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Fundamentals of Pathology

LEARNING OBJECTIVES

Define the etiology, pathogenesis, morphology, and clinical significance of disease
List techniques for staining pathologic specimens

Overview of Pathology

DEFINITIONS OF PATHOLOGY

- The study of the essential nature of disease, including symptoms/signs, pathogenesis, complications, and morphologic consequences including structural and functional alterations in cells, tissues, and organs
- The study of all aspects of the disease process focusing on the pathogenesis leading to classical structural changes (gross and histopathology) and molecular alterations

DISEASE CONSIDERATIONS

The etiology (cause) of a disease may be genetic or environmental. The pathogenesis of a disease defines the temporal sequence and the patterns of cellular injury that lead to disease. Morphologic changes of the disease process include both gross changes and microscopic changes. The clinical significance of a disease relates to its signs and symptoms, disease course including complications, and prognosis.
Cellular Injury and Adaptation

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** is the most common cause of injury; it occurs when lack of oxygen prevents the cell from synthesizing sufficient ATP by aerobic oxidation. Major mechanisms leading to hypoxia are ischemia, cardiopulmonary failure, and decreased oxygen-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 decreased arterial flow or decreased 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.

Inherited genetic mutations cause congenital disorders, e.g., lysosomal storage disorders.

**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 forms of injury** include 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), and kwashiorkor (decrease in total protein intake).
- **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** is less commonly a problem but can result in tissue-specific abnormalities.
CELLULAR CHANGES DURING INJURY

**Cellular responses to injury** include adaptation (hypertrophy or atrophy, hyperplasia or metaplasia), reversible injury, and irreversible injury and cell death (necrosis, apoptosis, or necroptosis).
Figure 2-2. Cellular Response to Stress and Injurious Stimuli

- Homeostatic cell
- Metabolic changes
  - Ischemia
  - Toxins, etc.
- Adaptation
- Injury
- Reversible changes
- Irreversible changes
- Apoptosis
- Necrosis
- Point of no return
The cellular response to injury depends on several important factors, including the type of injury, duration (including pattern) of injury, severity and intensity of injury, type of cell injured, the cell’s metabolic state, and the cell’s ability to adapt.

### NOTE

Protective factors against free radicals include:

- **Antioxidants**
  - Vitamins A, E, and C
- **Superoxide dismutase**
  - Superoxide ? hydrogen peroxide
- **Glutathione peroxidase**
  - Hydroxyl ions or hydrogen peroxide ? water
- **Catalase**
  - Hydrogen peroxide ? oxygen and water

The **critical intracellular targets that are susceptible to injury** are DNA, production of ATP via aerobic respiration, cell membranes, and protein synthesis.

**Important 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$_2^-$), hydroxyl radical (OH$^-$), and hydrogen peroxide (H$_2$O$_2$).
- **ATP depletion**: 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.
- **Increased cell membrane permeability**: 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).
Figure 2-3. Classic Example of Cellular Injury Caused by Hypoxia
NOTE

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

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
- Pancreatitis: amylase and lipase
- Biliary tract obstruction: alkaline phosphatase
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
Inflammation

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

#### 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).

#### NOTE

- **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).
- **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.

#### PRIMARY (AZUROPHILIC) GRANULES

<table>
<thead>
<tr>
<th>Endothelium</th>
<th>Leukocyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selectins</td>
<td>P-Selectin</td>
</tr>
<tr>
<td>E-Selectin</td>
<td></td>
</tr>
<tr>
<td>GlyCam-1/CD34</td>
<td></td>
</tr>
</tbody>
</table>

- **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.
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.

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

<table>
<thead>
<tr>
<th>Integrins</th>
<th>ICAM-1</th>
<th>LFA-1 &amp; MAC-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCAM-1</td>
<td>VLA-4</td>
<td></td>
</tr>
</tbody>
</table>

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

**Figure 3-1.** Adhesion and Migration

**CLINICAL CORRELATE**

*Leukocyte adhesion deficiency type I*

- Autosomal recessive
- Deficiency of \( \beta_2 \) integrin subunit (CD18)
- Recurrent bacterial infection
- Delay in umbilical cord sloughing
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 ?-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 Chdiak-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).
Figure 3-2. Oxygen-Dependent Killing
**Nitroblue Tetrazolium Reduction**

**Oxygen-independent killing** involves lysozyme, lactoferrin, acid hydrolases, bactericidal permeability increasing protein (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 \(\rightarrow\) kallikrein
- Kallikrein cleaves high molecular weight kininogen (HMWK) \(\rightarrow\) bradykinin
- Effects of bradykinin include increased vascular permeability, pain, vasodilation, bronchoconstriction, and pain

![Diagram of Chemical Mediators of Inflammation](image)

**Figure 3-3. Sources of Chemical Mediators of Inflammation**

Arachidonic acid products

**NOTE**

*Mediators of Pain*

- Bradykinin
- Prostaglandins (E₂)
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 E2 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.

**Mediators of Fever**
- Cytokines IL-1, IL-6, and TNF-
- Prostaglandins

**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.

**FOUR OUTCOMES OF ACUTE INFLAMMATION**
- Complete resolution with regeneration
- Complete resolution with scarring
- Abscess formation
- Transition to chronic inflammation
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.

**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 ? (TGF-?) drive fibroblast activation for the formation of granulation tissue.
- Then, TGF-?, PDGF, and FGF drive ECM deposition. Cytokines IL-1 and IL-13 stimulate collagen production for scar formation.
Circulatory Pathology

LEARNING OBJECTIVES

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

NOTE

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

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.

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).
Genetic Disorders and Disorders of Sexual Development

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.

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.

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).

NOTE

Mosaicism is defined as the presence of 2 populations of cells within an individual.

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

Median life expectancy is 47 years.
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.
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

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.

**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**

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

- Short stature
- Low posterior hairline
- Webbing of neck
- Constriction of aorta
- Broad chest and widely set nipples
- Cubitus valgus (elbows turned in)
- Rudimentary ovaries, infertility, amenorrhea
- Small fingernails
- Pigmented nevi (brown spots)
- Peripheral lymphedema (swollen feet)
Immunopathology

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; eosinophili 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.

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
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).
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 which 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.
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

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.

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.

---

**Figure 10-2. Vitiligo**

*Richard P. Usatine, MD Used with permission.*
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’s disease* causes generalized hyperpigmentation due to increased melanin in the basal layer. (See the endocrine pathology chapter.)
Red Blood Cell Pathology: Anemias

LEARNING OBJECTIVES

Explain information related to red blood cell 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.
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

**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.

**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 VASCULITIDIES**

*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.

**SMALL VESSEL VASCULITIDIES**

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.
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).
- **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.
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 coronary artery disease 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.

**CLINICAL CORRELATE**

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

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.
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>
<thead>
<tr>
<th>Detection Markers</th>
<th>Elevated by</th>
<th>Peak</th>
<th>Returns to Normal by</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK-MB</td>
<td>4?8 h</td>
<td>18 h</td>
<td>2?3 days</td>
</tr>
<tr>
<td>Cardiac-specific troponin I &amp; T</td>
<td>3?6 h</td>
<td>16 h</td>
<td>7?10 days</td>
</tr>
<tr>
<td>LDH</td>
<td>24 h</td>
<td>3?6 days</td>
<td>8?14 days</td>
</tr>
</tbody>
</table>

**Table13-1. Serum Markers Used to Diagnose Myocardial Infarctions**

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>
<thead>
<tr>
<th>Time Post-Infarction</th>
<th>Gross Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0?12 h</td>
<td>No visible gross change</td>
</tr>
<tr>
<td>12?24 h</td>
<td>Vague pallor and softening</td>
</tr>
<tr>
<td>1?7 days</td>
<td>Yellow pallor</td>
</tr>
<tr>
<td>7?10 days</td>
<td>Central pallor with a red border</td>
</tr>
<tr>
<td>6?8 wks</td>
<td>White, firm scar</td>
</tr>
</tbody>
</table>

**Table13-2. Gross Sequence of Changes**

<table>
<thead>
<tr>
<th>Time Post-Infarction</th>
<th>Microscopic Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1?4 h</td>
<td>None or wavy myocyte fibers at border or contraction band necrosis</td>
</tr>
<tr>
<td>4 h?3 days</td>
<td>Coagulative necrosis</td>
</tr>
<tr>
<td>1?3 days</td>
<td>Neutrophilic infiltrate</td>
</tr>
<tr>
<td>3?7 days</td>
<td>Macrophages</td>
</tr>
<tr>
<td>7?10 days</td>
<td>Granulation tissue</td>
</tr>
<tr>
<td>3?8 wks</td>
<td>Remodeled type III collagen becoming dense, collagenous scar</td>
</tr>
</tbody>
</table>
Complications of MI include cardiac arrhythmias that may lead to sudden cardiac death; congestive heart failure; cardiogenic shock (>40\% myocardium is necrotic); mural thrombus and thromboembolism; fibrinous pericarditis; ventricular 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.

**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).

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).

Coronary artery disease 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.
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.
Renal Pathology

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.

**NOTE**

*Oligohydramnios (Potter) Sequence*

Renal agenesis

?

Oligohydramnios
Fetal compression

Flattened facies and positional abnormalities of hands and feet

**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.
Gastrointestinal Tract Pathology

LEARNING OBJECTIVES
Answer questions about esophagus, stomach, small and large intestines
Solve problems concerning gastric lymphoma

Esophagus

CONGENITAL AND MECHANICAL DISORDERS

CLINICAL CORRELATE

The most common type of tracheo-oesophageal fistula:
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
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. Chagas disease can cause:

- Romaña’s sign (unilateral swelling of the eyelid)
- Cardiomyopathy
- Megaesophagus and megacolon

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.

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.

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.

NOTE

The incidence of Barrett esophagus is increasing in the United States.

ESOPHAGEAL CARCINOMA

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.

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.
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.

NOTE
Pancreatic pseudocyst is a fluid-filled sac adjacent to the pancreas. The wall of granulation tissue lacks an epithelial lining.

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.

- Gross pathologic examination shows focal hemorrhage and liquefaction 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.
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.

NOTE

Formation of cholesterol stones involves the precipitation of cholesterol from supersaturated bile.

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.

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.
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*]).
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>
<thead>
<tr>
<th>Unconjugated (Indirect) Bilirubinemia</th>
<th>Conjugated (Direct) Bilirubinemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased RBC turnover (hemolytic\anemias)</td>
<td>Biliary tract obstruction</td>
</tr>
<tr>
<td>Physiologic (newborn babies)</td>
<td>Biliary tract disease (PSC and PBC)</td>
</tr>
<tr>
<td>Hereditary (Gilbert and Crigler-Najjar syndromes)</td>
<td>Hereditary (Dubin-Johnson and Rotor syndromes)</td>
</tr>
<tr>
<td></td>
<td>Liver disease (cirrhosis and hepatitis)</td>
</tr>
</tbody>
</table>

*Table 19-1. Unconjugated Versus Conjugated Bilirubinemia*

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 red blood cell (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).

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 ?-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.

VIRAL HEPATITIS

Non-hepatitis viruses which may infect the liver include:

- Epstein-Barr virus (EBV)?infectious mononucleosis
- Cytomegalovirus (CMV)
- Herpes
- Yellow fever

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.

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>
<thead>
<tr>
<th>Common Virus Name</th>
<th>Hepatitis A (HAV)</th>
<th>Hepatitis B (HBV)</th>
<th>Hepatitis C (HCV)</th>
<th>Hepatitis D (HDV)</th>
<th>Hepatitis E (HEV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus</td>
<td>Hepatovirus nonenveloped capsid RNA</td>
<td>Hepadnavirus enveloped DNA</td>
<td>Flavivirus enveloped RNA</td>
<td>Defective enveloped circular RNA</td>
<td>Hepevirus nonenveloped capsid RNA</td>
</tr>
<tr>
<td>Transmission</td>
<td>Fecal-oral</td>
<td>Parenteral, sexual, perinatal</td>
<td>Parenteral, sexual</td>
<td>Parenteral, sexual</td>
<td>Fecal-oral</td>
</tr>
<tr>
<td>Severity</td>
<td>Mild</td>
<td>Occasionally severe</td>
<td>Usually subclinical</td>
<td>Co-infection with HBV occasionally severe; super-infection with HBV often severe</td>
<td>Normal patients: mild; pregnant patients: severe</td>
</tr>
<tr>
<td>Chronicity or carrier state</td>
<td>No</td>
<td>Yes</td>
<td>Yes (high)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Clinical diseases</td>
<td>Acute hepatitis</td>
<td>Chronic hepatitis</td>
<td>Cirrhosis</td>
<td>Hepatocellular carcinoma (HCC)</td>
<td>Acute hepatitis</td>
</tr>
<tr>
<td>Laboratory diagnosis</td>
<td>Symptoms and anti-HAV IgM</td>
<td>Symptoms and serum levels of HBsAg, HBeAg, and anti-HBe IgM</td>
<td>Symptoms and EIA for anti-HCV</td>
<td>Anti-HDV ELISA</td>
<td>Tests not routinely available</td>
</tr>
<tr>
<td>Prevention</td>
<td>Vaccine, hygiene</td>
<td>Vaccine</td>
<td></td>
<td></td>
<td>Hygiene</td>
</tr>
<tr>
<td>Treatment</td>
<td>Supportive</td>
<td>Antivirals, interferons, transplant</td>
<td>Antivirals, interferons, transplant</td>
<td>See hepatitis B</td>
<td>Supportive</td>
</tr>
</tbody>
</table>

Table 19-2. The Hepatitis Viruses

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Name and Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopically, chronic persistent hepatitis</td>
<td>Shows inflammation confined to portal tracts.</td>
</tr>
<tr>
<td>Chronic active hepatitis</td>
<td>Shows inflammation spilling into the parenchyma, causing interface hepatitis (piecemeal necrosis of limiting plate).</td>
</tr>
</tbody>
</table>
### Table 19-3. Hepatitis B Terminology and Markers

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>Hepatitis B virus, a hepadnavirus (enveloped, partially doublestranded DNA virus); Dane particle = infectious HBV</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Antigen found on surface of HBV; also found on spheres and filaments in patient’s blood: positive during acute disease; continued presence indicates carrier state</td>
</tr>
<tr>
<td>HBsAb</td>
<td>Antibody to HBsAg; provides immunity to hepatitis B</td>
</tr>
<tr>
<td>HbcAg</td>
<td>Antigen associated with core of HBV</td>
</tr>
<tr>
<td>HbcAb</td>
<td>Antibody to HbcAg; positive during window phase; IgM HbcAb is an indicator of recent disease</td>
</tr>
<tr>
<td>HbcAb*</td>
<td>A second, different antigenic determinant on the HBV core; important indicator of transmissibility</td>
</tr>
<tr>
<td>Delta agent</td>
<td>Small RNA virus with HBsAg envelope; defective virus that replicates only in HBV-infected cells</td>
</tr>
</tbody>
</table>

### Table 19-4. Hepatitis A Serology

<table>
<thead>
<tr>
<th></th>
<th>Acute or recent infection</th>
<th>Prior infection or immunization</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-HAV IgM</td>
<td></td>
<td>anti-HAV IgG</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Term</th>
<th>Acute infection</th>
<th>Window period</th>
<th>Prior infection</th>
<th>Immunization</th>
<th>Chronic infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>HbcAb*</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>HbcAb IgM</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>HbcAb IgG</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>HBsAb IgG</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
</tbody>
</table>

*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.

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.
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 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.

？-1-antitrypsin deficiency is an autosomal recessive disorder characterized by production of defective ?-1-antitrypsin (?1-AT), which accumulates in hepatocytes and causes liver damage and low serum levels of ?1-AT.

**NOTE**

**Protease-Antiprotease Imbalance**

?-1-antitrypsin is an important protease inhibitor.

- Responsible for inhibiting neutrophil elastase
- Inhibits trypsin, chymotrypsin, and bacterial proteases

?-1-antitrypsin 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.

?-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 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).
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.

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>
<thead>
<tr>
<th>Condition</th>
<th>Cells/?L</th>
<th>Glucose (?g/dL)</th>
<th>Proteins (mg/dL)</th>
<th>Pressure (mm H2O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal values</td>
<td>&lt;5 lymphocytes</td>
<td>45?85 (50?70% glycemia)</td>
<td>15?45</td>
<td>70?180</td>
</tr>
<tr>
<td>Purulent (bacterial)</td>
<td>Up to 90,000 neutrophils</td>
<td>Decreased (&lt;45)</td>
<td>Increased (&gt;50)</td>
<td>Markedly elevated</td>
</tr>
<tr>
<td>Aseptic (viral)</td>
<td>100?1,000 most lymphocytes</td>
<td>Normal or decreased</td>
<td>Normal or slightly increased (&gt;50)</td>
<td>Normal or slightly elevated</td>
</tr>
<tr>
<td>Granulomatous (mycobacterial/fungal)</td>
<td>100?1,000 most lymphocytes</td>
<td>Decreased (&lt;45)</td>
<td>Increased (&gt;50)</td>
<td>Moderately elevated</td>
</tr>
</tbody>
</table>

**Table 20-1. CSF Parameters in Different Forms of Meningitis**

**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.
- **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.
Figure 20-1. MRI Showing Edema of Bilateral Temporal Lobes, Related to Herpes Simplex Encephalitis

Paul J. Shogan, National Capital Consortium. Used with permission.
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 papilledema). 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.

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 ß-helix: PrP\textsubscript{c}. In disease states, PrP\textsubscript{c} changes to a ß-pleated sheet conformation: PrP\textsubscript{sc}. A low rate of spontaneous change results in sporadic cases of CJD. Mutations of PrP result in hereditary cases of CJD. PrP\textsubscript{sc} facilitates conformational change of other PrP\textsubscript{c} molecules into PrP\textsubscript{sc}.
- PrP\textsubscript{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 Creutzfeldt-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-Jakob disease** occurs in younger patients and results from exposure to bovine spongiform encephalopathy.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Infectious Agent</th>
<th>Host</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuru</td>
<td>Prion</td>
<td>Human</td>
<td>Subacute spongiform encephalopathy (SSE); Fore Tribe in New Guinea; consuming infected brains</td>
</tr>
<tr>
<td>Creutzfeldt-Jakob</td>
<td>Prion</td>
<td>Human</td>
<td>SSE</td>
</tr>
<tr>
<td>Gerstmann-Straussler</td>
<td>Prion</td>
<td>Human</td>
<td>SSE</td>
</tr>
<tr>
<td>Fatal familial insomnia</td>
<td>Prion</td>
<td>Human</td>
<td>SSE</td>
</tr>
<tr>
<td>Scrapie</td>
<td>Prion</td>
<td>Sheep</td>
<td>SSE?scraping their wool off on fences</td>
</tr>
</tbody>
</table>

Table 20-2. Prion Diseases
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 white blood cell 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.

- **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 white blood cell 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 sequestration 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).
Female Genital Pathology

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.
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.
Breast Pathology

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.
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

NOTE

Both epispadias and hypospadias may be associated with undescended testes.

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.

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.
Endocrine Pathology

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.

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).

- Lab studies:
  - In primary hyperthyroidism, TSH is decreased.
  - In secondary and tertiary hyperthyroidism, TSH is elevated.
  - Free T4 is elevated.
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.

**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 hyperplasia 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.

**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. Riedel 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).

**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.
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.
Bone Pathology

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 $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, 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 parathyroid hormone (PTH), calcitonin, vitamin D, estrogen,
thyroid hormone, cortisol, and growth hormone.

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.
LEARNING OBJECTIVES

Solve problems concerning osteoarthritis, rheumatoid arthritis, and seronegative spondyloarthropathies
Describe arthritis related to crystal deposition, infectious arthritis, and neuropathic arthropathy (Charcot joint)

<table>
<thead>
<tr>
<th>Osteoarthritis</th>
<th>RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>?Wear and tear?</td>
<td>Systemic autoimmune disease</td>
</tr>
<tr>
<td></td>
<td>(+) Rheumatoid factor</td>
</tr>
<tr>
<td></td>
<td>(+) Rheumatoid nodules</td>
</tr>
<tr>
<td>Degeneration of articular cartilage</td>
<td>Synovial proliferation</td>
</tr>
<tr>
<td>Knees and hands (DIP) in women; hips in men</td>
<td>Hands (PIP) and feet</td>
</tr>
<tr>
<td>Asymmetrical</td>
<td>Symmetrical and migratory</td>
</tr>
</tbody>
</table>

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, achondroplasia, 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.
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 4x 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.

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.
SERONEGATIVE SPONDYLOARTHROPATHIES

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 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.
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.

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.

BRIDGE TO BIOCHEMISTRY

Uric acid is the end product of purine metabolism.

- **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.

NOTE
Lesch-Nyhan Syndrome

- X-linked recessive
- Deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HPRT)
- Cognitive impairment
- Dystonia
- Self-mutilating behaviors
- Hyperuricemia

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.

![Gout](image-url)
In the presence of pseudogout age <50, suspect one of these metabolic abnormalities (4H):

- Hemochromatosis
- Hyperparathyroidism
- Hypophosphatemia
- Hypomagnesemia

**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.

**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 dammini*). 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.
Figure 27-6. Large Targetoid Lesion of Erythema Chronicum Migrans Considered Pathognomonic of Lyme Disease

Richard P. Usatine, MD Used with permission.
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

NOTE

Skeletal muscle fiber type is determined by innervation.

**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.

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twitch rate</td>
<td>Slow twitch</td>
<td>Fast twitch</td>
</tr>
<tr>
<td>Function</td>
<td>Postural weight bearing</td>
<td>Purposeful movement</td>
</tr>
<tr>
<td></td>
<td>Sustained tension</td>
<td>Short, quick bursts</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Aerobic (Krebs cycle)</td>
<td>Anaerobic (glycolysis)</td>
</tr>
<tr>
<td>Energy source</td>
<td>Fatty acids</td>
<td>Glycogen</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>Many</td>
<td>Few</td>
</tr>
<tr>
<td>Color</td>
<td>Red</td>
<td>White</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Slow fatigue</td>
<td>Rapid fatigue</td>
</tr>
</tbody>
</table>

*Table 28-1. Type I (Slow-Twitch) Versus Type II (Fast-Twitch) Muscles*
Anti-tRNA synthetase antibodies such as the anti-Jo-1 antibody are known to be highly specific for 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.

Figure 28-1. Periorbital Heliotrope Rash of Dermatomyositis

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