, 109, 112, 112*t,* 113*f*
Triple repeat mutations, 50–51
Tropheryma whipplei, 161
Tropical sprue, 161
Troponin, myocardial injury, 9
Truncus arteriosus, 112, 112*t,* 113*f*
TSH test, 243
Tuberculosis (TB), 121–122, 122*f*
Tuberculous osteomyelitis, 258
Tuberous sclerosis complex, 116
Tubular adenoma, 164, 164*f*
Tubular carcinoma, breast, 235
Tubulointerstitial nephritis, 145
Tumor lysis syndrome, 213
Tumor necrosis factor (TNF), apoptosis, 11
Tumors
  bone, 259–262
  breast, 232–236, 233*f,* 235*f*
  cardiac, 116–117
  central nervous system, 200–204, 200*t,* 201*f*–203*f*
  colonic, 165–166
  defined, 65
  gastrointestinal stromal, 166
  grading and staging, 72, 200, 200*t*
  kidney, 149–151
  liver, 182–183
  neuroendocrine, 168–169
  ovarian, 226
  pericardial, 117
  peripheral nerve sheath, 274, 275*f*
  progression, 66
  pulmonary, 131–133
  soft tissue, 273
  uterine, 224–225
  vaginal, 220–221
  vascular, 102–103
  vulvar, 220, 220*f*
  Wilms tumor, 151
Tumor suppressor genes
  clinical importance, 69*t*
  inactivation, 69
Turcot syndrome, 164
Turner syndrome, 41, 42*f*
Tutal ectopic pregnancy, cervical infection and, 222
Twins, placentation, 230
Tylosis, 156
Type 1 diabetes (T1D), 251
Type 2 diabetes (T2D), 251
Tyrosine kinase inhibitors, lung cancer, 133

U

Ulcerative colitis, 160–162, 161*f,* 162*t*
Unilateral agenesis, 137
Unilateral hydronephrosis, 151
Urachal cyst remnants, 152
Urate nephropathy, 145
Ureteral disorders, 152
Ureteritis cystica, 152
Ureteropelvic junction (UPJ), 152
Uric acid
  arthritis and, 266–267
  stones, 146
Urinary bladder pathology, 152–153, 153*f*
Urinary system, obstructive disorders, 151
Urokinase plasminogen activator (uPA), breast cancer, 236
Urolithiasis, 146–147, 147*f*
Uterus
  endometrial hyperplasia and adenocarcinoma, 224–225, 225*f*
  nonneoplastic conditions, 224
  tumors, 225

V

Vagina
  developmental disorders, 221
  tumors, 220–221
Vaginal adenosis, 220
Vaginitis/vaginosis, 221
Valvular heart disease, 109–111
Varicocele, 238, 238*f*
Vascular disorders
  cerebrovascular disease, 189–191, 190*t,* 191*f*
  diabetes, 251–252, 251*f*
  small and large intestine, 163
Vascular ectasias, 102
Vascular tumors, skin, 85
Vascular wall injury, 28
Vasculitides, 97–98
Vas deferens, obstruction, 238
Vasoactive amines, 18, 19*f*
Venous disease, 101–102
Venous insufficiency, 102
Ventricular septal defect (VSD), 112–114, 114*f*
Verrucae (warts), 78
Vesicle (skin lesion), 79
Villous adenoma, 164, 164*f*
VIPoma, 169
Viral encephalitides, 185–187, 187*f*
Viral hepatitis, 177–178, 178*t,* 179*t*
Viral meningitis, 184
Virchow's triad, 34
Viridians streptococci, endocarditis and, 110
Vitamin B12 (cobalamin) deficiency, 95, 199
Vitamins
  cellular injury, 7
  deficiencies, 5–6
Vitiligo, 75–76, 76*f*
Volvulus, 159–160
Von Gierke disease, 45
Von Hippel-Lindau disease, 49
Von Recklinghausen disease, 48, 48*f,* 246, 257
Von Willebrand disease, 32–33
V/Q lung scan, 34–35
Vulva, disorders, 219–220
Vulvovaginal candidiasis, 221

W

WAGR syndrome, 151
Waldenstrom macroglobulinemia, 211
Warfarin therapy, 29
Waterhouse-Friderichsen syndrome, 249
Weibel-Palade bodies, 17
Werner syndrome, 250
Wernicke encephalopathy, 200
Wernicke-Korsakoff syndrome, 200
Whipple disease, 161
White skeletal muscle, 269–271, 269*t*
Wilms tumor, 151
Wilson disease, 180–181
Wiskott-Aldrich syndrome (WASP), 57
Women, cancer in, 66
Wound healing, 24–25, 25*f*

X

Xerosis, 82
X-linked dominant conditions, 50
X-linked ocular albinism, 76
X-linked recessive conditions, 50

Y

Y chromosome, sex chromosome disorders, 41
Yellow fever, 177
Yolk sac tumor, testicular, 240

Z

Zebra bodies, 46
Ziehl-Neelsen stain, 3*t*
Zollinger-Ellison syndrome, 157

KP00710.indb 287 13/10/22 1:53 PM